

Higher Incidence of HCV in Females Compared to Males Who Inject Drugs

A Systematic Review and Meta-analysis

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Abstract and Introduction

Abstract

Women who inject drugs have been shown to have higher incidence of HIV and risk behaviours than men, but there are conflicting reports about hepatitis C virus (HCV) incidence. We systematically reviewed the literature to examine the female-to-male (F:M) HCV incidence in female and male persons who inject drugs (PWID), and also to explore the heterogeneity (i.e. methodological diversity) in these differences. We searched PubMed and EMBASE for studies published between 1989 and March 2015 for research that reported incidence of HCV infection by sex or HCV incidence F:M rate ratio. A total of 28 studies, which enrolled 9325 PWID, were included. The overall pooled HCV incidence rate (per 100 person-years observation) was 20.36 (95% CI: 13.86, 29.90) and 15.20 (95% CI: 10.52, 21.97) in females and males, respectively. F:M ratio was 1.36:1 (95% CI: 1.13, 1.64) with substantial heterogeneity ($I^2=71.6\%$). The F:M ratio varied by geographic location from 4.0 (95% CI: 1.80, 8.89) in China to 1.17 (95% CI: 0.95, 1.43) in the U.S. In studies which recruited participants from community settings, the F:M ratio was 1.24 (95% CI: 1.03, 1.48), which was lower than that reported in the clinical settings (1.72, 95% CI: 0.86, 3.45). The number of studies included provided sufficient statistical power to detect sex differences in this analysis. Our findings raise questions and concerns regarding sex differences with respect to the risk of HCV. Both behavioural and biological studies are needed to investigate causes and potential mechanisms as well as sex-specific prevention approaches to HCV infection.

Introduction

Estimates of the global prevalence of hepatitis C virus (HCV) infection range from 1.6% to 2.8%, corresponding to between 80 and 185 million people.^[1–3] The morbidity and mortality associated with this widespread infection is a major global health burden. Persistent HCV infection can lead to up to 0.5 million deaths every year.^[4] Recent studies showed mortality rate due to viral hepatitis increased in the past two decades and HCV was the seventh leading cause of death worldwide in 2013, compared with tenth in 1990.^[5] Disability-adjusted life-years (DALYs) for HCV also have more than doubled since 1990. Compared with other viral hepatitis, HCV is the only infection, which is associated with increasing age-specific DALYs rates.^[5] Parenteral exposures, especially injection drug use, account for the majority of HCV infections.^[6] In the United States (U.S.), 2.6% (95% confidence interval (95% CI): 1.8%–3.3%) of the population aged 13 or older have reported any lifetime injection drug use.^[7] The rate of current illicit drug use is higher for males than for females, and males are more likely than females to be current users of several different illicit drugs. As a result, more numbers of males are infected than females.^[7] However, several studies have shown that injection practices of women, including higher rates of equipment and syringe sharing, women using injecting equipment following their male partners and being injected by others, may put them at higher risk.^[8–12] In addition, women who inject drugs have been shown to have higher incidence of HIV and higher injection-related risk behaviours.^[13–16]

HCV surveillance data generally show lower HCV detection rates among females compared to men. Viral hepatitis statistics and surveillance in 2013 in the U.S. reported 0.5 and 0.7 cases/10 000 among females and males, respectively.^[17] HCV surveillance data in European Centers of Disease Prevention reported the male-to-female ratio of 1.9 to 1 in 2013.^[18] In Canada, from 1998 to 2004, the enhanced Hepatitis Strain Surveillance System found HCV detection rates per 100 000 people were 1.31 times (95% CI 1.09, 1.58) higher among males than among females, and sex-specific rate for HCV detection showed the same trend over the time.^[19] The literature on HCV prevalence does not suggest differences between women and men. Hagan et al.^[20] evaluated 58 studies that reported HCV prevalence in relation to biological sex. The crude and weighted odds ratio (OR) for the difference in HCV prevalence between males and females were 0.95 and 1.0, respectively (95% CI for weighted OR: 0.94, 1.07). Both surveillance data and studies of prevalence, however, are limited in the capacity of informing the overall burden and incidence of HCV due to challenges in case detection associated with asymptomatic infection, low reporting overall and resource limitations.^[21]

For these reasons, prospective cohort studies, which assess newly or recently acquired infections systematically, offer the most

reliable information on incidence of HCV infection.^[22] HCV differences by sex in longitudinal studies of people who inject drugs (PWID) appear to be inconsistent upon brief review. In a retrospective cohort study, in Sydney, Australia, Micallef et al.^[23] reported that women were less likely than men to become infected with HCV, whereas Maher et al.^[24] in a prospective study found that women were significantly more likely to become infected. Two prospective studies, in Canada and Switzerland, in PWID found nonsignificant differences by sex.^[25,26] Other reports suggest a significantly higher incidence among female PWID compared to male PWID, including in San Francisco, The Netherlands and China.^[12,27,28] These discrepancies point to the need for more systematic analysis of studies of HCV infection differences between females and males who inject drugs.

We systematically searched the literature to explore the heterogeneity (i.e. methodological diversity) reported in HCV incidence rate between female and male PWID. We conducted a meta-analysis including studies that reported HCV incidence by sex or HCV incidence F:M rate ratio by countries/regions, screening test (anti-HCV and/or RNA), nature of data collection (retrospective vs. prospective), recruitment setting [community, prison, clinic (which included drug treatment or other health care setting) and "multiple" setting], type of analysis model and reported effect size (whether adjusted for covariates or not).

Methods

Search Strategies and Study Identification

Methods used to search and identify the target articles were based on the methodology described by Stern et al.^[29] Briefly, three collaborators worked closely to assess literature review, data extraction and quality of included studies. We conducted a comprehensive literature search in PubMed and EMBASE (in English language), using the following search terms: (hepatitis C OR HCV) AND (intravenous drug OR drug misuse OR drug addict OR injecting drug use OR drug abuse OR IDU OR PWID) AND (incidence OR seroincidence OR seroconversion) AND "name of country". Reference lists of obtained articles were searched as well. The search was limited to the period of 1989 to 2015.

We retrieved and/or requested all the required full text from the library of the Icahn School of Medicine at Mount Sinai. We included longitudinal studies, including intervention studies that reported incidence of HCV infection in both female and male PWID. To be eligible for inclusion in this project, studies must have reported crude and/or adjusted HCV incidence rates by sex or female:male (F:M) rate ratio (Hazard Ratio, Rate ratio or Risk Ratio). We excluded studies that assessed HCV incidence in haemodialysis patients, blood donors, post-transfusion, mixed injection and noninjecting populations (with unstratified estimates) and noninjecting populations including studies that reported incidence in noninjecting men who have sex with men (MSM).

