

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does psychedelic drug use reduce risk of suicidality? Evidence from a longitudinal community-based cohort of marginalized women in a Canadian setting
AUTHORS	Argento, Elena; Strathdee, Steffanie; Tupper, Kenneth; Braschel, Melissa; Wood, Evan; Shannon, Kate.

VERSION 1 - REVIEW

REVIEWER	Peter Hendricks University of Alabama at Birmingham USA
REVIEW RETURNED	21-Feb-2017

GENERAL COMMENTS	<p>This intriguing manuscript presents provocative findings suggesting naturalistic psychedelic use may protect against suicidality among sex workers in Canada. The topic is timely, addresses an important public health issue, and is likely to advance the field and encourage further scientific inquiry. For these reasons, I am very positively inclined toward this well-written paper. Of course all studies are subject to scrutiny, but given the heightened political lens surrounding psychedelic compounds, it is likely that the current study could be subject to greater scrutiny than average. I therefore offer the following suggestions assuming the perspective of a skeptical/critical reader. My hope is that the following comments will allow the authors to pre-empt any potential criticisms of their important work.</p> <p>1) In the Introduction and Methods: whether MDMA, salvia divinorum, and other substances such as DXM, PCP, ketamine, and ibogaine qualify as psychedelics is somewhat debatable. I am not uncomfortable classifying these substances as psychedelics broadly speaking because they do appear to share some common underpinnings, but it's important to note that the most commonly used psychedelics (DMT/ayahuasca, LSD, psilocybin, mescaline/peyote) are primarily 5-HT_{2A} agonists and are frequently labeled "classic psychedelics" whereas the others have different primary mechanisms of action. MDMA has been labeled an "entactogen" or "empathogen" and salvia divinorum is a kappa-opioid agonist, for instance. I therefore suggest the authors use the term "hallucinogens" throughout, or limit analyses to DMT/ayahuasca, LSD, psilocybin, and mescaline/peyote and use the term "classic psychedelics" throughout. Note that references 27-29 limited analyses to classic psychedelics specifically, whereas references 25-26 evaluated hallucinogens more broadly.</p>
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	<p>2) Related to #1 above, it would be helpful to report the frequency with which participants report lifetime use of each specific hallucinogen or classic psychedelic. It could potentially be interesting if, for instance, dissociative anesthetics such as ketamine are used with some frequency by sex workers, insofar that this could suggest a particular coping strategy for this population (dissociation).</p> <p>3) Considering that psilocybin is being evaluated in a number of trials and is a leading candidate for approval by the US FDA and other regulatory bodies, it could be helpful if supplementary analyses evaluated the specific effect of psilocybin per se. See Hendricks, Johnson, & Griffiths: http://journals.sagepub.com/doi/abs/10.1177/0269881115598338.</p> <p>4) Minor issue: last paragraph of the Introduction, "...drug use may be protective with regard to suicidality [27-29]..." The Krebs & Johansen studies, as I recall, found no associations between classic psychedelic use and a range of mental health outcomes. I don't think they found protective effects, but I could be wrong--the authors may want to confirm and modify the citations accordingly.</p> <p>5) It might help if the authors explain why analyses were restricted to participants who were previously not suicidal. I realize the outcome of interest was first suicidal episode, but why is this the case? Is there some rationale for focusing on first suicidal episode?</p> <p>6) Minor issue: early in the Methods the authors suggest that the study comprised "over 800" participants, though in the Results N = 766 and then 209 is reported. It could be helpful to be a bit more clear and/or consistent throughout.</p> <p>7) Why were suicidal thoughts and attempts collapsed into one variable? I think the authors need to provide a rationale for this approach, especially considering that some might conceptualize the two outcomes as somewhat distinct (e.g., suicidal thoughts are more common than suicidal attempts, and predictors of suicidal thoughts may differ from predictors of suicidal attempts). Note that I don't find this especially problematic, but the hypothetical skeptical/critical reader might!</p> <p>8) Why did the authors evaluate only ever use of substances as predictors (vs. current use, frequency of use, recency of use, etc?). In the studies making use of the National Survey on Drug Use and Health (NSDUH) data (e.g., references 27-29), ever use of classic psychedelics was the primary independent variable of interest because the NSDUH only inquires about ever use. In other words, the authors of references 27-29 were making do with the available data. However, a more refined analysis might evaluate more nuanced indicators of classic psychedelic use. For instance, perhaps more frequent use is more protective? Perhaps more recent use is more protective? And so on.</p> <p>9) Table 2 could use a note, at a minimum to explain why not all Adjusted HRs and p-values are reported (what do the dashes mean?). Ideally, the tables could stand alone with minimal reference to the text needed to understand them.</p> <p>10) I was surprised that the authors found a protective effect of given the relatively small N, infrequent outcome (n = 31), and use of multivariate analyses. Perhaps this simply suggests that the effect</p>
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	<p>size is large--a 60% reduced likelihood of suicidality certainly seems large to me--and if this is the case I encourage the authors to specifically discuss the size of the effect. Of course, I defer to the study statistician to ensure all assumptions were met, the N was sufficient for the analyses, no biases were at play (e.g., overadjustment bias), etc.</p> <p>11) The authors write that "variables hypothesized a priori to be predictors of suicidality and those that were significantly correlated with the outcome at the $p < 0.05$ level in bivariate analyses were subsequently fitted into a multivariable Cox model." This does not appear to be true of psychedelic use, since $p = .99$ in bivariate analyses, unless I'm misunderstanding something. I suggest clarifying the analytic plan.</p> <p>12) In the Discussion, note that reference 27 was not longitudinal. It combined data from multiple years of an annual cross-sectional survey. This means that the authors study is the first to show a longitudinal relationship between lifetime psychedelic use and suicidality--this is good!</p> <p>13) I think it's important to acknowledge that the authors could not control for all sources of potential confounding. It could be that those who use psychedelics possess some characteristic(s) that also makes them less likely to be suicidal (e.g., openness to experience, curiosity, spirituality). None of the covariates appear to control for these sort of "positive psychology" variables.</p> <p>14) Minor issue: in the Discussion, "...correlations found between psilocybin sessions and elevated ratings of personal meaningfulness..." This wording is a little confusing--how could sessions be correlated with anything at all? I think the authors mean to say that in-session mystical experience is correlated with these outcomes.</p> <p>15) My last comment is speculative, but could it be that those who report psychedelic use are less likely to be suicidal because they are less likely to exchange sex for money in the future? I wonder if, as a secondary analysis, the authors might see if use is associated with a decreased likelihood of exchanging sex for money within the past 30 days at follow-up.</p>
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REVIEWER	Louise Brådvik Lund University, Department of Clinical Sciences, Lund, Psychiatry, Sweden
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	<p>This study deals with an important topic, namely suicidality among a stigmatized group, female sex workers.</p> <p>However, there are several shortcomings of the paper, which must be addressed before the paper could be considered for publication. Most of all, limitations should be more clearly addressed. A more thorough comparison with relevant literature is needed.</p> <p>Though new treatments are urgently needed in order to reduce suicidality, it should not be neglected that there are evidence that more traditional psychopharmacological treatment and psychosocial intervention may reduce the risk of suicidal behaviour. There has been evidence that among psychedelics, especially psilocybin in</p>
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	<p>therapeutic doses reduces depression and also suicidality (some of these studies are referred to in the paper). Those doses are low to reduce the risk of negative side effects (several have been reported and even occasional suicidal ideation*). In the present paper the women's use of illegal psychedelic is studied, which probably means higher doses than usually prescribed. This fact ought to be discussed.</p> <p>Type of psychedelics are mentioned, but not number of each type used. How many used psilocybin, which is probably the most efficient one. Representativeness of the sample and attrition should be stated and discussed. The study is not randomized and possible confounders should be discussed.</p> <p>Finally, the risk of serious side effects in higher doses should not be neglected.</p> <p>More specifically: Abstract: conclusion goes beyond what is found in the study. First sentence is a background statement, not a conclusion.</p> <p>Strengths and limitation: There are four strengths and one limitation reported. This appears scewed. I suggest more limitations to be mentioned.</p> <p>Introduction: first §: the problem of suicide in general is presented. What about the risk among women sex workers? It is reported among women sex workers who had experienced violence and childhood abuse. Other? Is sex work as such a risk regardless of violence etc? Completed suicide or non-fatal suicide behaviour? P 4 last § states 'in the wake largely ineffective interventions'? There is good evidence that some interventions, such as psychotherapy and psychotropics do reduce suicidal behaviour, which should not be overlooked. After that it is correct to state that there is a need for innovative treatments.</p> <p>Methods: Data are drawn from a large... cohort... How are they drawn, random order, invited? What about attrition?</p> <p>Statistical analyses: First § concerns selection of participants rather than statistics. This § should be included in the Method section instead.</p> <p>Results: The number of completers ought to be mentioned under participants in the Method section. Proportion of suicidality, on the other hand, is a result. Missing observations, too, belongs to the Method. Subheadings would make the text more comprehensive. First sociodemographic and then substance use.</p> <p>Discussion: Needs more focus. Limitations and strengths should be discussed in a separate §. What are the limitations? The sample is rather small for instance. This should be elaborated. Third § p 10 is of limited relevance for the present findings, rather a background which states the problem. Reduced suicidality has been shown for therapeutic use of psychedelics, especially psilocybin. Are previous findings to be expected to be generalized to the present sample of women sex workers, who may use higher than therapeutic doses? In therapeutic</p>
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	<p>settings the doses are small, but what about the doses used among the study participants? Possible side effects? The possibility that those who had escaped side effects are more able to participate? If suicidality could be a side effect, the exclusion of those who had experienced suicidal ideation may be a confounder.</p> <p>Conclusion: 'This study supports call for further research..' is irrelevant, other possible drugs, psychosocial intervention could also be further explored. The present study does not first of all give evidence of the problem, which has been known before. In fact, the knowledge of the problem gave the authors a reason to start the research. However, the last part of the sentence 'further investigations ... psychedelic drugs ..' is a relevant statement. There are many important limitations in the present study, and therefore more research is needed before psychedelic drugs should be recommended. The present study may however, encourage more research on the topic.</p> <p>* Peden NR, Pringle SD, Crooks J. The problem of psilocybin mushroom abuse. Hum Toxicol. 1982 Oct;1(4):417-24.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

