MAJOR ARTICLE

The Effect of Female Sex on Hepatitis C Incidence Among People Who Inject Drugs: Results From the International Multicohort InC3 Collaborative

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Background. The objective of this study was to assess differences in hepatitis C virus (HCV) incidence by sex in people who inject drugs (PWID), using a large international multicohort set of pooled biological and behavioral data from prospective observational studies of incident human immunodeficiency virus (HIV) and HCV infections in high-risk cohorts (the InC3 Collaborative).

Methods. HCV infection date was estimated based on a hierarchy of successive serological (anti-HCV), virological (HCV RNA), and clinical (symptoms and/or liver function tests) data. We used a Cox proportional hazards model to calculate the crude and adjusted female to male (F:M) hazard ratio (HR) for HCV incidence using biological sex as the main exposure.

Results. A total of 1868 PWID were observed over 3994 person-years of observation (PYO). Unadjusted F:M HR was 1.38 (95% confidence interval [CI], 1.15–1.65) and remained significant after adjusting for behavioral and demographic risk factors (1.39 [95% CI, 1.12–1.72]). Although syringe and equipment sharing were associated with the highest HCV incidence rate in women (41.62 and 36.83 PYO, respectively), we found no sex differences attributed to these risk factors.

Conclusions. Our findings indicate that women who inject drugs may be at greater risk of HCV acquisition than men, independent of demographic characteristics and risk behaviors. Multiple factors, including biological (hormonal), social network, and differential access to prevention services, may contribute to increased HCV susceptibility in women who inject drugs.

Keywords. sex; hepatitis C virus; people who inject drugs; incidence; survival analysis.

Parenteral exposures to infected blood especially via injection drug use account for the majority of hepatitis C virus (HCV) infections in high- and middle-income countries [1]. There is a significant body of research assessing sex and gender differences in injection risk behavior among people who inject drugs (PWID); however, little or no research has investigated sex differences in HCV disease susceptibility.

Human immunodeficiency virus (HIV) incidence and prevalence have been shown to be modestly higher in female compared to male PWID, findings that have been associated with both behavioral and biological factors [2, 3]. While rates of illicit drug use, including injection use, are higher in men than for women worldwide [4, 5], many studies have shown that women report higher prevalence of injection-related risk behaviors than men, including

receptive needle/syringe and equipment sharing [6–10]. Women are more likely to be initiated into injection drug use by their sex partners [11] and to have overlapping sexual and drug networks [12]. HCV prevalence is often higher in men compared to women, although in meta-analyses this has not been found [2, 13], Findings regarding prevalence differences are problematic to compare to incidence studies for several reasons: Studies use various measures of exposure (anti-HCV) and infection (RNA), and women are more likely to spontaneously clear HCV infection [14]. Sex differences in exposures to prevention programs, including medication-assisted treatment (MAT) programs for opioid dependence and needle and syringe programs (NSPs) [15], have also been associated with differences in HCV incidence. HCV transmission through sexual contact is very rare in heterosexual male-female couples (1 per 190000 sexual contacts) [16] and also low in HIV-infected men who have sex with men with presumable sexual acquisition (0.53%) [17] compared with parenterally acquired HCV infection.

HCV incidence differences by sex have not been well studied. Although some individual studies have shown nonsignificant sex differences in HCV incidence rates [18, 19], others have reported differential incidence among female PWID [7, 20, 21]. A recent systematic review and meta-analysis of longitudinal studies of

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HCV incidence found that women have a 36% higher risk of HCV infection [22]. However, that study did not control for individual-level demographic and injecting risk behavior, potentially confounding results. To further explore the relative risk of incident HCV by sex, we conducted analyses to assess incidence of primary HCV infection in susceptible HCV-negative female and male PWID, and calculate excess risk (female to male [F:M] ratio) among women independent of demographic characteristics, injection risk, and other risk and preventive exposures using individual-level data from the International Collaboration of Incident HIV and HCV in Injecting Cohorts (InC3) [23].