A worksheet was developed to extract data on recruitment years and location, nature of data collection (prospective vs. retrospective), study recruitment setting, type of analysis model used to reported effect size and screening test used to identify incident HCV [either by antibodies to HCV (anti-HCV) indicating exposure or by actual infection status (RNA)], and by sex, we extracted the data on cohort size, person-years of follow-up, incidence rate (with 95% CI) and F:M ratio (crude and adjusted effect size). In order to assess the quality of data reporting (selection bias, misclassification of exposure or outcome, and confounding due to noncomparability of the groups being compared), we used Newcastle-Ottawa Scale (NOS) for cohort studies.^[30]

Data Synthesis and Analysis

We extracted or calculated the crude and adjusted F:M ratio within the studies (and [Table S.3](#)). If the F:M rate ratio of HCV incidence was not reported in the article, we computed the effect size and its 95% CI in three ways: (i) if the number of cases and person-years observation (PYO) were reported by sex, we used the incidence rate ratio calculator of Stata 13.1 (StataCorp, LP, College Station, Texas, USA) to compute 95% CI; (ii) if the number of cases and total number of subjects were reported, we used the cohort study risk ratio calculator of Stata 13.1 to compute RR and 95% CI for analysis; and (iii) for three studies, Roy,^[26] Micallef^[23] and Broers,^[25] we obtained the 95% CI from a *P* value.^[31]

Table 1. Characteristics of included articles and summary data of female and male HCV incidence in PWID populations

1st Author Published Year	Location, Study setting (Recruitment periods)	Total Cohort Size (N) (Female)	Female Incidence per 100 PYO (95%)	Male Incidence per 100 PYO (95%)	F:M IRR crude (95% CI)/Type of analysis	F:M IRR adjusted (95%)	Selected F:M IRR (95%)
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(Journal ^e)		N, Male N)	CI)	CI)	model	CI)/Type	CI)/Type
Iversen 2013 (<i>Am J Public Health</i>)	Australia, Community (1995–2010)	724 (269, 453)	18.1 (14.3, 23)	16.5 (13.7, 19.8)	1.01 (0.746, 1.37)/HR ^c		1.01 (0.746, 1.37)/HR
Snow 2014 (<i>BMC Public Health</i>)	Australia, Queensland, Prisoner (1999–2013)	735 (169, 566)	9.8 (7.33, 13.12) ^d	5.74 (4.69, 7.02) ^d	1.65 (1.14, 2.39)/HR	1.36 (0.91, 2.03)/AHR	1.36 (0.91, 2.03)/AHR
Teutsch 2010 (<i>BMC Public Health</i>)	Australia, New South Wales, Prisoner (2005–2009)	488 (170, 318)	42 (30.4, 56.5)	26.2 (19.5, 34.4)	1.6 (1.1, 2.4)/IRR	NA	1.6 (1.1, 2.4)/IRR
White 2014 (<i>Vaccine</i>)	Australia, New South Wales, Community 2008–2011	129 (33, 96)	12.9 (6.7, 27.2)	6.2 (3.3, 11.5)	2.04 (0.84, 4.92)/RR ^{ac}	NA	2.04 (0.84, 4.92)/RR ^a
Micallef 2007 (<i>J Viral Hepat</i>)	Australia, New South Wales, Sydney, Clinical setting 93–2002	423 (253, 166)	15.3 (11.9, 19.6)	19 (14.4, 25)	0.72 (0.59, 1.27)/IRR ^c	NA	0.72 (0.59, 1.27)/IRR
Maher 2006 (<i>Addiction</i>)	Australia, New South Wales, Sydney, Multiple setting 1999–2002	368 (140, 228)	42.4 (30.6, 58.8)	23.5 (16.6, 33.2)	1.75 (1.09, 2.86)/HR	1.66 (0.99, 2.77)/AHR	1.66 (0.99, 2.77)/AHR
Aitken 2008 (<i>Hepatology</i>)	Australia, Victoria, Melbourne, Community 2005–2007	55 (19, 36)	NA	NA	1.35 (0.66, 2.70)/HR ^c	NA	1.35 (0.66, 2.70)/HR
Crofts 1997 (<i>Addiction</i>)	Australia, Victoria, Clinical setting 1991–1995	73 (35, 38)	NA	NA	1.21 (0.56, 2.62)/RR ^{ac}	NA	1.21 (0.56, 2.62)/RR ^a
Grebely 2014 (<i>PLoS One</i>)	Canada, British Columbia, Vancouver, Community 1996–2012	364 (115, 249)	NA	NA	1.42 (0.95, 2.1)/HR	1.42 (0.95–2.1)/AHR	1.42 (0.95, 2.1)/AHR
Puri 2014 (<i>J Adolesc Health</i>)	Canada, British Columbia, Vancouver, Community 2005–2011	512 (151, 361)	NA	NA	2.1 (1.24, 3.56)/HR	2.01 (1.18, 3.44)/AHR	2.01 (1.18, 3.44)/AHR
Spittal 2012 (<i>BMC Public Health</i>)	Canada, British Columbia, Vancouver and Prince George, Community 2003–2009	148 (79, 69)	NA	NA	1.43 (0.79, 2.6)/HR	NA	1.43 (0.79, 2.6)/HR
Bruneau 2012 (<i>Addiction</i>)	Canada, Quebec, Montreal, Community 2004–2009	246 (45, 201)	13.45 (7.29, 22.86)	20.49 (16.13, 25.69)	0.7 (0.38, 1.29)/HR	0.9 (0.46, 1.74)/AHR	0.9 (0.46, 1.74)/AHR
Roy 2007 (<i>Int J STD AIDS</i>)	Canada, Quebec, Community 1997–2003	359 (97, 262)	NA	NA	1.44 (0.84, 1.63)/HR	NA	1.44 (0.84, 1.63)/HR
Ruan 2007 (<i>AIDS</i>)	China, Community 2002	86 (11, 75)	76.3 (54.49, 106.94) ^d	29.8 (22.91, 38.76) ^d	2.6 (1.2, 5.5)/IRR	4 (1.8, 8.9)/AIRR	4 (1.8, 8.9)/AIRR
Lucidarme							

2004 (<i>Epidemiol Infect</i>)	France, Clinical setting 1999–2000	165 (29, 136)	16.67 (2–31)	7.41 (3–12)	2.38 (0.82, 6.667)/HR ^c	2 (0.63, 6.67)/AHR ^c	2 (0.63, 6.67)/AHR
Smyth 2003 (<i>J Epidemiol Community Health</i>)	Ireland, Dublin, Clinical setting 1992–1998	100 (34, 66)	60 (38, 89)	70 (51, 94)	0.85 (0.49, 1.44)/IRR ^c	NA	0.85 (0.49, 1.44)/IRR
Rezza 1996 (<i>Scand J Infect Dis</i>)	Italy, Naples, Clinical setting 1991–1993	106 (3, 103)	NA	NA	5.72 (3.76, 8.71)/RR ^{ac}	NA	5.72 (3.76, 8.71)/RR ^a
van de Laar 2009 (<i>J Hepatol</i>)	Netherlands, Amsterdam, Clinical setting 1985–2005	456 (137, 319)	NA	NA	1.71 (1.06, 2.76)/RR ^{ac}	NA	1.71 (1.06, 2.76)/RR ^a
Brunton 2000 (<i>N Z Med J</i>)	New Zealand, Community 1994–1996	39 (16, 23)	NA	NA	0.72 (0.21, 2.46)/RR ^{ac}	NA	0.72 (0.21, 2.46)/RR ^a
Broers 1998 (<i>AIDS</i>)	Switzerland, Geneva, Clinical setting 1988–1995	576 (130, 446)	9.6 (4.49, 20.54) ^d	2.7 (1.23, 5.94) ^d	3.56 (0.62, 4.84)/IRR ^c	NA	3.56 (0.62, 4.84)/IRR
Craine 2009 (<i>Epidemiol Infect</i>)	UK, South Wales, Multiple setting 2004–2006	286 (83, 203)	6 (1.9, 14)	5.9 (3, 10.3)	1.02 (0.36, 2.88)/IRR	NA	1.02 (0.36, 2.88)/IRR
Hagan 2010 (<i>J Infect Dis</i>)	USA, 5 cities, Community 2002–2004	483 (321, 159)	12.94 (7.66, 21.85)	19.61 (14.44, 26.63)	0.75 (0.58, 1.78)/HR	NA	0.75 (0.58, 1.78)/HR
Thorpe 2002 (<i>Am J Epidemiol</i>)	USA, Illinois, Community 1997–1999	353 (128, 225)	NA	NA	1 (0.47, 2.09)/HR	NA	1 (0.47, 2.09)/HR
Stein 2009 (<i>J Addict Dis</i>)	USA, Rhode island, RCT 2001–2004	109 (28, 81)	NA	NA	0.87 (0.26, 2.93)/RR ^{ac}	NA	0.87 (0.26, 2.93)/RR ^a
Hagan 2004 (<i>Epidemiology</i>)	USA, Seattle, Multiple setting 1994–2001	484 (185, 299)	NA	NA	1.5 (1, 2.1)/HR	1.2 (0.9, 1.8)/AHR	1.2 (0.9, 1.8)/AHR
McDonald 2012 (<i>Int J Drug Policy</i>)	Scotland, Glasgow, Community 1993–2007	829 (290, 539)	10.6 (8.3, 13.5)	10.1 (8.3, 12.3)	1.05 (0.76, 1.43)/IRR	NA	1.05 (0.76, 1.43)/IRR ^b
Vallejo 2015 (<i>J Epidemiol Community Health</i>)	Spain, Barcelona, Madrid and Seville, Community 2001–2006	77 (21, 56)	43.8 (28.66, 66.93) ^d	38.5 (29.05, 50.93) ^d	1.1 (0.6, 2.2)/IRR	0.6 (0.3, 1.2)/AIRR	0.6 (0.3, 1.2)/AIRR
Tsui 2014 (<i>JAMA Intern Med</i>)	USA, San Francisco, Community 2000–2013	552 (176, 376)	NA	NA	NA	1.39 (1, 1.92)/AHR	1.39 (1, 1.92)/AHR