This intriguing manuscript presents provocative findings suggesting naturalistic psychedelic use may protect against suicidality among sex workers in Canada. The topic is timely, addresses an important public health issue, and is likely to advance the field and encourage further scientific inquiry. For these reasons, I am very positively inclined toward this well-written paper. Of course all studies are subject to scrutiny, but given the heightened political lens surrounding psychedelic compounds, it is likely that the current study could be subject to greater scrutiny than average. I therefore offer the following suggestions assuming the perspective of a skeptical/critical reader. My hope is that the following comments will allow the authors to pre-empt any potential criticisms of their important work.

Thank you for your comprehensive review of the manuscript and we believe that the revisions as outlined below have strengthened our manuscript considerably.

1) In the Introduction and Methods: whether MDMA, salvia divinorum, and other substances such as DXM, PCP, ketamine, and ibogaine qualify as psychedelics is somewhat debatable. I am not uncomfortable classifying these substances as psychedelics broadly speaking because they do appear to share some common underpinnings, but it's important to note that the most commonly used psychedelics (DMT/ayahuasca, LSD, psilocybin, mescaline/peyote) are primarily 5-HT2A agonists and are frequently labeled "classic psychedelics" whereas the others have different primary mechanisms of action. MDMA has been labeled an "entactogen" or "empathogen" and salvia divinorum is a kappa-opioid agonist, for instance. I therefore suggest the authors use the term "hallucinogens" throughout, or limit analyses to DMT/ayahuasca, LSD, psilocybin, and mescaline/peyote and use the term "classic psychedelics" throughout. Note that references 27-29 limited analyses to classic psychedelics specifically, whereas references 25-26 evaluated hallucinogens more broadly.

We appreciate this comment and your suggestion to clarify our terminology regarding the classification of psychedelics (vs. hallucinogens). As per your suggestion in query #2 below, we have reported the specific substances (and frequency of use) included in our analyses, which are LSD, psilocybin and MDMA. Given that these three substances might be more accurately labelled as psychedelics rather than hallucinogens, as MDMA is more of a psychedelic/empathogen than a classic hallucinogen, we have decided to keep the term “psychedelic” with the addition of the following text in the introduction to clarify:

“Psychedelic drugs include the classic serotonergic psychedelics or “hallucinogens” lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), and mescaline, as well as the “enactogen” or “empathogen” methylenedioxymethamphetamine (MDMA) [23–25], all of which are being investigated in clinical/pre-clinical studies for their neuropharmacological functions and potential as adjuncts to psychotherapy [26–28].”

We have also revised the references here to include the following:

Nichols DE. Hallucinogens. *Pharmacol Ther* 2004;101:131–81.

Bedi G, Hyman D, De Wit H. Is ecstasy an ‘empathogen’? Effects of 3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. *Biol Psychiatry* 2010;68:1134–40.

Oehen P, Schnyder U. A randomized, controlled pilot study of MDMA (± 3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *J Psychopharmacol* 2013;27:40–52

2) Related to #1 above, it would be helpful to report the frequency with which participants report lifetime use of each specific hallucinogen or classic psychedelic. It could potentially be interesting if, for instance, dissociative anesthetics such as ketamine are used with some frequency by sex workers, insofar that this could suggest a particular coping strategy for this population (dissociation).

Thank you for this comment and suggestion to report the frequencies for each specific psychedelic drug. We have added text under the results section as follows:

“Overall, 27% (n=79) of participants reported ever using a psychedelic substance, and of those, 75% (n=59) had used MDMA/ecstasy, 35% (n=28) had used LSD/acid, and 30% (n=24) had used psilocybin/magic mushrooms.”

Given that ketamine is a dissociative anesthetic, and its different mechanism of action from some of the other psychedelics, we decided to exclude it from the analyses. Interestingly, the association between psychedelic use and reduced risk of suicidality became stronger when ketamine was excluded. Future analyses with ketamine would certainly be interesting to investigate.

3) Considering that psilocybin is being evaluated in a number of trials and is a leading candidate for approval by the US FDA and other regulatory bodies, it could be helpful if supplementary analyses evaluated the specific effect of psilocybin per se.

See Hendricks, Johnson, & Griffiths:<http://journals.sagepub.com/doi/abs/10.1177/0269881115598338>.