METHODS

The InC3 Collaborative and cohorts contributing behavioral and serological data have been described previously [23]. In brief, InC3 houses data from 10 individual prospective studies of HIV and HCV among PWID, which is harmonized across all studies: Amsterdam Cohort Study (ACS), Australian Trial in Acute Hepatitis C (ATAHC, Sydney), Boston Acute HCV Study: Transmission, Immunity, Outcomes Network (BAHSTION), Baltimore Before and After Acute Study in Hepatitis (BBAASH), Hepatitis C Virus Cohort (HCVC) Study (Sydney), Hepatitis C Incidence and Transmission–Prison Study (HITS-p) and Hepatitis C Incidence and Transmission–Community Study (HITS-c) (both Sydney), HepCo Study (Montreal), SuperMIX Study (Networks II and MIX studies, Melbourne), and U-Find-Out (UFO) Study (San Francisco). A principal goal of InC3 is to provide a platform for analyses from pooled data regarding HCV risk and outcomes that a single study may fail to answer due to small numbers of outcomes and insufficient statistical power. This study includes data from 7 of the 10 cohorts. Excluded cohorts included BAHSTION and BBAASH (which lacked systematically injection exposure data) and ATAHC (whose design limited HCV incidence estimation) [24]. Analyses were restricted to participants who reported any history of drug injection and did not report being transgender.

InC3 includes data previously collected under approved protocols from each participating institution. The University of New Mexico Institutional Review Board determined that InC3 was exempt from review as all data are de-identified.

Measurement of Incident Hepatitis C Virus Infection

We defined incident HCV cases based on anti-HCV and/or HCV RNA tests among previously HCV-naive persons using the following criteria: (1) a negative anti-HCV test followed by either a positive anti-HCV or HCV RNA test; or (2) evidence of seroconversion illness, including clinically documented jaundice or alanine aminotransferase (ALT) >400 IU/L *and* a history of high-risk exposure within 3 months of clinical manifestation of acute HCV [25]. Anti-HCV and HCV RNA testing assays varied between but not within cohorts and have been described previously [14].

HCV infection date was estimated using a hierarchy of successive serological (anti-HCV), virological (HCV RNA), and clinical (symptoms and/or liver function tests) data in 3 groups as follows [25]: (1) in acute seronegative viremic patients (anti-HCV negative/HCV RNA positive), HCV infection date was estimated from the date of that test minus 28 days (incubation period) [14]; (2) among those with a seroconversion illness (jaundice or ALT >400 IU/mL), HCV infection date was estimated as 6 weeks prior to recorded symptom date [26]; and (3) based on documented seroconversion, wherein infection date was estimated as the midpoint between date of the last negative anti-HCV test and the first positive anti-HCV or HCV RNA test. Person-years of observation (PYO) was calculated for each subject from their baseline study visit date to the estimated date of HCV infection for incident infections. Data from subjects who remained both anti-HCV and HCV RNA negative were censored at the last cohort visit date with available laboratory results.

Statistical Analyses

We conducted descriptive analyses of demographic characteristics and risk behaviors from baseline data in male and female participants and assessed differences using Wilcoxon rank-sum test or χ^2 test. Then, we estimated the overall and sex-specific (female and male) HCV incidence rates using Kaplan-Meier methods. We used Cox proportional hazards models to calculate the crude and adjusted female-to-male (F:M) hazard ratio (HR) for HCV incidence using biological sex as the main exposure, controlling for demographic and recent injection related exposures ("recent" was either the 3- or 6-month interval prior to interview, depending on cohort). The following covariates were included in analyses: age (at baseline), race/ethnicity, education (less than high school or 12 years vs more), stable housing, employment status, incarceration (any history), MAT program (ever and recent), recent injection-related risks (receptive syringe sharing, receptive ancillary equipment sharing), NSP participation, recent injection of opioids (including heroin, speedball), psychostimulant (including amphetamines and methamphetamines) and cocaine use, obtained needles from safe source (NSP and/or pharmacy), recent number of sex partners (≥2 people vs less), ever engaged in transactional sex, recent alcohol use, duration of injection, and an indicator variable for site. Recent time frame was based on responses to the data collection interval: previous 3 or 6 months, depending on cohort.

Association Between Hepatitis C Virus Incidence and Injection-Related Risk Factors

We constructed multivariable Cox regression model to estimate the adjusted F:M HR using exposures as fixed and as time-varying covariates. This model was built as a saturated model that includes all behavioral risk exposure data in common for all sites. In addition to age at baseline and race/ethnicity, other variables associated with incident HCV and potentially sex were included: incarceration (ever) and recent MAT were considered as fixed covariates; and recent injecting, receptive syringe sharing, and stable housing were considered as time-varying covariates.

