Author’s response to reviews

Title: New types of drug use and risks of drug use among men who have sex with men: A cross-sectional study in Hangzhou, China

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Author’s response to reviews:

Dear Editor:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “New types of drug use and risks of drug use among men who have sex with men: A cross-sectional study in Hangzhou, China”. (INFD-D-17-01714).

We have studied reviewer’s comments carefully and have made revision which marked in red in the paper. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,
Lin He

Corresponding author:

Xiaohong Pan

List of Responses

Reviewer #1:

Abstract

1. Authors need to define "MSM" before using the acronym.

Reply:

We have defined men who have sex with men before using the acronym “MSM”

2. Authors need to provide some examples of the new drugs upfront being researched in the paper.

Reply:

We have provided some examples of new drugs such as methamphetamine, ketamine, ecstasy, and rush poppers.

3. The 2nd part of the Methods reads a bit awkward—I think it should be if previous HIV tests were negative or unknown then they need to have an HIV test upon study entry to confirm their serostatus. Besides, the Methods should be expanded with more details.

Reply:

MSM were included if subjects’ previous HIV test results were negative or unknown, or untested HIV. All the HIV positive MSM we have examined from the national epidemiologic database of Hangzhou, which tracks everyone who is diagnosed with HIV in China. We found no one positive have diagnosed before the survey. So we can confirm their serostatus.

The methods we have expanded with more details.

4. The 2nd sentence of Findings has grammatical error.
Reply:

We used Editage [www.editage.cn] for English language editing again, the manuscript need some language adjustments.

5. The 2nd sentence of Conclusion has grammatical error.

Reply:

We used Editage [www.editage.cn] for English language editing again, the manuscript need some language adjustments.

Background

1. Authors need to fix reference #2

Reply:

We have fixed reference #2.

2. Authors fail to provide references for several statements in the Background. Line 55 (several studies, but just list one reference); Line 63 (Previous studies, but no reference); Line 65 (independent risk factors of HIV, no reference), line 67 (the LA study; no reference),

Reply:

The references we have only add the main references, considering the Reviewer’s suggestion, we have added the reference in Line 55. Line 63 (Previous studies was the reference #6, we have put it at the end of the section, now we arrange the reference). The line 65 and 67, we have add the reference.

3. The 2nd paragraph starting from line 63, seems to recklessly itemize previous studies of some drugs among global MSM to prove these drugs are risk factors of HIV and UAI. However, much information described here are not well organized; some are also redundant. Perhaps authors need to re-arrange global evidence, make them informative yet concise.

Considering the Reviewer’s suggestion, we have rearranged the 2nd section (e.g. Background section, line 63-85, page 3)

4. Please consolidate evidence from Line 84-94 and provide a brief evidence-based reason why this may occurred at a high prevalence among Chinese MSM.
We have added the brief evidence-based reason why this may occurred at a high prevalence among Chinese MSM: the use of new types of drugs increased the frequency of unprotected sexual behaviors, and high-risk sexual behaviors might increase the risk of HIV infection.

5 The last paragraph - It seems recreational drug use research among Chinese MSM has been studied in many ways. The only "lack of such studies among Hangzhou MSM" may not be sufficient enough to justify the significance of the current study. Perhaps authors need to more clearly define the rationale and identify gaps that leads to the current study. Please also list the objectives of the study. It is also not clearly this current study aims to research this among HIV-positive or HIV-negative MSM.

Reply:

The number of newly diagnosed HIV infections is rapidly increasing on a yearly basis. Approximately 60% of HIV infections occurred in MSM in 2014. The HIV prevalence among MSM was 8.5% since 2008, during this same time period, the national HIV prevalence was 4.9% from 2008-2009. The HIV epidemic in the Hangzhou forecasts a future trend for China. Our study found the high proportions used ketamine, methamphetamine in Hangzhou. In addition, we think the patterns of drugs among Hangzhou was different from other regions such as Shenzhen and Shenyang.