Thank you for your suggestion to consider subanalyses with psilocybin, and we agree this could be an important contribution in the context of other research and clinical trials. We explored this as an option; however, we unfortunately did not have enough power to analyse the effect of psilocybin separately, as 24/79 (30%) of the women had used psilocybin or magic mushrooms at baseline, and by the end of the study the number was similar: 28/88 or 32%. Given that the majority of participants in our study had used MDMA, it would certainly be interesting to also consider investigating the specific effects of MDMA use only in future analyses.

4) Minor issue: last paragraph of the Introduction, "...drug use may be protective with regard to suicidality [27-29]..." The Krebs & Johansen studies, as I recall, found no associations between classic psychedelic use and a range of mental health outcomes. I don't think they found protective effects, but I could be wrong--the authors may want to confirm and modify the citations accordingly.

We appreciate this comment and have reviewed the findings of the Krebs & Johansen studies in detail. In the 2013 study, findings demonstrated several cases in which psychedelic use was associated with lower rates of mental health problems. For example, lifetime psilocybin use (aOR 0.8, $p=0.009$), lifetime mescaline use (aOR 0.9, $p=0.04$), and past year LSD use (aOR 0.7, $p=0.01$) were all associated with lower rates of serious psychological distress. Further, lifetime psilocybin use was significantly associated with a lower rate of symptoms of panic attacks (aOR 0.9, $p=0.006$).

In the 2015 study, the authors noted that lifetime psychedelic use was associated with a lower likelihood of past year inpatient mental health treatment (aOR 0.8, $p = 0.01$), and among specific psychedelics, they found 10 associations with a lower likelihood of mental health problems (e.g., psilocybin use and lower likelihood of past year serious psychological distress, inpatient mental health treatment and psychiatric medication prescription were all statistically significant, aOR 0.9, $p = 0.007$; aOR 0.7, $p = 0.0004$; aOR 0.8, $p = 0.002$, respectively).

5) It might help if the authors explain why analyses were restricted to participants who were previously not suicidal. I realize the outcome of interest was first suicidal episode, but why is this the case? Is there some rationale for focusing on first suicidal episode?

Thank you for this comment. As you mentioned, we chose to restrict the analyses to women who did not report suicidality at baseline so that we could capture new events of suicidality. We decided that this approach, using a Cox regression model, would be preferable in that it can determine a temporal relationship between psychedelic use and suicidality. One of the strengths of this analysis is that it demonstrates that the use of psychedelics preceded, and therefore had a protected effect upon, suicidality.

6) Minor issue: early in the Methods the authors suggest that the study comprised "over 800" participants, though in the Results $N = 766$ and then 209 is reported. It could be helpful to be a bit more clear and/or consistent throughout.

Thank you for this helpful suggestion. We have removed the words "over 800" under the methods section to mitigate any potential confusion. Please also see the text under the results section where we describe the reasons for excluding women from the analysis:

"Of the total 766 women who completed the baseline questionnaire, 46% ($n=355$) reported ever experiencing suicidality (45%; $n=343$ reported suicidal thoughts, 32%; $n=245$ attempted suicide) and were thus excluded from this analysis. A total of 290 women without suicidality who completed at

least one follow-up visit were eligible for inclusion in the present analysis.”

7) Why were suicidal thoughts and attempts collapsed into one variable? I think the authors need to provide a rationale for this approach, especially considering that some might conceptualize the two outcomes as somewhat distinct (e.g., suicidal thoughts are more common than suicidal attempts, and predictors of suicidal thoughts may differ from predictors of suicidal attempts). Note that I don't find this especially problematic, but the hypothetical skeptical/critical reader might!

We appreciate your comment regarding our rationale for combining suicide attempts with ideation. We did consider parsing out attempts from ideation; however, we unfortunately did not have the statistical power to do so in this study. An examination of these variables separately could certainly be interesting and important in future analyses with additional data from follow-up questionnaires.

8) Why did the authors evaluate only ever use of substances as predictors (vs. current use, frequency of use, recency of use, etc?). In the studies making use of the National Survey on Drug Use and Health (NSDUH) data (e.g., references 27-29), ever use of classic psychedelics was the primary independent variable of interest because the NSDUH only inquires about ever use. In other words, the authors of references 27-29 were making do with the available data. However, a more refined analysis might evaluate more nuanced indicators of classic psychedelic use. For instance, perhaps more frequent use is more protective? Perhaps more recent use is more protective? And so on.

Thank you for this comment and we agree it would be interesting to evaluate more nuanced indicators of use. Unfortunately, as mentioned above, we did not have enough power to analyze the effects of these indicators. Only 22/290 participants used psychedelics recently (in the last six months) at follow-up.

9) Table 2 could use a note, at a minimum to explain why not all Adjusted HRs and p-values are reported (what do the dashes mean?). Ideally, the tables could stand alone with minimal reference to the text needed to understand them.

Thank you for your comment and suggestion to clarify the adjusted HRs. We have removed all dashes and added a note at the bottom of Table 2 explaining the final multivariable model:

“Final multivariable model determined using backward selection with best overall fit, as indicated by the lowest Akaike information criterion (AIC) value.”

10) I was surprised that the authors found a protective effect of given the relatively small N, infrequent outcome (n = 31), and use of multivariate analyses. Perhaps this simply suggests that the effect size is large--a 60% reduced likelihood of suicidality certainly seems large to me--and if this is the case I encourage the authors to specifically discuss the size of the effect. Of course, I defer to the study statistician to ensure all assumptions were met, the N was sufficient for the analyses, no biases were at play (e.g., overadjustment bias), etc.

We appreciate your comment and suggestion to discuss the size of the effect. The study statistician confirms that all assumptions were met for the analyses, and we have added the following text on page 11 discussing the size of the effect:

“The standard error for the association between psychedelic use and suicidality was somewhat high,

resulting in a wider confidence interval. However, a large and significant protective effect was demonstrated in multivariable analysis, despite the relatively small number of events for suicidality over follow-up. With a larger sample size, we would expect a narrower confidence interval for this association.”

11) The authors write that "variables hypothesized a priori to be predictors of suicidality and those that were significantly correlated with the outcome at the $p < 0.05$ level in bivariate analyses were subsequently fitted into a multivariable Cox model." This does not appear to be true of psychedelic use, since $p = .99$ in bivariate analyses, unless I'm misunderstanding something. I suggest clarifying the analytic plan.

We appreciate your comment. We have clarified that psychedelic drug use was hypothesized a priori to be a predictor of suicidality on page 8. Please also see text on page 5 stating our hypothesis:

“We postulated that psychedelic drug use would have an independent protective effect on suicidality over the study period.”

12) In the Discussion, note that reference 27 was not longitudinal. It combined data from multiple years of an annual cross-sectional survey. This means that the authors study is the first to show a longitudinal relationship between lifetime psychedelic use and suicidality--this is good!

Thank you for highlighting these important distinctions. We have corrected the description of the reference, noting that it was a large “population” study instead of a “longitudinal” one. We have also added the following text under the conclusion:

“This is the first study to longitudinally investigate the relationship between psychedelic drug use and suicidality.”

13) I think it's important to acknowledge that the authors could not control for all sources of potential confounding. It could be that those who use psychedelics possess some characteristic(s) that also makes them less likely to be suicidal (e.g., openness to experience, curiosity, spirituality). None of the covariates appear to control for these sort of "positive psychology" variables.