^aCohort study risk ratio calculator of Stata used to calculate RR for meta-analysis.

^bWe used incidence rate ratio calculator of Stata to compute confidence interval.

^cThe effect size or CI is calculated. F:M IRR: Female-to-male incidence rate ratio.

^dThe incidence rate or CI is calculated.

^eThe source of included studies is cited in supplementary documents as well.

Adjusted rate ratios were used in the analysis where they were reported in the source studies with the goal of minimizing bias in the estimate of measured effect as described by Hagan et al.^[32] We transformed the HCV incidence rate ratio into the natural logarithm. Results are presented as rate ratios (converted from the natural logarithm;). Forest plots were created to show pooled estimates of incidence rate and 95% CIs by sex and F:M rate ratio. Using a random-effects model, we estimated the overall ratio and in subgroups of geographic locations, type of collecting data, recruitment setting types and by model of analysing, types of effect size (if sex is included in adjusted model), NOS score and screening test (anti-HCV and/or RNA). The results were sorted by the estimated mid-point of recruitment date (Figures 2 and 3). Publication bias was evaluated using a funnel plot with Egger's bias indicator test.

Table 2. Summary of incident rate ratios (IRR) for female-to-male HCV incidence in studies of people who inject drugs (PWID) overall and by subgroups including geographic area, study setting, HCV test used to identify incident infection, type of analysis model, effect size, nature of data collection and NOS score

Subgroups (Number of studies)	Incidence rate ratio (95% CI)	Tests of heterogeneity		
		Heterogeneity statistic	P-Value	I ²
Overall (28)	1.36 (1.13, 1.64)	95.23	<.001	71.6%
Geographic area				
Australia (9)	1.21 (0.96, 1.53)	14.39	.072	44.4%
Canada (5)	1.44 (1.18, 1.77)	3.42	.491	0%
China (1)	4.00 (1.80, 8.89)	NA	NA	NA
Europe (8)	1.56 (0.86, 2.84)	58.46	<.001	88%
USA (5)	1.17 (0.95, 1.43)	3.90	.42	0%
Study setting				
Community (16)	1.24 (1.03, 1.48)	26.99	.029	44.4%
Prisons (2)	1.48 (1.12, 1.96)	0.32	.569	0%
Clinical setting (7)	1.72 (0.86, 3.45)	60.9	<.001	90.1%
Multiple setting (3)	1.30 (0.99, 1.72)	1.28	.527	0%
HCV test used to identify incident infection				
Anti-HCV (18)	1.39 (1.05, 1.85)	77.69	<.001	78.1%
HCV RNA (10)	1.29 (1.05, 1.57)	16.40	.059	45.1%
Type of analysis model				
Cox Model (14)	1.28 (1.14, 1.45)	12.95	.451	0%
Type of effect size				
Crude (18)	1.32 (1.01, 1.73)	77.44	<.001	78%
Adjusted (10)	1.41 (1.13, 1.76)	17.36	.043	48.2%
By nature of data collection				
Retrospective design (5)	0.99 (0.81, 1.2)	5.63	.229	28.9%
Prospective design (23)	1.49 (1.2, 1.86)	70.87	<.001	69%
By NOS score				
NOS=7 (11)	1.59 (1.03, 2.47)	61.05	<.001	83.6%

NOS=8 (12)	1.19 (0.94, 1.50)	25.09	.009	56.2%
NOS=9 (5)	1.37 (1.14, 1.66)	2.11	.716	0%

Random-effects model; NA, Not applied.

Analyses were conducted using Stata version 13.1 (StataCorp LP, College Station, Texas USA) for data analyses using the *metan* command, and heterogeneity was assessed using the I^2 statistics. We used meta-regression to evaluate trend of F:M IRR over the time (the estimated mid-point of recruitment date).

Results

A total of 2393 reports published from 1989 through March 2015 were identified. Of these, 103 were determined to be eligible for full text assessment (Figure 1). The cohort studies included overall had high NOS ratings, ranging from 7 to 9 (of 10). The characteristics of included studies (all the articles that reported the HCV incidence in PWID) are shown in and Table S.1. We identified duplicate data from same cohorts (Table S.2) based on matching cohort names, settings and geographic area; this was followed by comparing sample sizes, years of data collection and other study characteristics to select the most complete and informative report (cohorts) for final analysis.

Table 1. Characteristics of included articles and summary data of female and male HCV incidence in PWID populations

1st Author Published Year (Journal ^e)	Location, Study setting (Recruitment periods)	Total Cohort Size (N) (Female N, Male N)	Female Incidence per 100 PYO (95% CI)	Male Incidence per 100 PYO (95% CI)	F:M IRR crude (95% CI)/Type of analysis model	F:M IRR adjusted (95% CI)/Type	Selected F:M IRR (95% CI)/Type
Iversen 2013 (<i>Am J Public Health</i>)	Australia, Community (1995–2010)	724 (269, 453)	18.1 (14.3, 23)	16.5 (13.7, 19.8)	1.01 (0.746, 1.37)/HR ^c		1.01 (0.746, 1.37)/HR
Snow 2014 (<i>BMC Public Health</i>)	Australia, Queensland, Prisoner (1999–2013)	735 (169, 566)	9.8 (7.33, 13.12) ^d	5.74 (4.69, 7.02) ^d	1.65 (1.14, 2.39)/HR	1.36 (0.91, 2.03)/AHR	1.36 (0.91, 2.03)/AHR
Teutsch 2010 (<i>BMC Public Health</i>)	Australia, New South Wales, Prisoner (2005–2009)	488 (170, 318)	42 (30.4, 56.5)	26.2 (19.5, 34.4)	1.6 (1.1, 2.4)/IRR	NA	1.6 (1.1, 2.4)/IRR
White 2014 (<i>Vaccine</i>)	Australia, New South Wales, Community 2008–2011	129 (33, 96)	12.9 (6.7, 27.2)	6.2 (3.3, 11.5)	2.04 (0.84, 4.92)/RR ^{ac}	NA	2.04 (0.84, 4.92)/RR ^a
Micallef 2007 (<i>J Viral Hepat</i>)	Australia, New South Wales, Sydney, Clinical setting 93–2002	423 (253, 166)	15.3 (11.9, 19.6)	19 (14.4, 25)	0.72 (0.59, 1.27)/IRR ^c	NA	0.72 (0.59, 1.27)/IRR
Maher 2006 (<i>Addiction</i>)	Australia, New South Wales, Sydney, Multiple setting 1999–2002	368 (140, 228)	42.4 (30.6, 58.8)	23.5 (16.6, 33.2)	1.75 (1.09, 2.86)/HR	1.66 (0.99, 2.77)/AHR	1.66 (0.99, 2.77)/AHR
Aitken 2008 (<i>Hepatology</i>)	Australia, Victoria, Melbourne, Community 2005–2007	55 (19, 36)	NA	NA	1.35 (0.66, 2.70)/HR ^c	NA	1.35 (0.66, 2.70)/HR
Crofts 1997 (<i>Addiction</i>)	Australia, Victoria, Clinical setting 1991–1995	73 (35, 38)	NA	NA	1.21 (0.56, 2.62)/RR ^{ac}	NA	1.21 (0.56, 2.62)/RR ^a