Missing values were excluded from the adjusted model. The results of this multivariable model were compared with 2 other Cox regression models (model 2: saturated model [all covariates with <50% missing rate] that include all covariates in the model entering all variables to evaluate sensitivity of our reports; model 3: parsimonious model adjusting for covariates significant in bivariate analyses at *P* < .05). Survey and HCV testing data were collected at differing intervals, every 3 or 6 months (6 months: ACS, HCVC, HEPCO, HITS-c, and HITS-p; 3 months: SuperMIX and UFO) [23]. To address these differences in time frame and missing data, we conducted site-specific analyses and examined consistency between and over all sites.

Finally, we also assessed incidence rate (IR) and F:M incidence rate ratios (IRRs) stratified by subgroups (described below) and tested the heterogeneity by Mantel-Haenszel test. F:M IRRs were assessed in the following subgroups by those who reported the exposure vs those who did not: (1) recent receptive syringe exposure; (2) recent receptive ancillary equipment exposure; (3) any lifetime participation in MAT program; (4) any use of NSP services; and various factors associated with health disparities, including (4) education, (5) race/ethnicity, and (6) lifetime history of incarceration. We assessed interaction of HCV F:M HR and different behaviors and demographic characteristics using bivariate Cox proportional hazards regression. Then we did stratified Kaplan-Meier analysis to visualize possible interaction. Statistical hypotheses were tested using a 2-tailed *P* < .05 level of significance. All analyses were conducted using Stata version 13.1 (StataCorp LP, College Station, Texas).

RESULTS

Figure 1 details eligibility criteria and data selection from the overall InC3 participant pool. Overall, 1868 seronegative

Figure 1. Participant inclusion flowchart. Abbreviations: ATAHC, Australian Trial in Acute Hepatitis C; BAHSTION, Boston Acute HCV Study: Transmission, Immunity, Outcomes Network; BBAASH, Baltimore Before and After Acute Study in Hepatitis; HCV, hepatitis C virus; InC3, International Collaboration of Incident HIV and HCV in Injecting Cohorts.

PWID were enrolled in the 7 cohorts, 590 (31.58%) of whom were female. The baseline characteristics of the participants are presented in Table 1. Women were younger than men, and reported a shorter duration of injection drug use.

From the 1868 PWID, a total of 3994 PYO were collected over 8339 visits (Table 2). A total of 511 PWID were identified with incident HCV during follow-up, of whom 182 (31.5%) were female. Date of HCV infection was estimated in 106 of 511 (20.74%) based on acute seronegative viremia, 5 (0.98%) based on seroconversion illness, and 400 (78.28%) based on serial anti-HCV tests and documented anti-HCV seroconversion. HCV incidence (per 100 PYO) among women was 16.66 (95% confidence interval [CI], 14.41–19.27) and was significantly higher compared to men (11.34 [95% CI, 10.18–12.63]; $P = .001$). The crude F:M HR was 1.38 (95% CI, 1.15–1.65), corresponding to an attributable risk of 32.0% (95% CI, 18.0%–43.4%). In the adjusted model (Table 2), the F:M HR was 1.39 (95% CI, 1.12–1.72). The results are consistent with 2 other adjusted models (Supplementary Table 1). In analyses stratified by study site (Table 2), the highest HCV incidence rates among women were observed in the HCVC Study in Sydney (35.58/100 PYO) and the UFO Study in San Francisco (28.88/100 PYO). At all sites, after controlling for covariates, the F:M HR ratio was >1 except for in the ACS study (HR, 0.63), and it was not statistically significant. The highest adjusted HR ratio was observed in the HCVC Study in Sydney (HR, 2.11; $P = .014$). Figure 2A shows Kaplan-Meier time-to-event analyses of HCV incidence, stratified by sex.