Thank you for this important suggestion. We have added some text under the Discussion section acknowledging and expanding upon the limitations of this study, specifically with respect to the fact that this study did not examine all potential sources of confounding:

“While lifetime psychedelic drug use was found to reduce the hazard of suicidality, the associations uncovered in this analysis cannot be determined as causal. Suicidality is influenced by complex individual, interpersonal and structural variables, and not all potential confounding variables could be controlled for in this study. For example, women who use psychedelics may also possess some characteristic(s) associated with a reduced likelihood of being suicidal (e.g., openness to experience, curiosity, or spirituality), which were not examined in this study.”

14) Minor issue: in the Discussion, "...correlations found between psilocybin sessions and elevated ratings of personal meaningfulness..." This wording is a little confusing--how could sessions be correlated with anything at all? I think the authors mean to say that in-session mystical experience is

correlated with these outcomes.

We appreciate this comment. We have revised the sentence on page 13 as follows:

“For example, psilocybin-assisted psychotherapy demonstrated high success in smoking cessation outcomes at six months follow-up (abstinence rates of 80%), and mystical experiences generated from the psilocybin sessions were significantly correlated with elevated ratings of personal meaningfulness, wellbeing, and life satisfaction.”

15) My last comment is speculative, but could it be that those who report psychedelic use are less likely to be suicidal because they are less likely to exchange sex for money in the future? I wonder if, as a secondary analysis, the authors might see if use is associated with a decreased likelihood of exchanging sex for money within the past 30 days at follow-up.

Thank you for this comment. We appreciate your suggestion to explore the link between psychedelic use and exchanging sex for money, which could be an interesting association to consider in future analyses.

Reviewer #2

This study deals with an important topic, namely suicidality among a stigmatized group, female sex workers. However, there are several shortcomings of the paper, which must be addressed before the paper could be considered for publication.

Thank you for your comprehensive review of our manuscript. We appreciate your comments and believe that the revisions as outlined below have strengthened our paper considerably.

1. Most of all, limitations should be more clearly addressed. A more thorough comparison with relevant literature is needed.

Thank you for this helpful comment and suggestion to expand on the limitations of our study. We have revised the “Strengths and Limitations” section (following the abstract), highlighting more methodological limitations:

- This is the first study to longitudinally investigate the potential protective effect of psychedelic drug use on suicidality, drawing from a large, community-based cohort of marginalized women.
- Multivariable Cox regression analyses were used to examine the impact of lifetime psychedelic drug use on incidence of suicidality among a marginalized population.
- The associations between specific psychedelics, contexts of their use, and suicidality were not explored in this study.
- Not all potential confounding variables could be controlled for in this study and the associations uncovered cannot be determined as causal.
- Data were self-reported and variables examined included highly stigmatized topics, introducing the potential for recall bias, social desirability and reporting bias.

We have also included additional text on page 11 addressing further limitations of the study (please also see our responses to the other reviewer’s queries #10 and #13 above).

We appreciate your comment about providing a thorough comparison with the relevant literature. We have included text throughout the discussion situating our study and findings within the context of limited available data on suicidality among sex workers, and in relation to the growing body of research on the therapeutic potential of psychedelics. Please see the paragraph on pages 11-12 (This study is the first to longitudinally investigate associations with suicidality among women sex workers in North America, and builds upon prior cross-sectional research...) and page 14 (Marginalized and street-based sex workers experience complex and synergistic effects between trauma, lack of workplace safety, and mental health/substance use comorbidities that elevate risk of suicidality...) for relevant literature/data on suicidality among sex workers.

Please see the paragraph on pages 12-13 (Among the various scientific studies examining the potential benefits of psychedelic drug use...) for a discussion of the relevant work investigating psychedelics for various addiction and mental health issues.

2. Though new treatments are urgently needed in order to reduce suicidality, it should not be neglected that there are evidence that more traditional psychopharmacological treatment and psychosocial intervention may reduce the risk of suicidal behaviour. There has been evidence that among psychedelics, especially psilocybin in therapeutic doses reduces depression and also suicidality (some of these studies are referred to in the paper). Those doses are low to reduce the risk of negative side effects (several have been reported and even occasional suicidal ideation*). In the present paper the women's use of illegal psychedelic is studied, which probably means higher doses than usually prescribed. This fact ought to be discussed.

Thank you for this comment and we appreciate your suggestion to mention evidence on pharmacological and psychosocial interventions in reducing suicidality, and agree this should not be overlooked (while there remains a paucity of evidence among marginalized women, such as sex workers). We have added and revised text in the Introduction as follows:

"While evidence has demonstrated that some forms of cognitive behavioral therapy and pharmacological interventions may reduce suicidality, the literature is hampered by publication bias and significant heterogeneity of strategies and outcome measures [20,14]. There remains an urgency to better understand pathways to suicidality, with data highlighting the need for tailored intervention approaches for key vulnerable populations [20,21]. Given the complex etiological pathways to suicide and limited effectiveness of well-established evidence-based interventions to reduce the burden of suicidality, the US National Institute of Mental Health has called for innovative research on suicide prevention and treatment for suicidality [22]."

We have also added the following three references to support this:

O'Connor RC, Nock MK. The psychology of suicidal behaviour. *The Lancet Psychiatry* 2014;1:73–85. doi:10.1016/S2215-0366(14)70222-6

Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. *The Lancet Psychiatry* 2016;3:646–59. doi:10.1016/S2215-0366(16)30030-X

Klonsky ED, May AM, Saffer BY. Suicide, Suicide Attempts, and Suicidal Ideation. *Annu Rev Clin Psychol* 2016;12:307–30. doi:10.1146/annurev-clinpsy-021815-093204

We appreciate your suggestion to discuss doses and the potential differences between therapeutic doses and recreational doses. Clinical trials have used therapeutic doses ranging from low to high of various psychedelic substances, with no serious adverse effects (please see Tupper et al, 2015). In

addition to evidence from clinical trials, observational/population studies have demonstrated positive outcomes with naturalistic (non-medical) psychedelic use with unknown doses; for example, reduced recidivism (Hendricks et al, 2014), reduced intimate partner violence (Walsh et al, 2016), reduced psychological distress and suicidality (Hendricks et al, 2015), and improvements in various mental health outcomes (Krebs & Johansen 2013; Johansen & Krebs 2015). Additionally, the most recent Global Drug Use Survey ranked psilocybin (magic mushrooms) and LSD (along with cannabis) as the safest substances in a comparison of emergency medical treatment seeking for all substances (please see Winstock et al, 2017). Please also see Nutt et al, 2010 for harm score ratings for each substance used in the UK, where psilocybin mushrooms, LSD and MDMA/ecstasy are ranked among the least harmful drugs; significantly less harmful than many other substances such as alcohol, heroin, crack, cocaine, amphetamines, benzodiazepines, and tobacco.

Despite the relative safety of psychedelic drugs in both clinical and non-clinical settings, and that there is no evidence to suggest that sex workers use psychedelics in significantly higher doses than other drug using populations, we agree that the importance of not only dose, but also set and setting should be discussed. We have included the following text in the discussion of limitations on page 11:

“Despite the relative safety of psychedelic drug use as evidenced from the clinical and non-clinical literature [36,46–49], it should be noted that the use of psychedelics, particularly with unknown doses sourced from unregulated street markets, is not without risk, highlighting the importance of set and setting [23]; the doses and contexts of psychedelic use among women in the present study could not be determined.”