Grebely 2014 (<i>PLoS One</i>)	Canada, British Columbia, Vancouver, Community 1996–2012	364 (115, 249)	NA	NA	1.42 (0.95, 2.1)/HR	1.42 (0.95–2.1)/AHR	1.42 (0.95, 2.1)/AHR
Puri 2014 (<i>J Adolesc Health</i>)	Canada, British Columbia, Vancouver, Community 2005–2011	512 (151, 361)	NA	NA	2.1 (1.24, 3.56)/HR	2.01 (1.18, 3.44)/AHR	2.01 (1.18, 3.44)/AHR
Spittal 2012 (<i>BMC Public Health</i>)	Canada, British Columbia, Vancouver and Prince George, Community 2003–2009	148 (79, 69)	NA	NA	1.43 (0.79, 2.6)/HR	NA	1.43 (0.79, 2.6)/HR
Bruneau 2012 (<i>Addiction</i>)	Canada, Quebec, Montreal, Community 2004–2009	246 (45, 201)	13.45 (7.29, 22.86)	20.49 (16.13, 25.69)	0.7 (0.38, 1.29)/HR	0.9 (0.46, 1.74)/AHR	0.9 (0.46, 1.74)/AHR
Roy 2007 (<i>Int J STD AIDS</i>)	Canada, Quebec, Community 1997–2003	359 (97, 262)	NA	NA	1.44 (0.84, 1.63)/HR	NA	1.44 (0.84, 1.63)/HR
Ruan 2007 (<i>AIDS</i>)	China, Community 2002	86 (11, 75)	76.3 (54.49, 106.94) ^d	29.8 (22.91, 38.76) ^d	2.6 (1.2, 5.5)/IRR	4 (1.8, 8.9)/AIRR	4 (1.8, 8.9)/AIRR
Lucidarme 2004 (<i>Epidemiol Infect</i>)	France, Clinical setting 1999–2000	165 (29, 136)	16.67 (2–31)	7.41 (3–12)	2.38 (0.82, 6.667)/HR ^c	2 (0.63, 6.67)/AHR ^c	2 (0.63, 6.67)/AHR
Smyth 2003 (<i>J Epidemiol Community Health</i>)	Ireland, Dublin, Clinical setting 1992–1998	100 (34, 66)	60 (38, 89)	70 (51, 94)	0.85 (0.49, 1.44)/IRR ^c	NA	0.85 (0.49, 1.44)/IRR
Rezza 1996 (<i>Scand J Infect Dis</i>)	Italy, Naples, Clinical setting 1991–1993	106 (3, 103)	NA	NA	5.72 (3.76, 8.71)/RR ^{ac}	NA	5.72 (3.76, 8.71)/RR ^a
van de Laar 2009 (<i>J Hepatol</i>)	Netherlands, Amsterdam, Clinical setting 1985–2005	456 (137, 319)	NA	NA	1.71 (1.06, 2.76)/RR ^{ac}	NA	1.71 (1.06, 2.76)/RR ^a
Brunton 2000 (<i>N Z Med J</i>)	New Zealand, Community 1994–1996	39 (16, 23)	NA	NA	0.72 (0.21, 2.46)/RR ^{ac}	NA	0.72 (0.21, 2.46)/RR ^a
Broers 1998 (<i>AIDS</i>)	Switzerland, Geneva, Clinical setting 1988–1995	576 (130, 446)	9.6 (4.49, 20.54) ^d	2.7 (1.23, 5.94) ^d	3.56 (0.62, 4.84)/IRR ^c	NA	3.56 (0.62, 4.84)/IRR
Craine 2009 (<i>Epidemiol Infect</i>)	UK, South Wales, Multiple setting 2004–2006	286 (83, 203)	6 (1.9, 14)	5.9 (3, 10.3)	1.02 (0.36, 2.88)/IRR	NA	1.02 (0.36, 2.88)/IRR
Hagan 2010 (<i>J Infect Dis</i>)	USA, 5 cities, Community 2002–2004	483 (321, 159)	12.94 (7.66, 21.85)	19.61 (14.44, 26.63)	0.75 (0.58, 1.78)/HR	NA	0.75 (0.58, 1.78)/HR
Thorpe 2002 (<i>Am J</i>)	USA, Illinois, Community 1997–1999	353 (128, 225)	NA	NA	1 (0.47, 2.09)/HR	NA	1 (0.47, 2.09)/HR

<i>Epidemiol</i>)							
Stein 2009 (<i>J Addict Dis</i>)	USA, Rhode island, RCT 2001–2004	109 (28, 81)	NA	NA	0.87 (0.26, 2.93)/RRac	NA	0.87 (0.26, 2.93)/RR ^a
Hagan 2004 (<i>Epidemiology</i>)	USA, Seattle, Multiple setting 1994–2001	484 (185, 299)	NA	NA	1.5 (1, 2.1)/HR	1.2 (0.9, 1.8)/AHR	1.2 (0.9, 1.8)/AHR
McDonald 2012 (<i>Int J Drug Policy</i>)	Scotland, Glasgow, Community 1993–2007	829 (290, 539)	10.6 (8.3, 13.5)	10.1 (8.3, 12.3)	1.05 (0.76, 1.43)/IRR	NA	1.05 (0.76, 1.43)/IRR ^b
Vallejo 2015 (<i>J Epidemiol Community Health</i>)	Spain, Barcelona, Madrid and Seville, Community 2001–2006	77 (21, 56)	43.8 (28.66, 66.93) ^d	38.5 (29.05, 50.93) ^d	1.1 (0.6, 2.2)/IRR	0.6 (0.3, 1.2)/AIRR	0.6 (0.3, 1.2)/AIRR
Tsui 2014 (<i>JAMA Intern Med</i>)	USA, San Francisco, Community 2000–2013	552 (176, 376)	NA	NA	NA	1.39 (1, 1.92)/AHR	1.39 (1, 1.92)/AHR

^aCohort study risk ratio calculator of Stata used to calculate RR for meta-analysis.

^bWe used incidence rate ratio calculator of Stata to compute confidence interval.

^cThe effect size or CI is calculated. F:M IRR: Female-to-male incidence rate ratio.

^dThe incidence rate or CI is calculated.

^eThe source of included studies is cited in supplementary documents as well.

