ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with nicotine dependence during methadone maintenance treatment: findings from a multi-site survey in Vietnam
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VERSION 1 - REVIEW

REVIEWER	Joseph Guydish Institute for Health Policy Studies University of California San Francisco USA
REVIEW RETURNED	06-Feb-2017

GENERAL COMMENTS	This paper reports on smoking status (current, former, never) and Fagerstrom Nicotine Dependence (FTND) scores, and factors associated with these measures, in a sample of 1,016 persons recruited from 5 methadone maintenance treatment (MMT) clinics in Northern Vietnam. As I understand the paper, it first assessed bivariate relationships between these two outcomes (smoking status, FTND) and a number of predictor variables (demographics, alcohol use, drug use, health status). Then, when these outcomes and predictors met a pre-specified significance criteria, they were entered into a multivariate analysis (smoking status) or a Tobit regression (FTND score). Key findings are that 87.2% of the sample were current smokers, and that being in MMT for more months and being HIV positive were both associated with smoking status Other associations are reported for FTND scores.
	1. The Introduction, paragraph 1, says that death rates of smokers were four times greater than that of their counterparts, referring to the paper by Yi-Ing Hser. While this is correct, I think it would be helpful to specify that these were persons who had received narcotics treatment. Otherwise the reader cannot know why a higher death rate among smokers in the sample is important.
	2. The same paragraph goes on to say that smoking increased likelihood of suffering from a number of causes "among opioid abusers compared to their non-smoking counterparts." However I believe that the citation to Hurt et al., JAMA, 1996 referred to person who had received treatment for alcohol abuse (not opioid abuse). If the point being made is that smokers with a range of substance abuse problems more often die of smoking –related causes than their non-smoking counterparts, then the Hurt et al. citation fits. If the point is more specific to opioid users, then I think perhaps Hurt et al 1996 does not apply.

3. In the Introduction the paper offers that 23.8% of adults in Vietnam are current smokers. As smoking prevalence differs by gender in some countries, it may be helpful to know if this (23.8%) represents men, women, or men and women combined. For example, is smoking prevalence in Vietnam higher among men and lower among women, so that the combined prevalence of 23.8% underestimates smoking prevalence among men. This is of interest later because, although the interview collected data on gender, the proportion of men and women in the sample is not reported in Table 2, so the proportion of men and women in the study sample is not given in the paper.

4. The Methods say that "having an adequate number of MMT patients" was a criterion for inclusion of a clinic in the study. How many MMT cases did a clinic need to have to be considered for inclusion?

5. The primary outcome is given as smoking status, and in the multivariate logistic regression I assume that the outcome was current smoker (yes/no). If so, then I think that the bivariate comparisons given in Table 2 should also use the dichotomous outcome (current smoker Y/N) rather than the categorical outcome ((never, current, former smoker). As mentioned above, please report gender in Table 2, unless all participants were men.

6. Please not an error in the text and table concerning "currently perceived morbidity problem." If this is taken from the EQ-5D measure, then it may refer to "mobility" rather than "morbidity."
7. Please state whether analyses reported in Table 4 controlled for nesting of participants within each of the 5 clinic sites. If these analyses did not control for nesting, then I believe they should do so.

8. The Discussion says "we observed the difficulty of accessing smoking cessation support among MMT patients…" However this issue is not mentioned in the Introduction, no measure of smoking cessation is reported in the Methods section, and no data concerning such observations are registered in the Results section. So this specific observation seems not to be supported by data given in the paper, or at least it is not a study finding. Simplest may be to just remove this sentence.

8. The paper sometimes refers to findings as "associations," but sometimes uses more causal language such as "we observed a dramatic increase in FTND score in the first 5 months…" As this was a cross-sectional study it seems better to refer to an association rather than an increase.