We have also included the following relevant new references:

Winstock A, Barratt M, Ferris J, et al. Global Drug Survey. London: 2017.
https://www.globaldrugsurvey.com/wp-content/themes/globaldrugsurvey/results/GDS2017_key-findings-report_final.pdf

Nutt DJ, King LA, Phillips LD. Drug harms in the UK: A multicriteria decision analysis. *Lancet* 2010;376:1558–65. doi:10.1016/S0140-6736(10)61462-6

3. Type of psychedelics are mentioned, but not number of each type used. How many used psilocybin, which is probably the most efficient one. Representativeness of the sample and attrition should be stated and discussed. The study is not randomized and possible confounders should be discussed.

Finally, the risk of serious side effects in higher doses should not be neglected.

Thank you for this comment and we appreciate your suggestion to report the frequencies for each specific psychedelic drug. We have added text under the results section as follows:

“Overall, 27% (n=79) of participants reported ever using a psychedelic substance, and of those, 75% (n=59) had used MDMA/ecstasy, 35% (n=28) had used LSD/acid, and 30% (n=24) had used psilocybin/magic mushrooms.”

Please also see our response to the other reviewer’s query #3 above. Given the evidence from other research and clinical trials with psilocybin, we considered running subanalyses to explore the effect of psilocybin separately. Unfortunately, we did not have enough statistical power to do so in this study.

Regarding representativeness of the sample, we have included the following text on page 11:

“The study population included women from a wide-ranging representation of sex work environments, yet findings may not be fully generalizable to sex workers in other settings. The mapping of working areas and time–location sampling helped to ensure a representative sample and to minimize selection bias.”

We appreciate your suggestion to discuss possible confounders and risk of side effects. Please see additional text added on page 11, expanding on our limitations, as also suggested above:

“While lifetime psychedelic drug use was found to reduce the hazard of suicidality, the associations uncovered in this analysis cannot be determined as causal. Suicidality is influenced by complex individual, interpersonal and structural variables, and not all potential confounding variables could be controlled for in this study. For example, women who use psychedelics may also possess some characteristic(s) associated with a reduced likelihood of being suicidal (e.g., openness to experience, curiosity, or spirituality), which were not examined in this study.”

Please see our response (with additional text and references) to your query #2 above regarding the risks of using psychedelics, and the importance of dose, set, and setting.

More specifically:

4. Abstract: conclusion goes beyond what is found in the study. First sentence is a background statement, not a conclusion.

Thank you for this comment. We have revised the first sentence in the abstract conclusion as follows:

“The high rate of suicidality identified in this study is of major concern.”

5. Strengths and limitation:

There are four strengths and one limitation reported. This appears scewed. I suggest more limitations to be mentioned.

We appreciate this comment. We have expanded on our limitations in the “Strengths and Limitations” section – please see our response to your query, and the Editorial Requirements, above.

6. Introduction:

first §: the problem of suicide in general is presented. What about the risk among women sex workers? It is reported among women sex workers who had experienced violence and childhood abuse. Other? Is sex work as such a risk regardless of violence etc? Completed suicide or non-fatal suicide behaviour?

P 4 last § states ‘in the wake largely ineffective interventions’? There is good evidence that some interventions, such as psychotherapy and psychotropics do reduce suicidal behaviour, which should not be overlooked. After that it is correct to state that there is a need for innovative treatments.

Thank you for this helpful comment. We have included the following text in the Introduction highlighting that there are large gaps in research and data on suicidality among women sex workers, and we briefly summarize what is known from the limited available data on risk factors: this includes stigma, social exclusion, depression, and PTSD, in addition to experiences of violence and childhood abuse. We further note the multigenerational trauma experienced by indigenous women who are overrepresented among street-based sex workers in North America:

“Significant gaps remain in empirical research examining suicidality among marginalized populations. Marginalized women, such as sex workers who are street-involved or use drugs, experience disproportionately high levels of social and health-related risks and harms, including stigma, discrimination, and violence [5–7] as a result of dynamic structural drivers including poverty, criminalization, and racism. While sex workers are a diverse population working from indoor in-call and out-call venues to street-based settings, previous studies highlight substantial unmet mental health needs of more marginalized and street-involved sex workers. Studies among street-based sex workers and those who use drugs underscore the associations of social exclusion, depression, and post-traumatic stress disorder (PTSD) with suicidality [8–12]. Research demonstrates greater risk for suicidality among those with a history of trauma [1,13,14] and among women sex workers who report historical experiences of violence and childhood abuse [8–10,15,16]. Further, Indigenous women are vastly overrepresented among street-based sex workers in North America, and face devastating and multigenerational effects of trauma and socio-economic dislocation (e.g., high burden of mental illness and suicidality) as a result of colonialism, racialized policies, and displacement from land and home communities [17,18]”

To the best of our knowledge, there are no studies that have examined sex work in and of itself (without taking into account violence or other psychosocial factors) as a risk for suicide. Sex workers experience elevated risk and rates of suicidality as a result of complex interactions between individual, interpersonal and structural factors (e.g., stigma, unmet mental health needs, lack of protections for violence in the workplace). Further, our study focuses on suicidality (non-fatal suicidal ideation or attempts), rather than completed suicides.

We appreciate your suggestion to mention evidence demonstrating that psychotherapy and psychotropics can reduce suicidality and agree this should not be overlooked. Please see our response to your query #2 above. We have also revised the second to last sentence in the introduction as follows:

“Given the urgency of addressing and preventing suicide and calls for prioritizing innovative interventions, this study aimed to longitudinally investigate whether lifetime psychedelic drug use is associated with a reduced incidence of suicidality (suicide ideation or attempts) among a cohort of marginalized women.”

7. Methods:

Data are drawn from a large... cohort... How are they drawn, random order, invited? What about attrition?

Thank you for this comment. We have included the following text describing how women were invited to participate in the AESHA study and how we dealt with loss to follow-up/missing observations:

“Participants were recruited across Metro Vancouver using time-location sampling and community mapping strategies, with day and late-night outreach to outdoor sex work locations (i.e., streets, alleyways), indoor sex work venues (i.e., massage parlors, micro-brothels, and in-call locations), and online. Weekly outreach is conducted to over 100 sex work venues by outreach/nursing teams operating a mobile van, with regular contact as well as encouraging drop-in to women-only spaces at the research office, contributing to an annual retention rate of >90% for AESHA participants.” –page 5/6

“A complete case analysis was used, where observations with missing data were excluded from analyses, and participants who were lost to follow-up were right censored at their most recent study visit.” –page 8

“Those with missing observations for suicidality at baseline (n=50/766; 6.5%) were excluded from analysis, and one additional participant was excluded because reported suicidality was missing at follow-up.” – page 7

8. Statistical analyses:

First § concerns selection of participants rather than statistics. This § should be included in the Method section instead.

We appreciate this comment. We have moved the first sentence under statistical analyses to the methods section, as suggested.

9. Results:

The number of completers ought to be mentioned under participants in the Method section. Proportion of suicidality, on the other hand, is a result. Missing observations, too, belongs to the Method. Subheadings would make the text more comprehensive. First sociodemographic and then substance use.

Thank you for this comment and for your helpful suggestions. We unfortunately do not have data on the number of completed suicides among AESHA participants. As suggested, we have moved the information on missing observations to the methods section and we have added the subheadings “Socio-Demographic Characteristics,” “Substance Use” and “Bivariate and Multivariable Cox Analyses” for clarity under the results section.