In subgroup analyses (Table 3), we observed higher HCV incidence rates (per 100 PYO) in women (compared with men) who reported receptive syringe sharing (41.62 vs 24.51, respectively), and ancillary equipment sharing (36.83 vs 28.26, respectively). However, F:M IRR was not statistically different in exposed and unexposed group for receptive syringe and ancillary equipment sharing, education, incarceration, and NSP. The highest F:M IRR was observed among nonwhite women (2.15), which was significantly higher than nonwhite race/ethnicity (1.28; $P = .013$). Interaction effects between sex and alcohol, MAT, sex and education, and sex and race/ethnicity were also considered (Supplementary Table 2). Figure 2 shows Kaplan-Meier time-to-event analyses of HCV incidence, stratified by sex by MAT uptake (Figure 2B), sex by white vs nonwhite race/ethnicity (Figure 2C), and sex by low vs higher educational levels (Figure 2D). The F:M IRR was significantly higher in those who reported accessing MAT (2.18 [95% CI, 1.56–3.06]; $P = .035$) compared with those who did not access MAT (1.41 [95% CI, 1.10–1.81]) (Table 3). Women with lower education had higher risk of HCV than their male counterparts. No differences were found in F:M IRR for HCV associated with NSP participation or incarceration history.

DISCUSSION

Our findings, showing that women who inject, compared to men, have 38% higher risk of incident HCV, independent of injection-related exposures and covariates, provide important new perspective on HCV susceptibility, not previously studied in depth. This main finding is consistent with results of our recent systematic review and meta-analysis, which showed a 36% higher risk of HCV infection among female compared with male PWID [22]. The results point to the need to study additional factors not measured in these analyses including social, structural, and biological ones, that may contribute to higher HCV susceptibility in women, compared with men. Sexual dimorphism in HCV research has principally focused on differences following infection, wherein women show more favorable responses, including higher spontaneous clearance rates [14] and slower disease progression, including cirrhosis and hepatocellular carcinoma [27]. In the biological area, some researchers hypothesize that estrogen receptors and genetic variations in the estrogen receptor gene affect the pathology, infectivity, and progression of HCV infection [28, 29], and research showing slower fibrosis among women with higher estrogen levels and those on estrogen replacement therapy has supported this [30],. The effect of interferon-λ 4 genotype on spontaneous clearance of HCV has been shown to vary strongly by sex, with greater effects of CC homozygosity among women compared with men [14]. Differences in immune cell composition and activation between men and women may also contribute to observed sexual dimorphism following infection [31]; however, no studies have elucidated mechanisms for this to date. Our results showing higher HCV incidence, independent of individual injection risk behaviors, and the literature showing differences in response to infection, collectively, show a need to conduct further studies of potential biological, and genetic factors that may be associated with higher susceptibility to HCV in women.

Social and structural factors may also influence susceptibility. When examining differences in F:M incidence in stratified analyses, we found a strong differential in HCV incidence by exposure to MAT for opioids. MAT programs, including both methadone- and buprenorphine-based treatment for opioid dependence, have been shown to be associated with 40%–60% lower risk of incident HCV [13, 15, 32]. Our findings are consistent with these studies; however, we found that this protective effect was much less pronounced for women. MAT has significant potential to contribute reductions in HCV in opioid users, and increasing access to this important service is essential, especially in the United States, where opioid dependence and HCV infections are increasing [32]. Factors that may contribute to poor protective effects among women could include differences in how women compared to men reduce injection frequency while on MAT, or MAT dose and types of drugs used for women. In general, the prevalence of current illicit drug use is higher for men than women [4], and many studies report not only that higher numbers of men participate in MAT [15, 32], but also that women are less engaged and adherent to these programs than men [33, 34]. Factors contributing to these