REVIEWER	Hanns Moshammer Department Environmental Health, Medical University of Vienna, Austria
REVIEW RETURNED	30-Mar-2017

| GENERAL COMMENTS | Generally speaking I find the statistical methods well-chosen and well described by the authors of this paper. Maybe the abstract is not so clear in the description of the statistical results: "Longer duration of MMT (OR=0.98; 95%CI=0.96-0.99) … were associated with lower likelihood of smoking." How was "longer duration" |

measured? Are the ORs meant more than 1 year compared to less than one year, or per month, or per week, or…?

But in the main text the statistics are clear and straightforward. I do have some other concerns with the paper though:

Measures and instruments / Smoking related variables: this section introduces 3 groups: current smokers, former smokers, never smokers. According to the definition given a person that started smoking just now (less than 100 cigarettes in his life, but currently smoking) would not fit to any of the 3 categories. But in the end this is a sophisticated categorization that is not applied in the analysis. In table 3 current and former smokers are lumped together (although I am not sure if Fagerstrom score makes sense in former smokers) and from table 2 I understand that differences between the groups mostly concern the never smokers. But in the regression analysis (table 4) current smokers are compared to the other two groups. What was the aim of the study originally? Did the authors set out to study factors increasing current or ever smoking?

Does this question even make sense / is the hypothesis biologically plausible: When you study the OR for smoking (and for nicotine addiction) by methadone use you would insinuate that methadone (or heroin) caused smoking. But smoking on average started earlier (around age 17) than heroin use (around age 25). How then can methadone treatment explain the high smoking rate (Discussion: "This result can be explained by the interaction between nicotine and methadone, that smoking eases the craving for heroin and cocaine consumption [15]." Do the authors believe the smokers started smoking at the age of 17 because they knew they would become heroin addicts later and would need nicotine to ease their craving?

The curves (figure 1) are correctly produced regarding technical / statistical procedure. But the biological interpretation is more than brave! "We found that the smoking rates increased gradually in the first 30 months (but not significantly), and remarkably decrease afterwards. We suppose that in the initial stage of treatment, smoking helped patients to counter the aftertaste of MMT and improved the pleasing effect [57]." (etc.) This is likely an over-interpretation of a (non-significant) finding that would not have been visible in another (linear) model.

Generally speaking every former smoker must have been a current smoker earlier. Therefore in any survey you would expect to find former smokers to be on average older than current smokers. The same would hold for current smokers versus never smokers, if your survey targeted the whole population. But if smoking initiation generally occurs in adolescence and if your survey population is adults you would not expect a difference in average age between smokers and non-smokers if smoking rates are stable. In this study never smokers were on average older. This indicates that in that population smoking rates increased recently. So when the older people were adolescent (when most smokers are recruited) smoking was still less common. I believe this is not only true for MMT persons, but for Vietnam people in general. There might also be a general difference between urban and rural living area and between socio-economic statuses. These differences are not specific for injection drug users and are not even caused by some biological mechanisms. The main reason is marketing policy of tobacco industries: When they come to a country they first target the better of urban population and advertise their product as signifying a modern western life style. Only later the vice spreads to other groups and later on, when administration and the general public gets increasingly aware of the bad side effects of smoking, the smoking rates get higher in less educated people. I do not understand the

	added value of studying these general associations in such a special subgroup. I simply do not see the added value for the treatment of MMT patients: "Therefore, these relationships during the course of MMT are clinically important that should be carefully monitored and controlled, which could help to identify who may need to receive specific cessation interventions at MMT sites." Do the authors think that only some smokers should be offered cessation intervention? Those that also drink, or those that abstain from risky drinking? Multi-substance abuse might represent a special trait and it might need special treatment. But showing that such a trait (drug injection and drinking) also is associated with greater nicotine addiction is neither surprising nor does it help with any therapy decision for the individual smoker!
	We have seen that never smokers tend to be older. I also argued that this seems to be a general phenomenon when smoking rates are increasing. When initiation age of smoking is rather constant (which it appears to be), then older people are smoking for a longer period of time, have also a longer history of heroin abuse, and eventually also a longer history of methadone therapy. If this is true (I find it highly plausible), then any association between smoking risk and MMT duration etc. is simply a natural function of age.
	One last remark regarding the statistics, but I assume this is a typing error only: Table 4 depicts $p<0.05$ according to the foot-note with ** and $p<0.01$ with *. The latter must be wrong because all confidence ranges that are indicated with one * include the null (Coefficient) or 1 (OR). Therefore p must be larger than 0.05. Maybe on * indicates a "trend" ($p<0.1$)?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1. The Introduction, paragraph 1, says that death rates of smokers were four times greater than that of their counterparts, referring to the paper by Yi-Ing Hser. While this is correct, I think it would be helpful to specify that these were persons who had received narcotics treatment. Otherwise the reader cannot know why a higher death rate among smokers in the sample is important.
Response: We had revised the sentence in the manuscript.