We have listed the objective of study in the methods section, and the research among HIV negative study, MSM were excluded from the study if they were HIV infected before the survey.

Methods

1. Sampling methods: (1) it looks like it was just a multiple convenience sampling. If it is literally a snowball sampling, please describe more details. (2) What are the inclusion criteria? (3) Sentence is too long with grammatical errors, Line 117-120. (4) Sample size formula and rationale need to be explained in more details.

Reply:

(1) We have describe the snowball sampling: The initial participants were asked to recruit partners or peers to participate in the survey. After the participants completed the study questionnaires and underwent HIV testing, they were provided with recruitment coupons to incentivize other participants. Using these incentives, the participants then recruited MSM peers from their social network to participate in the survey.

(2) The inclusion criteria were put the 2and in methods.
(3) We have arranged the sentence and used Editage [www.editage.cn] for English language editing again, the manuscript needs some language adjustments.

(4) The sample size based on the use of new types of drugs ranged from 5% to 25%. \( P \)-values \( \leq 0.05 \) and \( \beta=0.1 \) were considered statistically significant. Thus, it was estimated that the minimum sample size required for this study would be 400 people. The sample size was calculated using WINPEPI (PEPI-for-windows) version 9.5 software.

2. Did participants need to be local residents or live in the city for a certain length of time?

Reply:

NO, all the participants did not need local residents or live time in Hangzhou before the survey. MSM were at least 16 years old; had anal sex with men in the last 3 months before the study; had previous HIV test results that were negative or unknown;

3. Authors need to clearly and specifically define and list the "new types of drugs" being researched in this study. The measurement of outcome and exposure variables need to be clearly defined as well.

Reply:

We have added the definition and list the "new types of drugs" including methamphetamine, ketamine, ecstasy, and rush poppers (in the section of Questionnaire and data collection).

The measurement of outcome and exposure variables have been put in the statistical analysis section: the primary outcomes of interest were the new types of drugs used in past 3 months, HIV infection, and MSM who were HIV infected and used new types of drugs in the past 3 months.

4. Fisher's exact test should be used for those with sparse cell (n<5). Authors need to check table 1 distribution and then use the correct statistical test.

Reply:

Considering the Reviewer’s suggestion, we have corrected table 1 use the Fisher’s exact test.

5. Statistical analysis: Authors do not explain the modeling building strategy. Was there any backward selection procedure to retain the minimal sufficient set of covariates? Were collinearity assessed? Any effect modification pre-defined and assessed?

Reply:
We performed series of regression models to test the mediation effect of the new types of drugs used in past 3 months, HIV infection, and MSM who were HIV infected and used new types of drugs in the past 3 months. The new types of drugs used in past 3 months as mediators, HIV infection served as an independent variable. For the mediation effect of new types of drugs used in past 3 months, we regressed new types of drugs used in past 3 months on HIV, then regressed on multiple partnerships, respectively. Similarly, we tested the mediation effect HIV infection, and MSM who were HIV infected and used new types of drugs in the past 3 months.

6. It is not clear the authors are building a predictive or explanatory model. If an explanatory model was attempted, then the "table 2 fallacy" was committed in such a multivariable modeling strategy. Please justify.

Reply:

Table 2 was differences in the general behaviors characteristics were calculated using the Student’s t-tests or chi-squared ($\chi^2$) or fisher's exact and Kruskal-Wallis tests. Factors from univariate analysis with P-values <0.10 and/or those previously shown to be associated with the differences in social demographic characteristics were included in the multivariate regression models.

Results

1. One of the primary weaknesses of the current study was lumping all types of new drugs into one category. This may increase analytical sample size, but scientifically, it masks important information. Rush Poppers deserves special attention. This should be discussed in the limitation.

Reply:

Thank you for the reviewer, we have add in the limitation.

2. Authors need to describe total sample size in the title of each table (1-5)

reply:

We added the total sample size in the title of each table.