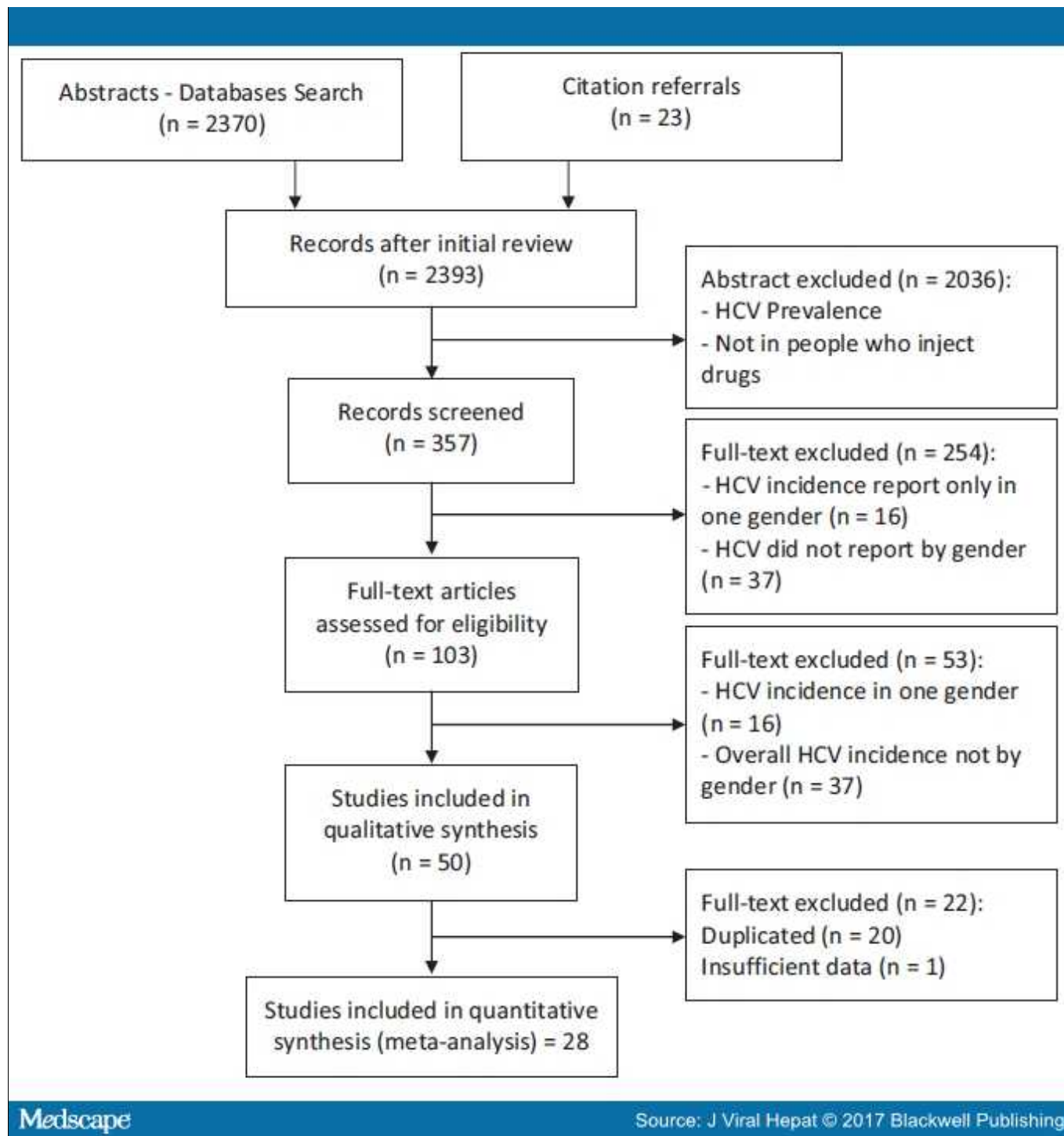


Figure 1.

Flow chart of selection process of reviewed studies

After evaluating the eligibility criteria and removing duplicate cohorts (Table S.2), we found 28 studies eligible for inclusion in our final analysis. One of these studies was a randomized clinical trial;^[33] all others were observational longitudinal studies, including five retrospective and 22 prospective cohort studies. These 28 studies included a total of 9325 enrolled PWID, with 6049 male and 2098 female participants, and 14 787.42 PYO.

In Figure 2, we report HCV incidence rates (IRs) and variability within five continents and overall in females and males; results were sorted by the recruitment date mid-point. In 16 studies that reported HCV IRs in both females and males, the overall pooled HCV estimate was 20.36/100 PYO (95% CI: 13.86, 29.90) in females and 15.20/100 PYO (95% CI 10.52, 21.97) in

males. The pooled HCV IRs reported in Australian studies were 20.18/100 PYO in females and 14.02/100 PYO in males. The variability was considerable in both sexes ($I^2 > 93\%$, $P < .001$); however, no time trend was observed. In six European studies that reported IRs, the pooled HCV IRs in females and males were 18.11 and 12.65/100 PYO, respectively. The variability was also considerable in both groups and significant ($I^2 > 95\%$, $P < .001$) with no time trend pattern. In the only study from China, the HCV IR was 76.30/100 PYO in females compared to 29.80/100 PYO in males, higher than rates reported by any other studies.