Table 1. Baseline Characteristics of 1868 Participants by Sex

Variable	Category	Female, No. (%)	Male, No. (%)
Overall		590 (31.58)	1278 (68.42)
Age, y, median (IQR) (n = 1868)		24.37 (8.26)	26.00 (9.00)
Duration of injection, y, median (IQR) (n = 1866)		6.00 (7.00)	7.00 (8.00)
Race/ethnicity (n = 1748)	Nonwhite	138 (23.39)	268 (20.97)
	White	407 (68.98)	935 (73.16)
	Unknown[a]	45 (7.63)	75 (5.87)
Educated[b] (n = 1645)	No	267 (45.25)	550 (43.04)
	Yes	248 (42.03)	580 (45.38)
	Unknown[a]	75 (12.71)	148 (11.58)
Stable housing (n = 1136)	No	189 (32.03)	441 (34.51)
	Yes	168 (28.47)	338 (26.45)
	Unknown[a]	233 (39.49)	449 (39.05)
Unemployed (n = 1010)	No	124 (21.02)	320 (25.04)
	Yes	195 (33.05)	371 (29.03)
	Unknown[a]	271 (45.93)	587 (45.93)
Incarceration ever (n = 1779)	No	224 (37.97)	306 (23.94)
	Yes	333 (56.44)	916 (71.67)
	Unknown[a]	33 (5.59)	56 (4.38)
Medication-assisted treatment (ever) (n = 1272)	No	255 (43.22)	611 (47.81)
	Yes	132 (22.37)	274 (21.44)
	Unknown[a]	203 (34.41)	393 (30.75)
Recent injection[c] (n = 1362)	No	53 (8.98)	132 (10.33)
	Yes	364 (61.69)	813 (63.62)
	Unknown[a]	173 (29.32)	333 (26.06)
Receptive syringe sharing (n = 1233)	No	247 (41.86)	617 (48.28)
	Yes	124 (21.02)	245 (19.17)
	Unknown[a]	219 (37.12)	416 (32.55)
Receptive ancillary equipment sharing (n = 1070)	No	158 (26.78)	460 (35.99)
	Yes	165 (27.97)	287 (22.46)
	Unknown[a]	267 (45.25)	531 (41.55)
Needle and syringe programs (n = 938)	No	93 (15.76)	199 (15.57)
	Yes	204 (34.58)	442 (34.59)
	Unknown[a]	293 (49.66)	637 (49.84)
Illicit opioid use[d] (n = 781)	No	57 (9.66)	128 (10.02)
	Yes	198 (33.56)	398 (31.14)
	Unknown[a]	335 (56.78)	752 (58.84)
Medication-assisted treatment (recent) (n = 1207)	No	238 (40.34)	577 (45.15)
	Yes	127 (21.53)	265 (20.74)
	Unknown[a]	225 (38.14)	436 (34.12)
Obtained needles from safe source (n = 985)	No	31 (5.25)	64 (5.01)
	Yes	278 (47.12)	612 (47.89)
	Unknown[a]	281 (47.63)	602 (47.10)
Multiple sex partners[e] (n = 822)	0 or 1	110 (18.64)	314 (24.57)
	≥2	123 (20.85)	275 (21.52)
	Unknown[a]	357 (60.51)	689 (53.91)
Ever traded sex for goods, drug, money, housing, or favors (n = 426)	No	53 (8.98)	300 (23.47)
	Yes	34 (5.76)	39 (3.05)
	Unknown[a]	503 (85.25)	939 (73.47)
Recent alcohol use[c] (n = 1048)	No	79 (13.39)	179 (14.01)
	Yes	239 (40.51)	551 (43.11)
	Unknown[a]	272 (46.10)	548 (42.88)
Collaborating sites	Amsterdam, Netherlands (ACS)	52 (8.81)	115 (9.00)
	Sydney, Australia (HCVC)	100 (16.95)	156 (12.21)
	Montreal, Canada (HepCo)	50 (8.47)	218 (17.06)
	Sydney, Australia (HITS-c)	37 (6.27)	124 (9.70)
	Sydney, Australia (HITS-p)	172 (29.15)	322 (25.20)
	Melbourne, Australia (SuperMIX)	43 (7.29)	79 (6.18)
	San Francisco, California (UFO)	136 (23.05)	264 (20.66)

Abbreviations: ACS, Amsterdam Cohort Studies; HCVC, Hepatitis C Virus Cohort Study; HepCo, St Luc Cohort; HITS-c, Hepatitis C Incidence and Transmission Study–Community; HITS-p, Hepatitis C Incidence and Transmission Study–Prison; IQR, interquartile range; SuperMIX, Networks 2 and MIX studies; UFO, U-Find-Out Study.

[a]Data not collected by cohort or not reported by participant.

[b]Educated: completed high school and higher.

[c]Reported at the interview prior to primary hepatitis C virus infection diagnosis, recent indicates last 3–6 months prior to interview. Interview interval varies for each site: 6 months: ACS, HCVC, HEPCO, HITS-c, and HITS-p; 3 months: SuperMIX and UFO.