2. The same paragraph goes on to say that smoking increased likelihood of suffering from a number of causes "among opioid abusers compared to their non-smoking counterparts." However I believe that the citation to Hurt et al., JAMA, 1996 referred to person who had received treatment for alcohol abuse (not opioid abuse). If the point being made is that smokers with a range of substance abuse problems more often die of smoking –related causes than their non-smoking counterparts, then the Hurt et al. citation fits. If the point is more specific to opioid users, then I think perhaps Hurt et al 1996 does not apply.
Response: We had revised the sentence in the manuscript.

3. In the Introduction the paper offers that 23.8% of adults in Vietnam are current smokers. As smoking prevalence differs by gender in some countries, it may be helpful to know if this (23.8%) represents men, women, or men and women combined. For example, is smoking prevalence in Vietnam higher among men and lower among women, so that the combined prevalence of 23.8% underestimates smoking prevalence among men. This is of interest later because, although the interview collected data on gender, the proportion of men and women in the sample is not reported in Table 2, so the proportion of men and women in the study sample is not given in the paper.
Response: We had added the data for male (47.4%) and female smokers (1.4%) in Vietnam (2010) in the introduction. The table 2 is not mentioned gender because 100% of respondents were men.

4. The Methods say that "having an adequate number of MMT patients" was a criterion for inclusion of a clinic in the study. How many MMT cases did a clinic need to have to be considered for inclusion?
Response: This criterion ensures that all MMT clinics were selected at the similar size with at least 150 current patients. We have added in the manuscript

5. The primary outcome is given as smoking status, and in the multivariate logistic regression I assume that the outcome was current smoker (yes/no). If so, then I think that the bivariate comparisons given in Table 2 should also use the dichotomous outcome (current smoker Y/N) rather than the categorical outcome (never, current, former smoker). As mentioned above, please report gender in Table 2, unless all participants were men.
Response: We have revised the binary comparison of outcome variable (current smoking Y/N). Noted that all respondents were men.

6. Please not an error in the text and table concerning "currently perceived morbidity problem." If this is taken from the EQ-5D measure, then it may refer to "mobility" rather than "morbidity."
Response: We had fixed errors in the manuscript

7. Please state whether analyses reported in Table 4 controlled for nesting of participants within each of the 5 clinic sites. If these analyses did not control for nesting, then I believe they should do so.
Response: We did control for nesting of 5 clinic sites and stated in the method (Statistical analysis).

8. The Discussion says "we observed the difficulty of accessing smoking cessation support among MMT patients…" However this issue is not mentioned in the Introduction, no measure of smoking cessation is reported in the Methods section, and no data concerning such observations are registered in the Results section. So this specific observation seems not to be supported by data given in the paper, or at least it is not a study finding. Simplest may be to just remove this sentence.
Response: We have removed this sentence.