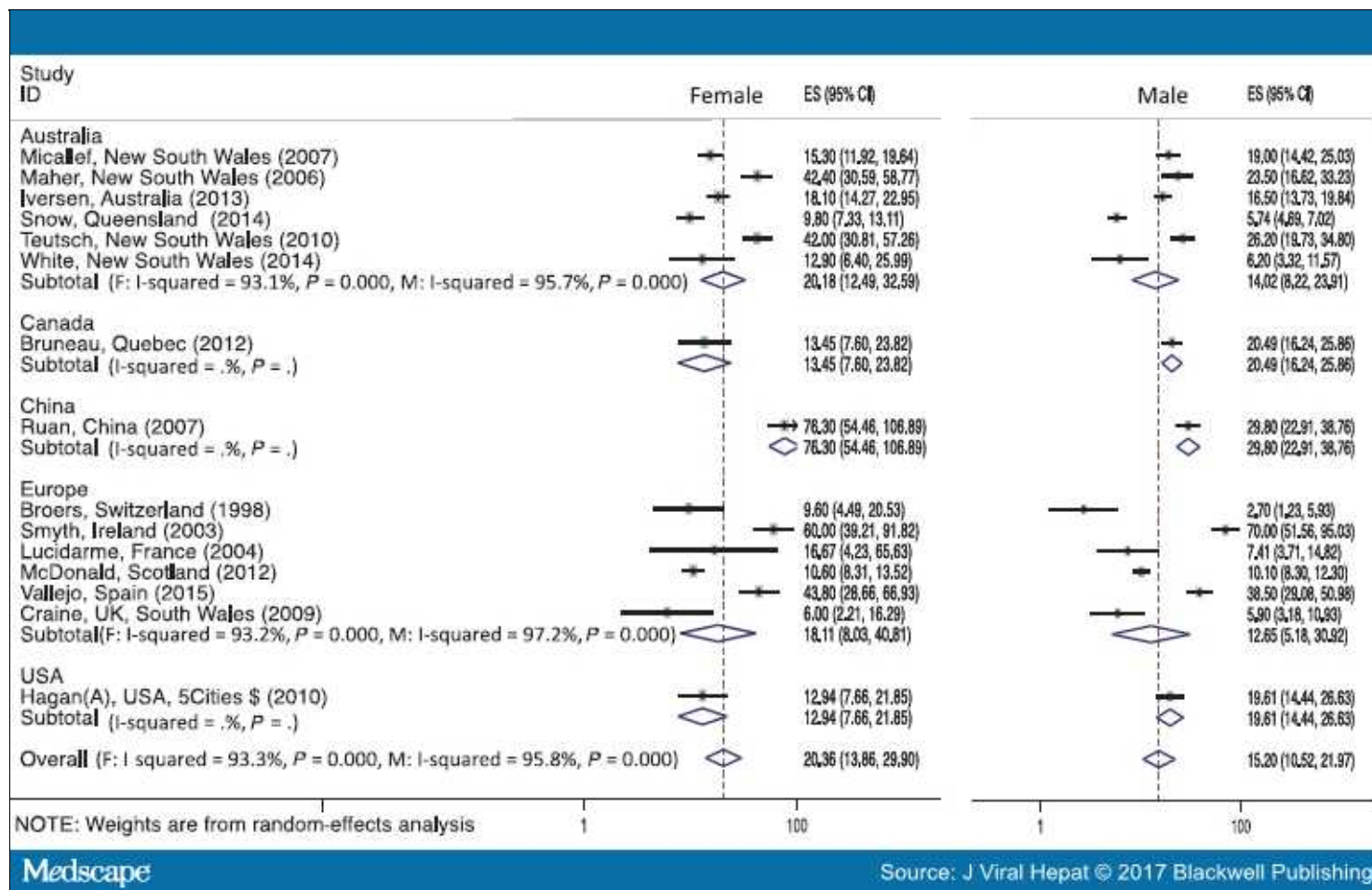


Figure 2.

Forest plot of the studies and pooled estimates of incident HCV per 100 person-years observation in female and male PWID (ES: effect size which is the HCV incidence)

shows results for F:M HCV incidence rate ratios (IRR) overall and stratified by geographic area, research setting, type of data collection, analysis model and by types of effects size. Overall, the pooled F:M HCV IRR was 1.36:1 (95% CI 1.13, 1.64), with relatively high heterogeneity ($I^2 = 71.6\%$, $P < .001$). Subgroup analyses shed light on potential causes of this variability. Lower heterogeneity and I^2 statistics were observed with higher NOS scores. Five studies with NOS score of 9 (Table S.4) were accompanied by zero I^2 and F:M IRR of 1.37, comparable to the overall estimate of 1.36. By geographic area, studies in the U.S. ($N=5$) and Australia ($N=9$) had comparable pooled estimates of relative risk of HCV for females compared to males: IRR: 1.17 and 1.21, respectively, followed by European studies ($N=8$) at 1.56. We observed elevated but nonsignificant higher F:M IRR (95% CI) in Australia and the U.S., respectively: 1.21 (0.96–1.53) and 1.17 (0.95–1.43).

Table 2. Summary of incident rate ratios (IRR) for female-to-male HCV incidence in studies of people who inject drugs (PWID) overall and by subgroups including geographic area, study setting, HCV test used to identify incident infection, type of analysis model, effect size, nature of data collection and NOS score

	Tests of heterogeneity

Subgroups (Number of studies)	Incidence rate ratio (95% CI)	Heterogeneity statistic	P-Value	I^2
Overall (28)	1.36 (1.13, 1.64)	95.23	<.001	71.6%
Geographic area				
Australia (9)	1.21 (0.96, 1.53)	14.39	.072	44.4%
Canada (5)	1.44 (1.18, 1.77)	3.42	.491	0%
China (1)	4.00 (1.80, 8.89)	NA	NA	NA
Europe (8)	1.56 (0.86, 2.84)	58.46	<.001	88%
USA (5)	1.17 (0.95, 1.43)	3.90	.42	0%
Study setting				
Community (16)	1.24 (1.03, 1.48)	26.99	.029	44.4%
Prisons (2)	1.48 (1.12, 1.96)	0.32	.569	0%
Clinical setting (7)	1.72 (0.86, 3.45)	60.9	<.001	90.1%
Multiple setting (3)	1.30 (0.99, 1.72)	1.28	.527	0%
HCV test used to identify incident infection				
Anti-HCV (18)	1.39 (1.05, 1.85)	77.69	<.001	78.1%
HCV RNA (10)	1.29 (1.05, 1.57)	16.40	.059	45.1%
Type of analysis model				
Cox Model (14)	1.28 (1.14, 1.45)	12.95	.451	0%
Type of effect size				
Crude (18)	1.32 (1.01, 1.73)	77.44	<.001	78%
Adjusted (10)	1.41 (1.13, 1.76)	17.36	.043	48.2%
By nature of data collection				
Retrospective design (5)	0.99 (0.81, 1.2)	5.63	.229	28.9%
Prospective design (23)	1.49 (1.2, 1.86)	70.87	<.001	69%
By NOS score				
NOS=7 (11)	1.59 (1.03, 2.47)	61.05	<.001	83.6%
NOS=8 (12)	1.19 (0.94, 1.50)	25.09	.009	56.2%
NOS=9 (5)	1.37 (1.14, 1.66)	2.11	.716	0%

Random-effects model; NA, Not applied.

In studies which recruited participants from community settings, the pooled F:M IRR was 1.24 (95% CI: 1.03, 1.48), which was lower than seen in studies conducted in prison settings (1.48, 95% CI: 1.12, 1.96), and in studies conducted in clinical settings (1.72, 95% CI: 0.86, 3.45). The results of studies conducted in prison and multiple setting were more consistent ($I^2=0\%$), compared to the high variability ($I^2=90.1\%$) observed in studies conducted in clinical settings. The pooled F:M IRR estimate was not elevated in studies which used a retrospective design (0.99), whereas prospective studies showed a significantly elevated pooled F:M IRR at 1.49, but with high variability ($I^2=69\%$). Another factor that impacted F:M IRR was found by type of analyses: those that used Cox proportional hazards modelling and reported a hazard ratio (HR) or adjusted hazard ratio (AHR) had elevated pooled F:M IRR at 1.28 and showed no significant variability in the F:M ratio ($I^2=0\%$). We found that only ten of 28 (35.7%) studies included sex in their adjusted model when examining HCV incidence (in addition to covariates such as age, duration of injecting, drug usually injected, recruitment strategy, shared syringe, needle and equipment exposures, ethnicity,

sexually transmitted infection, geographic region, opiate agonist treatment, recent incarceration and homelessness). In the studies grouped by those that presented unadjusted models, the crude pooled F:M IRR was 1.32, compared to 1.41 in those that adjusted for sex and other covariates (). Studies that identified incident HCV based on RNA testing showed a F:M IRR of 1.29 and lower variability ($I^2=45%$) compared to those that identified incidence using anti-HCV (F:M IRR=1.39; $I^2=78.1%$).

Table 2. Summary of incident rate ratios (IRR) for female-to-male HCV incidence in studies of people who inject drugs (PWID) overall and by subgroups including geographic area, study setting, HCV test used to identify incident infection, type of analysis model, effect size, nature of data collection and NOS score

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Random-effects model; NA, Not applied.

Figure 3 illustrates the F:M IRR variability within five continents. Sorting the results by the recruitment date mid-point provides further clarity on underlying variability in Australian and European studies. For the eight studies in Europe that reported IRRs (England, Nederland, Spain, France, Italy, Scotland and Switzerland), we noted high variability ($I^2=88\%$). The F:M ratio in Europe decreased significantly (coefficient: $-0.12, P=.039$) from 5.72 in the Rezza et al. study (1996) to 0.6 in the Craine et al. study (2015; Figure 3). In contrast, we noted moderate variability in Australia (I^2 of 44.4%). In Australia, we observed a borderline increase (coefficient: $.05, P=.064$) in the trend of F:M IRR from 0.72 (95% CI: 0.21, 2.46) in the Brunton et al. study (2000) to 2.04 (95% CI: 0.84, 4.92) in the White et al. study (2015, Figure 3). In Canada and USA, the observed variability was due to chance only (sampling error) as both had I^2 of 0% ($P>.42$) with no time trend in results.