[d]Heroin/other opioids includes heroin. other opioids. and speedball. Pychostimulants includes amphetamines (including methamphetamines) and cocaine.

[e]Recent number of sex partners (≥2 people vs less).

Table 2. Hepatitis C Virus Incidence by Sex Overall and by Site

Participants[a]	Rate per 100 PYO (95% CI)	Crude		Adjusted Model[b]	
		HR (95% CI)	P Value	HR (95% CI)	P Value[c]
All sites (n = 1868, 1616)					
Women	16.66 (14.41–19.27)	1.38 (1.15–1.65)	**.001**	1.39 (1.12–1.72)	**.003**
Men	11.34 (10.18–12.63)				
By sites					
ACS (n = 167, 72)					
Women	3.72 (2.16–6.41)	1.25 (.64–2.44)	.516	0.63 (.045–8.76)	.729
Men	2.80 (1.89–4.14)				
HCVC (n = 256, 159)					
Women	35.58 (24.57–51.53)	1.78 (1.04–3.05)	**.036**	2.11 (1.16–3.84)	**.014**
Men	20 (13.52–29.6)				
HepCo (n = 268, 262)					
Women	14.44 (8.85–23.58)	0.93 (.54–1.60)	.794	1.15 (.57–2.31)	.697
Men	15.48 (12.31–19.47)				
HITS-c (n=161, 141)					
Women	7.59 (2.85–20.22)	1.82 (.53–6.22)	.339	1.22 (.29–5.14)	.784
Men	4.1 (1.95–8.59)				
HITS-p (n = 494, 481)					
Women	28.74 (22.45–36.79)	1.69 (1.22–2.33)	**.001**	1.12 (.76–1.64)	.571
Men	14.78 (12.1–18.05)				
SuperMIX (n = 122, 119)					
Women	7.39 (3.69–14.77)	0.63 (.28–1.43)	.271	1.13 (.44–2.89)	.798
Men	11.26 (7.34–17.27)				
UFO Study (n = 400, 382)					
Women	28.88 (21.89–38.1)	1.38 (.97–1.96)	.075	1.23 (.81–1.87)	.331
Men	20.27 (16.32–25.17)				

Crude and adjusted HR is shown for biological sex effect.

Abbreviations: ACS, Amsterdam Cohort Studies; CI, confidence interval; HCVC, Hepatitis C Virus Cohort Study (Sydney, Australia); HepCo, St Luc Cohort (Montreal, Canada); HITS-c, Hepatitis C Incidence and Transmission Study–Community; HITS-p, Hepatitis C Incidence and Transmission Study–Prison; HR, female to male hepatitis C virus hazard ratio; PYO, person-years of observation; SuperMIX, Networks 2 and MIX studies; UFO, U-Find-Out Study.

[a]Sample sizes for crude and adjusted model, respectively, are shown.

[b]Saturated model that includes all common covariates (age at the time of screening, race/ethnicity, prison [ever], recent medication-assisted treatment and considering that following variables vary over time: recent injection, stable housing, receptive syringe sharing).

[c]The values in bold were statistically significant based on a-priori P value determination of P < .05.

disparities include stigma, having children, and other social barriers [35, 36]. All of these factors should be studied further to better understand sex-related differences in risk and to maximize prevention effects of drug treatment programs and their potential to reduce acquisition of blood-borne viruses including HCV and HIV.

Differential risk for HCV among women was also found in association with race/ethnicity, education, and incarceration history. HCV disease has been shown to vary by race/ethnicity in studies of HCV natural history [27, 37] as well as incarceration history. Our recent systematic review and meta-analysis found 48% higher HCV IRR in women compared with men in correctional populations [22]. This difference has been hypothesized to be associated with age as well as with differential incarceration rates of women compared with men relative to their injecting career (women may be incarcerated later than men and thus more likely to be infected); differences in offenses for which women are incarcerated for, and differential access to drug treatment [38]. NSP programs are also important for

HCV prevention [13]; however, we found no F:M differences in association with this exposure. Higher incidence of HCV in PWID involved with NSP has been associated with "volunteer bias" due to higher proportion of those injectors whose patterns of drug use place them at elevated risk of blood-borne viral infections [39], and also with low syringe coverage, a factor that varies by geographic site in this study [40]. Research shows that combination prevention approaches, especially those that synergize NSP and MAT, will have the highest population attributable protection impacts on HCV incidence [15]. Our results show the need to further study sex differences with respect to these important social and prevention dynamics, and further elucidate prevention opportunities.