10. Discussion:

Needs more focus. Limitations and strengths should be discussed in a separate §. What are the limitations? The sample is rather small for instance. This should be elaborated. Third § p 10 is of limited relevance for the present findings, rather a background which states the problem. Reduced suicidality has been shown for therapeutic use of psychedelics, especially psilocybin. Are previous findings to be expected to be generalized to the present sample of women sex workers, who may use higher than therapeutic doses? In therapeutic settings the doses are small, but what about the doses used among the study participants? Possible side effects? The possibility that those who had escaped side effects are more able to participate? If suicidality could be a side effect, the exclusion of those who had experienced suicidal ideation may be a confounder.

We appreciate your comment on clarifying aspects of the discussion section. We have compiled the strengths and limitations of the study into a single paragraph (the second paragraph under the discussion) and we have expanded upon the limitations in particular (please also see our response to your query #1 above regarding limitations, as well as our response to the other reviewer’s queries #10 and #13). We have added the following text regarding sample size and effect size in this paragraph as well:

“The standard error for the association between psychedelic use and suicidality was somewhat high, resulting in a wider confidence interval. However, a large and significant protective effect was demonstrated in multivariable analysis, despite the relatively small number of events for suicidality over follow-up. With a larger sample size, we would expect a narrower confidence interval for this association.”

Thank you for your suggestion regarding the third paragraph in the discussion – we have re-framed

and revised text to improve focus and relevance of prior research findings in the context of our results and study overall:

“This study is the first to longitudinally investigate associations with suicidality among women sex workers in North America, and builds upon prior cross-sectional research highlighting significantly elevated rates of suicidality and unmet mental health needs in this population. For example, a study...”

We appreciate your comment regarding therapeutic vs. potentially higher recreational doses of psychedelics. Please see our response to your query #2 above for a discussion on dose, set and setting, as well as the potential risks involved with psychedelic use.

Please see our response to your query #3 above regarding potential confounders.

11. Conclusion:

‘This study supports call for further research..’ is irrelevant, other possible drugs, psychosocial intervention could also be further explored. The present study does not first of all give evidence of the problem, which has been known before. In fact, the knowledge of the problem gave the authors a reason to start the research. However, the last part of the sentence ‘further investigations ... psychedelic drugs ..’ is a relevant statement. There are many important limitations in the present study, and therefore more research is needed before psychedelic drugs should be recommended. The present study may however, encourage more research on the topic.

Thank you and we appreciate this comment. As suggested, we have revised the sentence in the conclusion (as well as in the abstract conclusion) to more concisely summarize the implication of our study and need for further investigation on the therapeutic utility of psychedelics:

“While observational, this study supports calls for further investigation of the therapeutic utility of psychedelic drugs in treating mental illness and promoting mental wellness.”

VERSION 2 – REVIEW

REVIEWER	Peter Hendricks University of Alabama at Birmingham USA
REVIEW RETURNED	14-Jun-2017

GENERAL COMMENTS	No further comments.
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REVIEWER	Louise Brådvik Lund University, Department of Clinical Sciences, Lund, Psychiatry, Sweden
REVIEW RETURNED	28-Jun-2017

GENERAL COMMENTS	1. We have revised the “Strengths and Limitations” section (following the abstract), highlighting more methodological limitations: I SUGGEST YOU TO WRITE ‘TO THE BEST OF OUR KNOWLEDGE’, AS YOU CAN NEVER BE SURE THAT YOU HAVE DETECTED ALL POSSIBLE STUDIES.
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	<p>2. You have added three references, O'Connor, Zalsman, and Klonsky, but they could be referred to more accurately. A major problem in suicide research is "The paucity of RCTs is a major limitation in the evaluation of preventive interventions." (Zalsman). These studies could not be performed for ethical reasons, as suicide as a possible outcome is not acceptable and ethical approval for such studies could not be achieved. Therefore, virtually all studies are more indirect, as the present one. However, there is probably some effect of the interventions all the same. It is also generally agreed that suicide is multi-factoral and different treatment approaches are needed.</p> <p>O'Connor states: "Some evidence suggests that different forms of cognitive and behavioural therapies can reduce the risk of suicide reattempt, but hardly any evidence about factors that protect against suicide is available" In other words, most studies deal with non-fatal rather than fatal suicidal behaviour, like the present one.</p> <p>The Klonsky study refers mainly to the transition between different levels of suicidality, ideation to attempt and attempt to accomplished suicide, a transition that could not be investigated in the present sample. This reference is less suitable.</p> <p>I suggest that the authors rephrase these references in a more accurate way.</p> <p>3. "The standard error for the association between psychedelic use and suicidality was somewhat high, resulting in a wider confidence interval. However, a large and significant protective effect was demonstrated in multivariable analysis, despite the relatively small number of events for suicidality over follow-up. With a larger sample size, we would expect a narrower confidence interval for this association."</p> <p>THE LAST SENTENCE IS UNNECESSARY, AS WIDTH OF CONFIDENCE INTERVAL FOLLOWS SAMPLE SIZE.</p> <p>It says on p 3, line 5, that 'Marginalized women, such as sex workers who are street-involved... experience... social and health-related risks and harms, including stigma, discrimination and violence [5-7]'. These risks probably remain despite the use of psychedelics, even if the women no longer are suicidal. This fact that may be mentioned in the discussion, calling for other interventions.</p> <p>Some points from reviewer 1 needs addressed in the paper and not only as a response to reviewer's comments to improve the quality of the paper:</p> <p>5) It might help if the authors explain why analyses were restricted to participants who were previously not suicidal. I realize the outcome of interest was first suicidal episode, but why is this the case? Is their some rationale for focusing on first suicidal episode?</p> <p>Thank you for this comment. As you mentioned, we chose to restrict the analyses to women who did not report suicidality at baseline so that we could capture new events of suicidality. We decided that this approach, using a Cox regression model, would be preferable in that it can determine a temporal relationship between psychedelic use and suicidality. One of the strengths of this analysis is that it demonstrates that the use of psychedelics preceded, and therefore</p>
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	<p>had a protected effect upon, suicidality. PLEASE, CLARIFY IN THE MANUSCRIPT AS WELL!</p> <p>7) Why were suicidal thoughts and attempts collapsed into one variable? I think the authors need to provide a rationale for this approach, especially considering that some might conceptualize the two outcomes as somewhat distinct (e.g., suicidal thoughts are more common than suicidal attempts, and predictors of suicidal thoughts may differ from predictors of suicidal attempts). Note that I don't find this especially problematic, but the hypothetical skeptical/critical reader might!</p> <p>We appreciate your comment regarding our rationale for combining suicide attempts with ideation. We did consider parsing out attempts from ideation; however, we unfortunately did not have the statistical power to do so in this study. An examination of these variables separately could certainly be interesting and important in future analyses with additional data from follow-up questionnaires. PLEASE MENTION IN THE TEXT!</p> <p>8) Why did the authors evaluate only ever use of substances as predictors (vs. current use, frequency of use, recency of use, etc?). In the studies making use of the National Survey on Drug Use and Health (NSDUH) data (e.g., references 27-29), ever use of classic psychedelics was the primary independent variable of interest because the NSDUH only inquires about ever use. In other words, the authors of references 27-29 were making do with the available data. However, a more refined analysis might evaluate more nuanced indicators of classic psychedelic use. For instance, perhaps more frequent use is more protective? Perhaps more recent use is more protective? And so on.</p> <p>Thank you for this comment and we agree it would be interesting to evaluate more nuanced indicators of use. Unfortunately, as mentioned above, we did not have enough power to analyze the effects of these indicators. Only 22/290 participants used psychedelics recently (in the last six months) at follow-up. PLEASE ADD TO LIMITATIONS</p> <p>11) The authors write that "variables hypothesized a priori to be predictors of suicidality and those that were significantly correlated with the outcome at the $p < 0.05$ level in bivariate analyses were subsequently fitted into a multivariable Cox model." This does not appear to be true of psychedelic use, since $p = .99$ in bivariate analyses, unless I'm misunderstanding something. I suggest clarifying the analytic plan.</p> <p>We appreciate your comment. We have clarified that psychedelic drug use was hypothesized a priori to be a predictor of suicidality on page 8. Please also see text on page 5 stating our hypothesis:</p> <p>"We postulated that psychedelic drug use would have an independent protective effect on suicidality over the study period." ON P 8 IT SAYS '(E.G. PSYCHEDELIC DRUG USE)'. E.G. REFERS TO ONE OF TWO OR MORE. WERE THERE MORE? PLEASE, CLARIFY! I FIND ONLY ONE EXAMPLE ON P 5.</p> <p>12) In the Discussion, note that reference 27 was not longitudinal. It combined data from multiple years of an annual cross-sectional survey. This means that the authors study is the first to show a</p>
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	<p>longitudinal relationship between lifetime psychedelic use and suicidality--this is good!</p> <p>Thank you for highlighting these important distinctions. We have corrected the description of the reference, noting that it was a large "population" study instead of a "longitudinal" one. We have also added the following text under the conclusion:</p> <p>"This is the first study to longitudinally investigate the relationship between psychedelic drug use and suicidality." TO THE BEST OF OUR KNOWLEDGE IS MORE APPROPRIATE, AS YOU CANNOT GRANT YOU HAVE READ ALL STUDIES.</p> <p>15) My last comment is speculative, but could it be that those who report psychedelic use are less likely to be suicidal because they are less likely to exchange sex for money in the future? I wonder if, as a secondary analysis, the authors might see if use is associated with a decreased likelihood of exchanging sex for money within the past 30 days at follow-up.</p> <p>Thank you for this comment. We appreciate your suggestion to explore the link between psychedelic use and exchanging sex for money, which could be an interesting association to consider in future analyses. I SUGGEST YOU TO MENTION THIS IN THE TEXT!</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer #2