3. What does it mean by "high-risk behaviors in the past 3 months"? How was it defined?

Reply:

High-risk sexual behavior mean that MSM have sexual behavior without condom use. MSM had sexual behavior with condom use or had not sexual defined as no high-risk behavior.
4. It is uncertain how authors choose covariates to be evaluated for table 4 and 5. Is there any supplemental table to show the significance from any univariate analysis?

Reply:

All the variables we have done the univariate analysis, due to the total table less than 5, so we only list the section of multivariate regression models. We could provide the original supplemental table for univariate analysis.

5. Table 5 is of concern because of "overfitting" issue. The N for "case" (HIV+ and drug user) might be too small.

Reply:

Thank you for the reviewer, the sampling size in table 5 only 101 new type drugs user, and the analysis actual might too small.

Discussion

The Discussion section need to be significantly improved by discussing linkage between findings from the current study, evidence from other Chinese studies as well as international studies.

Reply:

We have adjustment the discussion section.

In addition, the entire manuscript needs to heavily proofread and enhanced in terms of language and scientific writing.

Reply:

Thank you for the reviewer, we have do the manuscript adjustment and used Editage [www.editage.cn] for English language editing again, the manuscript need some language adjustments.

Reviewer# 2

Abstract:

1, "Little is known about the patterns of drugs use among MSM." This is not true. I have at least review three papers on this in the last year, including one study from Shenzhen, one study from Peizhen Zhao et al.
Considering the Reviewer’s suggestion, we have reviewed the study in Shenzhen, Peizhen Zhao et al. Our study conducted from 2015 to 2016, the papers was completed in June 2017, and the study in Shenzhen et al had not publish online. Our study found the high proportions used ketamine, methamphetamine in Hangzhou. In addition, we think the patterns of drugs among Hangzhou was different from other regions such as Shenzhen and Shenyang. Thirdly, the use of new types of drugs increased the risk of unprotected behaviors and the risk of HIV infection. However, there is a lack of data on the use of new types of drugs in Hangzhou among HIV infected MSM. Although the use of new types of drugs is increasingly popular among MSM, little is known about the patterns of drug use.

2, for respective purpose, please change "subjects" to "participants";

Reply:
We have changed "subjects" to "participants"

3, "Programs should provide support to high risk MSM and provide interventions to mitigate the risk of HIV acquisition" this is too board, please be specify.

Reply:
We have specify the sentence: the use of new types of drugs increased the frequency of unprotected sexual activities among MSM; high-risk sexual behaviors might increase the risk of HIV infection. We suggest that attention should be given to the use of new types of drugs in MSM, and supervision programs should be strengthened to combat the use of new types of drugs.

1) The manuscript need some language adjustments.

Reply:
We used Editage [www.editage.cn] for English language editing again, the manuscript need some language adjustments.

Background:

1, for the last sentence of P1 (line 49-51), refer to whom? MSM or general population. I believe it is among MSM. Be specify.

Reply:
The last sentence means that among drug users the proportions of new type increased from 28% in 2010 to 49.4% in 2014, exceeding the traditional prevalence of heroin use.

2, Short P2 (line 53-76)

Reply:

Considering the Reviewer’s suggestion, we have shorted the 2nd section (e.g. Background section, line 63-85, page 3)

3, the first sentence of P3 is awkward, please revise.

Reply:

We have arranged the sentence.

4, Line 96-106, Are Hangzhou MSM different from other MSM in China? If not, what's the rational for this study. Few studies (From Xu Junjie, Zhao Jin and Zhao Peizhen) have reported very similar results as this study, but few of them were did not mentioned in this manuscript, the literature review of this manuscript is not enough. Please cite this paper and tell the readers what's new for this paper.

