

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Higher risk of incident hepatitis C virus among young females who inject drugs compared to young males in association with sexual relationships: a prospective analysis from the UFO Study Cohort
AUTHORS	Tracy, Daniel; Page, Kimberly; Hahn, Judith; Fuller Lewis, Crystal; Evans, Jennifer; Briceno, Alya; Morris, Meghan; Lum, Paula

VERSION 1 - REVIEW

REVIEWER	Basmattee Boodram University of Illinois at Chicago United States
REVIEW RETURNED	26-Mar-2014

GENERAL COMMENTS	<p>The authors presented important and under-reported data on female injection drug users, who may indeed report differences in injection behaviors that put them at greater risk for HCV incidence. The data for these analyses come from the well-characterized UFO Study, an ongoing prospective study of incident and acute HCV infection and its early natural history conducted in San Francisco, California.</p> <p>The article is well-written and the analyses are sound. A few suggested revisions as follows:</p> <ol style="list-style-type: none">1) Tables require some clearer definitions for the variables, perhaps as footnotes. E.g. Borrowing vs. Pooling partners.... Especially for those who may be familiar with the IDU jargon. Table 2 has a typo "poole".2) Table 3: Since there is no significant p for interaction with sex, suggest delete this column and summarizing in a footnote.3) The use of the term "mediators" is not advised since mediation analyses were not performed. This is in regard to the following: "We examined risk behaviors and other factors as mediators of the association between sex and HCV incidence, and found that in many cases the effect size and the statistical significance of the sex/HCV associations were diminished..."
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REVIEWER	Holly Hagan New York University USA
REVIEW RETURNED	28-Mar-2014

GENERAL COMMENTS	This paper has a lot of strengths, including that, for the most part, it is clearly written and the data are from a well-defined cohort of
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	<p>young injectors with excellent followup. In addition, the measures are excellent.</p> <p>Concerns relate to the fact that objective # 3 in the introduction, "[addressing whether there are] risk factors associated with HCV infection that differ between males and females" would seem to be best addressed by separate multivariate analyses for males and females (with appropriate adjustment for age and other confounders). In addition, there is a need to say something about HIV in the cohort, especially as it may affect the risk of sexual HCV transmission.</p> <p>Moreover, the results section needs a bit more synthesis. As written, it is too "listy" - just naming all the associations and their CIs from the tables. Perhaps grouping them in terms of exposure type would make it more interesting to read.</p> <p>Finally you may want to note that HCV incidence in another cohort of young PWID (the CIDUS-DUIT study) was almost identical - 19.1/100PY - but this is just a suggestion.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1: We are pleased that this reviewer found the paper well written and with potential to contribute to the literature on differences in risk for HCV in male and female injection drug users. Suggested revisions included:

1) Tables require some clearer definitions for the variables, perhaps as footnotes. E.g. Borrowing vs. Pooling partners.... Especially for those who may be familiar with the IDU jargon. Table 2 has a typo "poole".

We've added additional text, both in the methods section (page 9) of the document and in the tables, to clarify variable definitions. The typo in Table 2 has been corrected.

2) Table 3: Since there is no significant p for interaction with sex, suggest delete this column and summarizing in a footnote.

We agree with this suggestion and have removed the column from the table and added a footnote.

3) The use of the term "mediators" is not advised since mediation analyses were not performed. This is in regard to the following: "We examined risk behaviors and other factors as mediators of the association between sex and HCV incidence, and found that in many cases the effect size and the statistical significance of the sex/HCV associations were diminished...".

We acknowledge that the specified aspect of our analysis does not meet the definition of mediation analysis and have revised pertinent sections of the text (See Abstract, and Methods: page 10) to address this oversight. Our intention was to illustrate that the inclusion of direct exposure variables significantly associated both with female sex and with incident HCV infection reduces the strength and significance of female sex as an independent predictor of HCV, to which we conclude that female sex serves as a proxy for high-risk behavior when modeled as a stand-alone predictor of new HCV infection.

Reviewer: 2: We thank the reviewer for noting the strengths of the study including methods and follow up. We address the concerns below, which we believe have helped the paper.

1. Concerns relate to the fact that objective # 3 in the introduction, "[addressing whether there are] risk factors associated with HCV infection that differ between males and females" would seem to be

best addressed by separate multivariate analyses for males and females (with appropriate adjustment for age and other confounders).

Out of concern that multicollinearity between related predictor variables, especially equipment sharing variables, would affect risk estimates when modeled in aggregate, we elected to limit our analysis to bivariable models (see Hagan et al, JID 2010). We agree, however, that objective #3 (as initially stated) calls for a multivariable modeling approach. As the results of our analyses cover objectives 1 and 2 of the paper, we omitted objective 3 so as to not confound the conclusions.

2. There is a need to say something about HIV in the cohort, especially as it may affect the risk of sexual HCV transmission

We add information regarding baseline HIV prevalence to the results (page 11, 12, and Table 1). As prevalence was low in the cohort overall we chose not to examine associations between baseline HIV status and HCV incidence.

3. Moreover, the results section needs a bit more synthesis. As written, it is too "listy" - just naming all the associations and their CIs from the tables. Perhaps grouping them in terms of exposure type would make it more interesting to read.

The discussion section was revisited with this important comment in mind and edited significantly with special attention to not repeat Results sections. IN particular edits are made to the first few sections regarding differences between females and males.

4. Finally you may want to note that HCV incidence in another cohort of young PWID (the CIDUS-DUIT study) was almost identical - 19.1/100PY - but this is just a suggestion.

Excellent suggestion; we have included this citation in the Discussion (page 14).