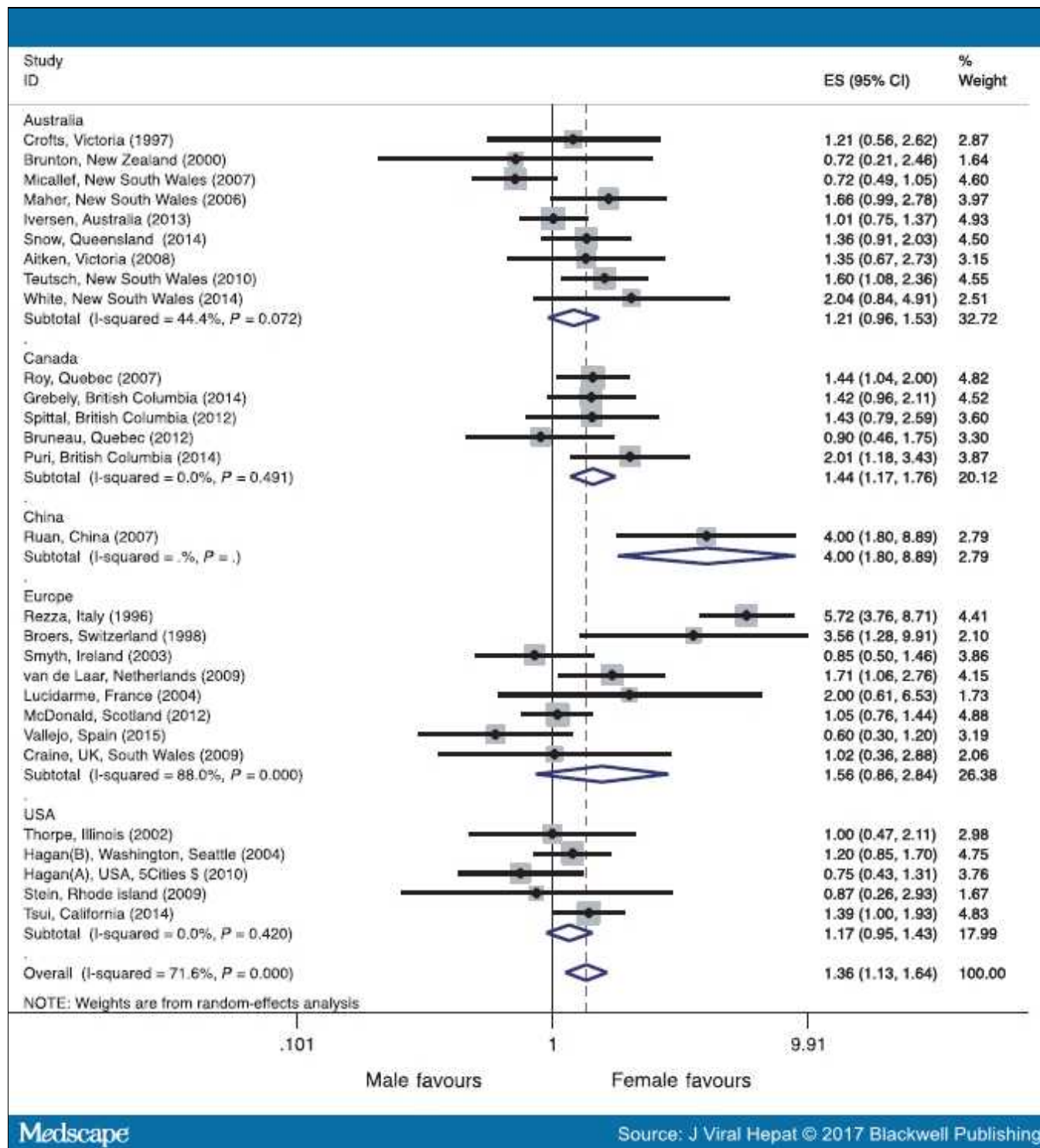


Figure 3.

Forest plot of the studies and pooled estimates of female-to-male rate ratios of HCV infection in people who inject drugs by geographic area. Within each continent, studies are sorted by recruitment date mid-point. F-M IRR ranges between 0 and +infinity; 1 would be the F-M equality and amount less than 1 is favours males

Discussion

The higher pooled estimated IR among females (20.36/100 PYO) compared to men (15.20/100 PYO) is consistent with an overall 36% higher risk of infection. This effect is seen from pooling data from a substantive number ($N=28$) of studies, thus providing sufficient statistical power to detect and test for sex differences. Substantial heterogeneity ($I^2=71.6\%$) was observed overall, and when restricting analyses to studies with high NOS scores ($=9$), pooled M:F IRR estimates were similar to the overall pooled estimate (1.37) and variability in this subgroup was null. Inconsistency in results was seen in association with various study factors, most notably geographic locations, study setting, type of analysis model and type of HCV screening test used to identify incident infection.

In all geographic regions, studies showed elevated F:M IRRs; those conducted in North America (Canada and USA) had the least heterogeneity, while those conducted in Australia and Europe the most. These results suggest that risk differential between females and males is not constant. The variability in the studies from Europe and Australia appears to be in part associated with temporal changes, which is demonstrated in Figure 3. However, when examining these, it is not clear what potential changes, for instance in behavioural or structural factors, might have contributed to the trends seen in female-to-male risk differential. In Australia, comprehensive harm reduction and drug treatment programmes (including needle and syringe programmes, peer education and opioid agonist therapy programmes) have contributed to decreased overall HCV infection rate,^[9,34] yet the F:M IRR among PWID shows an upward trend over the past 18 years, suggesting that women are increasingly at disproportionate risk. In contrast, studies conducted in European countries show downward trends in the F:M IRR. One study in Spain describes a programme specifically targeting HCV risk reduction in women,^[35] but it is difficult to know whether there has been wider implementation of this or similar programmes, and whether such programmes contributed to the downward trend in F:M IRR. There remain significant gaps in information and data from these and many other regions where HCV is epidemic among PWID. The single study from China, which found a fourfold higher risk for females, points to a need for more work in Asia. No studies were found from South or South-East Asia where there are large populations of PWID.^[3,36] As well, there is a lack of data from the Middle East and North Africa as well as sub-Saharan Africa.^[3,36] Data from these regions would add significantly to characterizing factors involved in differential risk between female and male PWID.

Behavioural and social risks have been shown to differ between female and male injectors,^[9,12,13,16] and some studies that have investigated sex differences have found that some of these risk exposures can account for differences in HCV incidence.^[8,12,37] In addition to differential behavioural risks, studies are needed to assess other potential causes and mediators, including biological and structural factors, that contribute to differential HCV risk. Biological factors that may contribute to increased susceptibility, oestrogen receptors and genetic variations in the oestrogen receptor gene (the oestrogen receptor 2 gene) are potential factors which might contribute to higher HCV incidence in females.^[38] The natural history of HCV infection does differ significantly in females compared to males including higher rates of viral clearance,^[39] reclearance after reinfection^[40] and differences in response to HCV treatment for chronic HCV.^[41,42] Overall, a lack of information on sex-specific differences is the norm; we found that just over a third (34.5%) of studies on HCV incidence examined sex-related differences in HCV incidence. Further work should go beyond controlling for sex differences and begin to examine factors that contribute to differences, and especially higher risk in women.