Reply:

The number of newly diagnosed HIV infections is rapidly increasing on a yearly basis. Approximately 60% of HIV infections occurred in MSM in 2014. The HIV prevalence among MSM was 8.5% since 2008, during this same time period, the national HIV prevalence was 4.9% from 2008-2009. The HIV epidemic in the Hangzhou forecasts a future trend for China. Our study found the high proportions used ketamine, methamphetamine in Hangzhou. In addition, we think the patterns of drugs among Hangzhou was different from other regions such as Shenzhen and Shenyang.

Reference#19 20 from Xu Junjie and reference#22 from Zhang H. We added reference from Zhao Jin #21.

Methods:

1, the sample size calculation was based on which assumptions? If 400 people are enough, why 555 people were recruited?

Reply:
The sample size based on the use of new types of drugs ranged from 5% to 25%. P-values ≤ 0.05 and β = 0.1 were considered statistically significant. Thus, it was estimated that the minimum sample size required for this study would be 400 people. The sample size was calculated using WINPEPI (PEPI-for-windows) version 9.5 software. At the end of survey, 555 participants were recruited.

2. "had anal sex with men in the last 3 127 months before the study" would exclude a large number of MSM, why this was chosen?

Reply:

The recruited participants need had anal sex with men in the last 3 months, firstly, to identify the real MSM, in additional, we chose the 3 months want to choose high sexual behavior MSM.

3. Why use " had previous HIV test results that were negative or unknown", HIV positive MSM would be another key group for the study.

Reply:

The papers focus on HIV negative MSM. HIV positive MSM were record in the national epidemiologic database of Hangzhou, which tracks everyone who is diagnosed with HIV in China.

4. for the measures, be specific, which categories were collected for each variable?

Reply:

The questions about socio-demographic characteristics age, marital status, education, income, sexual orientation, registered residence and living time in Hangzhou, sexual behavior, sexual partner networks in the past 3 months, history of the new types of drugs used, and history of counseling, alcohol use HIV testing, ever see friends using new types of drug and ever known new types of drug. (Questionnaire and data collection section, and table 1-2)

5. Sine you excluded people with known HIV-positive status, what's the purpose to know "HIV infection, and MSM 167 who were HIV infected and used new types of drugs in the past 3 months"?

Reply:

We want to know the proportion of new type drugs among HIV negative MSM, and prevalence of the HIV, to identify the use of new types of drugs whether increased the risk of unprotected behaviors and the risk of HIV infection in negative population.
Results and conclusion:

1, 14.8% people were HIV positive, and the sampling is skewed to HIV negative and unknow people. The author need to discuss this further

Reply:

Thank you for the reviewer, we have add in the discussion: 14.8% participants were HIV positive and before the survey all the persons HIV negative or unknown. The reason might be that we choose the participants had sexual behavior in the last 3 months had high activities sexual behavior. In additional, our study confirmed that the use of new types of drugs increased the frequency of unprotected sexual activities among MSM; risky sexual behaviors might increase the risk of HIV infection.

2, what's the implication for the results discussed in P2 and P3 of the discussion part? The discussion in P2 is so boring, what's new messages does this finding bring to the existing literature?

Reply:

We have adjustment the P2 and P3, and shorted the discussion

3, P3 of the discussion is based on which finding? Should be combined with P4.

Reply:

We shorted the discussion, and P3 was based the finding P2 and P4, we combined with P4.

4, for P4 (line 288-291), please delete this sentence "Because higher educational levels were associated with 289 the use of new types of drugs, we assumed that educated MSM could have been more 290 familiar with the internet; and therefore, they may have had easier access to rush 291 poppers"

Reply:

We have delete the sentence.

5, what's the main discussion point for P4?

We have add the main discussion point for P4 combined with P3.

6, compare P5 to SZ data, as well as the national data;
Reply:

We have compare P5 to Shenzhen data.

7, the authors have so many discussion points. Which are the three main findings/discussion points for this study? Pick out these three, and delete or combine other unimportant ones.

Reply:

We have picked out three main findings, and delete or combine the unimportant.

8, please rewrite the conclusion part, not just merely repeat all the results.

Reply:

We rewrite the conclusion part.