1. We have revised the "Strengths and Limitations" section (following the abstract), highlighting more methodological limitations:

I SUGGEST YOU TO WRITE 'TO THE BEST OF OUR KNOWLEDGE', AS YOU CAN NEVER BE SURE THAT YOU HAVE DETECTED ALL POSSIBLE STUDIES.

Thank you for your comprehensive review of our revised manuscript and we appreciate your minor comments to further amend. As suggested, we have revised the first point under the "Strengths and Limitations" section as follows:

- To the best of our knowledge, this is the first study to longitudinally investigate the potential protective effect of psychedelic drug use on suicidality, drawing from a large, community-based cohort of marginalized women.

We have also revised the related sentence on page 12 as follows:

"To the best of our knowledge, this study is the first to longitudinally investigate associations with suicidality among women sex workers in North America, and builds upon prior cross-sectional research highlighting significantly elevated rates of suicidality and unmet mental health needs in this population."

2. You have added three references, O'Connor, Zalsman, and Klonsky, but they could be referred to more accurately. A major problem in suicide research is "The paucity of RCTs is a major limitation in the evaluation of preventive interventions." (Zalsman). These studies could not be performed for ethical reasons, as suicide as a possible outcome is not acceptable and ethical approval for such studies could not be achieved. Therefore, virtually all studies are more indirect, as the present one. However, there is probably some effect of the interventions all the same. It is also generally agreed that suicide is multi-factoral and different treatment approaches are needed.

O'Connor states: "Some evidence suggests that different forms of cognitive and behavioural therapies can reduce the risk of suicide reattempt, but hardly any evidence about factors that protect against suicide is available" In other words, most studies deal with non-fatal rather than fatal suicidal behaviour, like the present one.

The Klonsky study refers mainly to the transition between different levels of suicidality, ideation to attempt and attempt to accomplished suicide, a transition that could not be investigated in the present sample. This reference is less suitable.

I suggest that the authors rephrase these references in a more accurate way.

We appreciate your helpful suggestion to rephrase and refer to the additional references (O'Connor, Zalsman, and Klonsky) more accurately.

We have revised text in the Introduction as follows:

"Due to ethical challenges and limitations to studying suicide and its proxies (i.e., ideation and attempts), there remains a paucity of evidence from randomized controlled trials to support the efficacy of prevention interventions [20]. Researchers have largely focused on examining suicidality outcomes (rather than suicide itself), which may not be fully generalizable to understanding suicide or accurately evaluating treatment approaches [21]. Further, stigma continues to hinder research and reporting of suicidality [21]. There remains an urgency to better understand pathways to suicidality, with literature highlighting the need for innovative psychological and psychosocial treatments [14] and tailored intervention approaches for key marginalized populations [20,21]."

3. "The standard error for the association between psychedelic use and suicidality was somewhat high, resulting in a wider confidence interval. However, a large and significant protective effect was demonstrated in multivariable analysis, despite the relatively small number of events for suicidality over follow-up. With a larger sample size, we would expect a narrower confidence interval for this association."

THE LAST SENTENCE IS UNNECESSARY, AS WIDTH OF CONFIDENCE INTERVAL FOLLOWS SAMPLE SIZE.

Thank you for this comment. As suggested, we have removed the last sentence that read: "With a larger sample size, we would expect a narrower confidence interval for this association."

4. It says on p 3, line 5, that 'Marginalized women, such as sex workers who are street-involved... experience... social and health-related risks and harms, including stigma, discrimination and violence [5-7]'. These risks probably remain despite the use of psychedelics, even if the women no longer are suicidal. This fact that may be mentioned in the discussion, calling for other interventions.

We appreciate this comment and certainly agree that there are key interventions that should be implemented to mitigate other socio-structural risks and harms, regardless of psychedelic use or suicidality among sex workers. We have revised and expanded upon the text in the discussion on page 13, as follows, to further highlight the role of workplace safety and the critical need for structural and community-led interventions among sex workers:

“Notably, our study demonstrated a lower risk of suicidality among women working indoors in bivariate analysis (HR 0.19, $p=0.009$), lending support to the critical role of safer workplace environments in mitigating risk. In studies conducted in Asia, recent suicide attempts ranged from 19% among sex workers in Goa, India [16] to 38% among sex workers in China [8,11,50], many of whom work in marginalized settings with few workplace protections. Transgender women involved in sex work, a sub-population experiencing significant psychosocial vulnerability and discrimination, report notably further elevated rates of suicidality: three quarters of participants in San Francisco reported suicide ideation, of whom 64% attempted suicide [51]. The global evidence is unequivocal that in settings where sex work is criminalized, sex workers are unable to access essential social, health, and legal protections (e.g., against violence), highlighting the need for structural (e.g., decriminalization) and community-led interventions to improve health and human rights [5]. A structural approach to mitigating suicidality risk requires a reform of laws and policies that perpetuate stigma, discrimination, violence, and unequal access to health and social supports among sex workers. Increased support for community-driven interventions that are gender and culturally appropriate are urgently needed, and any clinical treatment utilizing psychedelics must be developed alongside sex worker-led interventions and community empowerment.”