These findings regarding incident HCV are in contrast to those seen with respect to prevalent HCV infection, where meta-analyses show prevalence parity among PWID.^[20] Factors that can lead to differences in HCV infection measures, including in incidence and prevalence studies, include how HCV infection is measured, and how frequently. As women are significantly more likely to spontaneously clear HCV,^[39,43] variability in HCV testing interval in the different studies may also contribute to biased estimates of infection detection.^[44] Spontaneous clearance of HCV also may explain differences in the rate ratios observed between clinical settings where monitoring may be more frequent and have the highest rate ratio (1.72) compared with prison (1.48) or community (1.24) settings ().

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Random-effects model; NA, Not applied.

Our findings have some limitations. Overall and in most of the subgroup analysis, we had a large amount of heterogeneity which could not be solely explained by study type, study recruitment, study setting, geographic location, analytic approaches or screening test. Other factors that may contribute to this include factors which we could not control for, such as differences in drugs used, behavioural risk exposures, method of data collection and follow-up frequencies. The random-effects model we used, in part, addresses some of these variabilities. Evaluating the effect size based on testing methods (anti-HCV and HCV RNA) showed a small decrease in effect size in those studies using RNA testing compared to Anti-HCV (1.29 vs. 1.39, respectively). However, this does not impact the overall finding of significantly higher pooled F:M IRR. Significant effects size with low variability in subgroup analysis of study that used the Cox proportional survival model (1.28, I²=0%) support our inferences regarding sex differences (). Finally, we assessed the publication bias by looking at the symmetrical funnel plot

(Figure 4), indicating that there is no publication bias for the F:M ratios (Egger's test $P=.736$).

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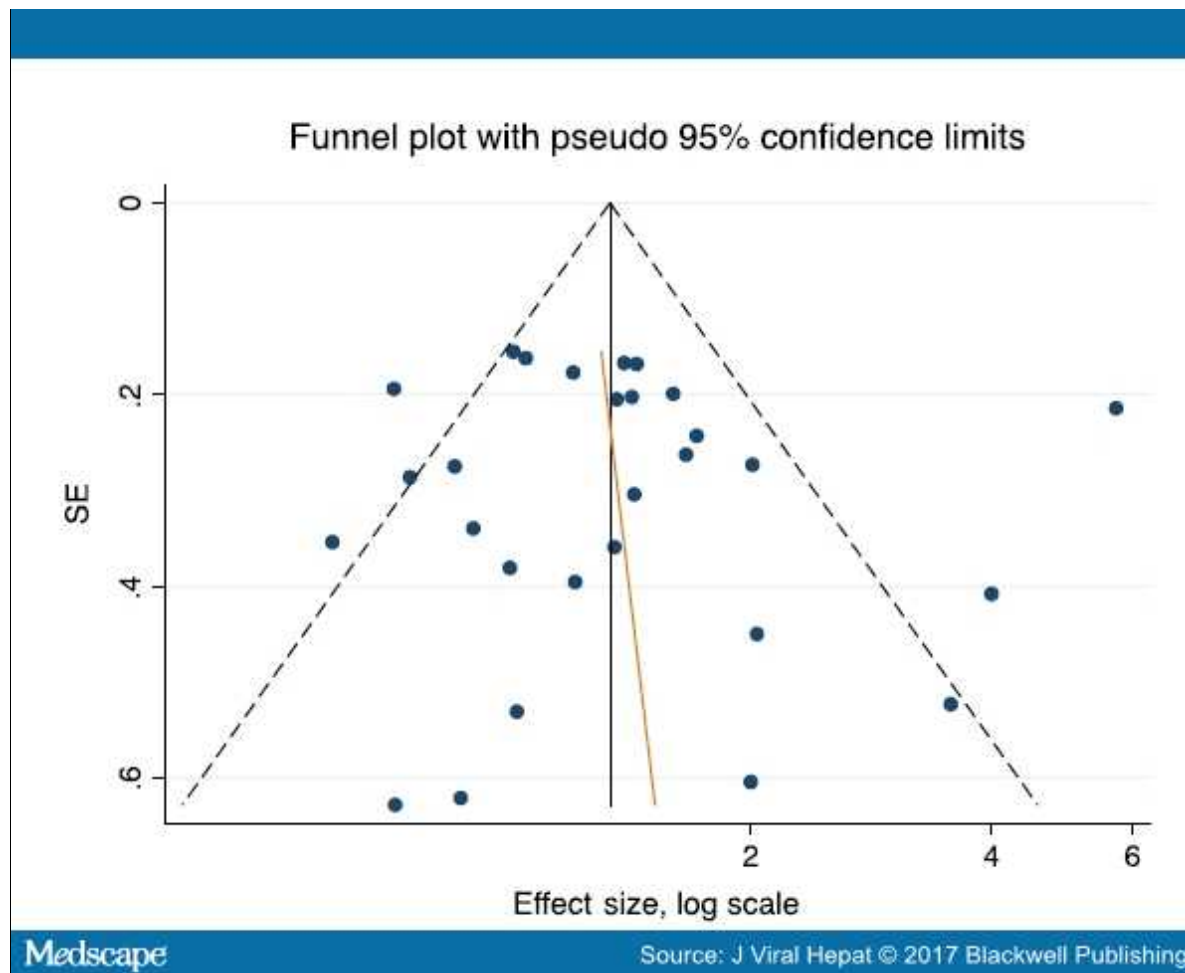


Figure 4.

Publication bias in studies of people who inject drugs: the female-to-male incidence rate ratio funnel plot is symmetrical, indicating that there is no publication bias (Egger's test $P=0.736$)

Globally, sexual differences in burden of HCV infection are not well studied. While our results show that there is a differential in HCV acquisition, in absolute numbers, among PWID more males are HCV-infected than females, due to the higher prevalence of injecting,^[7] and lower HCV clearance.^[39] Nevertheless, there is a need to assess and identify mechanisms for sex-related differences. Biological factors may contribute to differences in HCV susceptibility by sex, but potential mechanisms have not been studied. Certainly, other data show that women have different biological responses to HCV: female PWID have higher rates of spontaneous clearance and reclearance after reinfection^[39,40] than men, as well as lower rates of HCV-associated liver disease and mortality.^[45] Behavioural and social factors, however, pose the most proximal point for interventions to reduce sex-related differences, as many studies have shown that females who inject drugs have significantly higher HCV-associated risk exposures than males.^[8,10–12] Behavioural, social and structural factors play an important role in transmission of HCV and other infections such as HIV, and these are likely to differ by country and region, where cultural, social and political factors may differentially impact risk by sex. Sex-based interventions are under-implemented and may have potential to contribute to reducing some of the risk differential between male and female PWID. Studies show that female PWID often face significant stigma, leading to lower participation in harm reduction services.^[46,47] In addition to behavioural interventions, further integration of biomedical prevention especially targeting women is needed.^[48] Opiate agonist therapy and needle and syringe programmes are proven, safe and effective interventions to reduce HCV infection,^[32,49] and new sex-based approaches should be explored with the goal of reducing disparities in HCV infection rates. As with many meta-analyses, especially of observational research, findings from this analysis reveal gaps/need for more research in the area.^[50] Future investigations to assess mechanisms, mediators and moderators of the differences in HCV incidence between women and men will inform public health practice and approaches to prevention.

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Abbreviations

CI, confidence interval; F:M, female-to-male; HCV, hepatitis C virus; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; PWID, people who inject drugs; PYO, person-years observation; U.S., United States.

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