Our findings have some limitations. InC3 includes data that were retrospectively merged after study initiation and data collection, leading to differences in study measures, including frequency of collection and exposure intervals. We addressed this issue by stratifying and adjusting for covariates by each center and combining variable categories to create harmonized
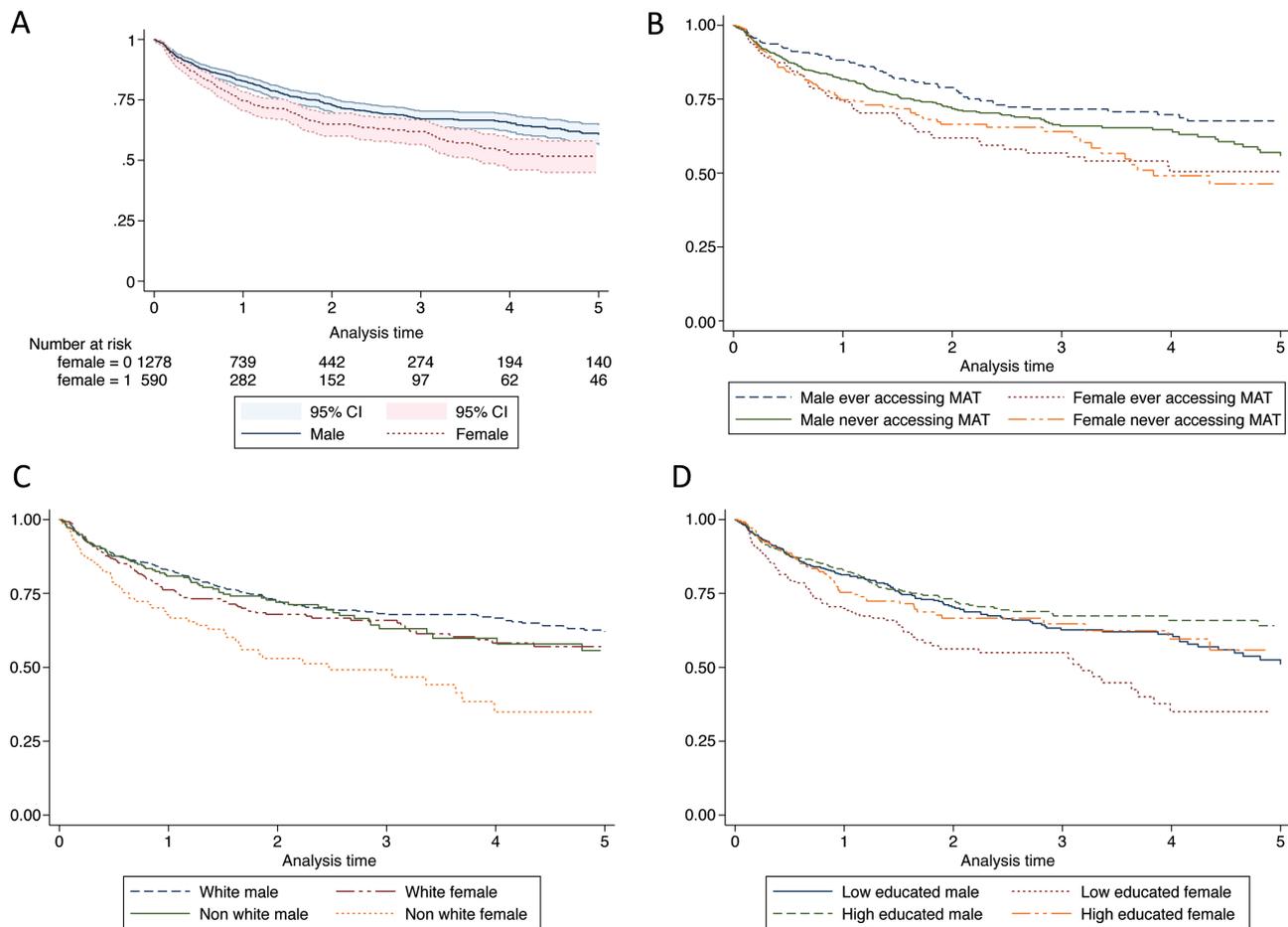
Figure 2. Kaplan-Meier time-to-event analyses of hepatitis C virus (HCV) incidence by sex (*A*), and by assessing the effect modifier of medication-assisted treatment (MAT), race/ethnicity, and education (*B–D*). Women who did and did not access MAT (*B*), nonwhite women (*C*), and low-educated women (*D*) constantly had the highest rate of HCV infection during the 5-year follow-up. Abbreviations: CI, confidence interval; MAT, medication-assisted treatment.