Some points from reviewer 1 needs addressed in the paper and not only as a response to reviewer's comments to improve the quality of the paper:

5) It might help if the authors explain why analyses were restricted to participants who were previously not suicidal. I realize the outcome of interest was first suicidal episode, but why is this the case? Is their some rationale for focusing on first suicidal episode?

Thank you for this comment. As you mentioned, we chose to restrict the analyses to women who did not report suicidality at baseline so that we could capture new events of suicidality. We decided that this approach, using a Cox regression model, would be preferable in that it can determine a temporal relationship between psychedelic use and suicidality. One of the strengths of this analysis is that it demonstrates that the use of psychedelics preceded, and therefore had a protected effect upon, suicidality.

PLEASE, CLARIFY IN THE MANUSCRIPT AS WELL!

Thank you for this comment and we appreciate your suggestion to further clarify our responses to Reviewer 1's queries throughout the manuscript. We have added the following text under the methods section on page 7:

“To capture initial episodes of suicidality, analyses for this study were restricted to AESHA participants who had never thought about or attempted suicide at baseline...”

We have also added the following text under the discussion section on page 11:

“However, the use of Cox regression analysis in this study was able to determine a temporal relationship between psychedelic use and suicidality. The sample was restricted to participants who had not experienced suicidal ideation or attempt at baseline, ensuring that psychedelic use preceded suicidality and thus providing evidence that psychedelics have a protective effect.”

7) Why were suicidal thoughts and attempts collapsed into one variable? I think the authors need to provide a rationale for this approach, especially considering that some might conceptualize the two outcomes as somewhat distinct (e.g., suicidal thoughts are more common than suicidal attempts, and predictors of suicidal thoughts may differ from predictors of suicidal attempts). Note that I don't find this especially problematic, but the hypothetical skeptical/critical reader might!

We appreciate your comment regarding our rationale for combining suicide attempts with ideation. We did consider parsing out attempts from ideation; however, we unfortunately did not have the statistical power to do so in this study. An examination of these variables separately could certainly be interesting and important in future analyses with additional data from follow-up questionnaires.
PLEASE MENTION IN THE TEXT!

Thank you for this comment. As suggested, we have provided additional text in the manuscript to reflect our response to this query, under the limitations on page 11:

“Due to a lack of statistical power, analyses evaluating the effects of more nuanced indicators of psychedelic use (e.g., frequency of use or recent use), as well as separate analyses for ideation and attempt outcomes, were not feasible. Further examination of these variables would certainly be interesting and important in future analyses with additional data from follow-up questionnaires.”

8) Why did the authors evaluate only ever use of substances as predictors (vs. current use, frequency of use, recency of use, etc?). In the studies making use of the National Survey on Drug Use and Health (NSDUH) data (e.g., references 27-29), ever use of classic psychedelics was the primary independent variable of interest because the NSDUH only inquires about ever use. In other words, the authors of references 27-29 were making do with the available data. However, a more refined analysis might evaluate more nuanced indicators of classic psychedelic use. For instance, perhaps more frequent use is more protective? Perhaps more recent use is more protective? And so on.

Thank you for this comment and we agree it would be interesting to evaluate more nuanced indicators of use. Unfortunately, as mentioned above, we did not have enough power to analyze the effects of these indicators. Only 22/290 participants used psychedelics recently (in the last six months) at follow-up.

PLEASE ADD TO LIMITATIONS

Thank you for this comment. We have included text, as suggested, under the limitations section. Please see our response to query #7 above.

11) The authors write that "variables hypothesized a priori to be predictors of suicidality and those that were significantly correlated with the outcome at the $p < 0.05$ level in bivariate analyses were subsequently fitted into a multivariable Cox model." This does not appear to be true of psychedelic use, since $p = .99$ in bivariate analyses, unless I'm misunderstanding something. I suggest clarifying the analytic plan.

We appreciate your comment. We have clarified that psychedelic drug use was hypothesized a priori to be a predictor of suicidality on page 8. Please also see text on page 5 stating our hypothesis:

“We postulated that psychedelic drug use would have an independent protective effect on suicidality over the study period.”

ON P 8 IT SAYS '(E.G. PSYCHEDELIC DRUG USE).' E.G. REFERS TO ONE OF TWO OR MORE. WERE THERE MORE? PLEASE, CLARIFY! I FIND ONLY ONE EXAMPLE ON P 5.

Thank you for this comment and we appreciate your suggestion to clarify the analytic plan. We have revised the text on page 8 as follows:

“Psychedelic drug use, hypothesized a priori to be a predictor of suicidality, and variables that were significantly correlated with the outcome at the $p < 0.10$ level in bivariate analyses were subsequently fitted into a multivariable Cox model.”

12) In the Discussion, note that reference 27 was not longitudinal. It combined data from multiple

years of an annual cross-sectional survey. This means that the authors study is the first to show a longitudinal relationship between lifetime psychedelic use and suicidality--this is good!

Thank you for highlighting these important distinctions. We have corrected the description of the reference, noting that it was a large "population" study instead of a "longitudinal" one. We have also added the following text under the conclusion:

"This is the first study to longitudinally investigate the relationship between psychedelic drug use and suicidality."

TO THE BEST OF OUR KNOWLEDGE IS MORE APPROPRIATE, AS YOU CANNOT GRANT YOU HAVE READ ALL STUDIES.

Thank you for this comment. As suggested, we have revised the sentence in the conclusion as follows:

"To the best of our knowledge, this is the first study to longitudinally investigate the relationship between psychedelic drug use and suicidality."

15) My last comment is speculative, but could it be that those who report psychedelic use are less likely to be suicidal because they are less likely to exchange sex for money in the future? I wonder if, as a secondary analysis, the authors might see if use is associated with a decreased likelihood of exchanging sex for money within the past 30 days at follow-up.

Thank you for this comment. We appreciate your suggestion to explore the link between psychedelic use and exchanging sex for money, which could be an interesting association to consider in future analyses.

I SUGGEST YOU TO MENTION THIS IN THE TEXT!

Thank you for your comment and we appreciate this suggestion. While we agree with Reviewer 1 that associations between psychedelic use and other factors, such as frequency of exchanging sex for money, could be interesting to consider in future analyses, we did not hypothesize in the present study that psychedelic use would be associated with a decreased likelihood of exchanging sex for money; psychedelic use may in fact alter dynamics with clients or stability of sex work, but not necessarily be associated with less work. Further, it is unclear if a reduction in exchanging sex for money would lead women to be less suicidal. Research and evidence suggest that sex work itself is not a direct risk factor for suicidality, but rather the socio-structural determinants experienced by some sex workers, especially those who are more marginalized and operating in street-based settings, are at play (e.g., unsafe work environments, lack of protections from violence, policing, laws, stigma...). Please see text included on page 13 and response to query #4 above.

VERSION 3 – REVIEW

REVIEWER	Louise Brådvik Department of Clinical Sciences, Psychiatry, Lund University, Sweden.
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	The revision is appropriate and I have no further comments.
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