Table 3. Hepatitis C Virus Incidence Rate by Sex, and Incidence Rate Ratios by Different Subgroup Analyses (Selected Demographic Characteristics and Risk Exposures)

Characteristic	Exposed/ Nonexposed	Female HCV Incidence /100 PYO (95% CI)	Male HCV Incidence/100 PYO (95% CI)	F:M Incidence Rate Ratio (95% CI)	Test of Homogeneity (M-H), *P* Value
Race/ethnicity	Other	28.50 (21.99–36.95)	13.23 (10.52–16.64)	2.15 (1.50–3.09)	.013
	White	13.97 (11.68–16.72)	10.89 (9.61–12.34)	1.28 (1.02–1.60)	
Receptive syringe sharing	No	19.23 (15.85–23.32)	13.13 (11.40–15.13)	1.46 (1.14–1.87)	.479
	Yes	41.62 (32.25–53.72)	24.51 (19.76–30.39)	1.70 (1.20–2.40)	
Receptive ancillary equipment sharing	No	19.97 (15.74–25.32)	11.83 (9.92–14.14)	1.69 (1.23–2.29)	.234
	Yes	36.83 (29.09–46.63)	28.26 (23.36–34.19)	1.30 (.95–1.78)	
Completed high school and higher	No	28.97 (23.72–35.38)	16.02 (13.71–18.71)	1.81 (1.39–2.34)	.078
	Yes	17.71 (13.86–22.63)	13.93 (11.73–16.54)	1.27 (.93–1.73)	
Incarceration ever	No	16.40 (12.56–21.42)	13.84 (10.74–17.82)	1.19 (.81–1.74)	.099
	Yes	19.30 (16.10–23.14)	11.36 (10.04–12.86)	1.70 (1.35–2.12)	
Medication-assisted treatment (ever)	No	20.64 (16.84–25.29)	14.59 (12.74–16.72)	1.41 (1.10–1.81)	.035
	Yes	16.51 (13.14–20.73)	7.56 (6.02–9.49)	2.18 (1.56–3.06)	
Needle and syringe programs	No	17.55 (13.15–23.43)	9.31 (7.42–11.68)	1.89 (1.28–2.76)	.167
	Yes	31.39 (26.02–37.88)	22.66 (19.58–26.23)	1.39 (1.08–1.77)	

Abbreviations: CI, confidence interval; F:M, female to male; HCV, hepatitis C virus; M-H, Mantel-Haenszel; PYO, person-years of observation.

variables. Not all studies collected the same data, and missingness emerges as a limitation. Subgroup analyses by relevant exposures and categories were conducted to present as much data as possible. Our analyses controlled for several demographic and risk exposures known to be associated with HCV risk, but there remains potential for unmeasured confounding, which could contribute to a higher F:M incidence ratio. For instance, factors difficult to measure and which could contribute to sex differences potentially include differential access to prevention services, gender-power dynamics, mental health factors, or social and injecting network mixing that introduce differential risk exposure.

Our findings provide important evidence that sex disparities in HCV acquisition exist independent of selected behavioral risk and demographic factors. Although several studies of PWID have shown that women report higher injection-associated risk behaviors, including receptive syringe and ancillary injecting equipment sharing, these exposures did not explain the higher incidence of HCV observed in women in these aggregated data. When considering HCV risk differential among women, multiple factors including biological, social, and network factors, as well as differential access to prevention services, need to be considered. We believe that these results and others strongly point to the need for more research and interventions designed specifically to assess and reduce HCV risk among women.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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