9. The paper sometimes refers to findings as "associations," but sometimes uses more causal language such as "we observed a dramatic increase in FTND score in the first 5 months…" As this was a cross-sectional study it seems better to refer to an association rather than an increase.
Response: We have revised the sentence

Reviewer #2:
1. Measures and instruments / Smoking related variables: this section introduces 3 groups: current smokers, former smokers, never smokers. According to the definition given a person that started smoking just now (less than 100 cigarettes in his life, but currently smoking) would not fit to any of the 3 categories. But in the end this is a sophisticated categorization that is not applied in the analysis. In table 3 current and former smokers are lumped together (although I am not sure if Fagerstrom score makes sense in former smokers) and from table 2 I understand that differences between the groups mostly concern the never smokers. But in the regression analysis (table 4) current smokers are compared to the other two groups. What was the aim of the study originally? Did the authors set out to study factors increasing current or ever smoking?
Response: We have revised the data with consistent of outcome variable (current smoking: Y/N). For those participants who smoked less than 100 cigarettes in their lifetime but currently smoking, we classified them into non-smoking group according to the definition of CDC. In this study, we applied FTND for current smokers only. We have clarified in the method section.

2. Does this question even make sense / is the hypothesis biologically plausible: When you study the OR for smoking (and for nicotine addiction) by methadone use you would insinuate that methadone

(or heroin) caused smoking. But smoking on average started earlier (around age 17) than heroin use (around age 25). How then can methadone treatment explain the high smoking rate (Discussion: "This result can be explained by the interaction between nicotine and methadone, that smoking eases the craving for heroin and cocaine consumption [15]." Do the authors believe the smokers started smoking at the age of 17 because they knew they would become heroin addicts later and would need nicotine to ease their craving?

Response: Thank you very much for your comment and we totally agreed with you that we were not in the position to conclude about the causal pathway between nicotine dependence and methadone treatment. This is also the shortcoming of this study and we would like to clarify it in the Discussion. In this case, we did not conclude that methadone caused smoking since OR only allowed to state the association, not the causal relation. We agree that patients tended to begin smoking earlier than using opioid. However, literature showed that methadone treatment reinforced the effects of nicotine, which resulted in the difficulty in quitting smoking among participants. Thus, smoking rate remains high among MMT patients.

3. The curves (figure 1) are correctly produced regarding technical / statistical procedure. But the biological interpretation is more than brave! "We found that the smoking rates increased gradually in the first 30 months (but not significantly), and remarkably decrease afterwards. We suppose that in the initial stage of treatment, smoking helped patients to counter the aftertaste of MMT and improved the pleasing effect [57]." (etc.) This is likely an over-interpretation of a (non-significant) finding that would not have been visible in another (linear) model.

Response: We agree that the linear correlation between smoking and MMT duration might not be statistically significant but the difference we observed indicated some changes that might be clinically important. Because It is not linear correlation, we used the non-linear curve in the figure 1 to better describe the relation between length of MMT treatment and level of nicotine dependence. From the graph, we can see the relation between nicotine dependence and MMT duration, which might suggest the sensitive stage of behavioral change.

4. Generally speaking every former smoker must have been a current smoker earlier. Therefore in any survey you would expect to find former smokers to be on average older than current smokers. The same would hold for current smokers versus never smokers, if your survey targeted the whole population. But if smoking initiation generally occurs in adolescence and if your survey population is adults you would not expect a difference in average age between smokers and non-smokers if smoking rates are stable. In this study never smokers were on average older. This indicates that in that population smoking rates increased recently. So when the older people were adolescent (when most smokers are recruited) smoking was still less common. I believe this is not only true for MMT persons, but for Vietnam people in general. There might also be a general difference between urban and rural living area and between socio-economic statuses. These differences are not specific for injection drug users and are not even caused by some biological mechanisms. The main reason is marketing policy of tobacco industries: When they come to a country they first target the better of urban population and advertise their product as signifying a modern western life style. Only later the vice spreads to other groups and later on, when administration and the general public gets increasingly aware of the bad side effects of smoking, the smoking rates get higher in less educated people. I do not understand the added value of studying these general associations in such a special subgroup. I simply do not see the added value for the treatment of MMT patients: "Therefore, these relationships during the course of MMT are clinically important that should be carefully monitored and controlled, which could help to identify who may need to receive specific cessation interventions at MMT sites." Do the authors think that only some smokers should be offered cessation intervention? Those that also drink, or those that abstain from risky drinking? Multi-substance abuse might represent a special trait and it might need special treatment. But showing that such a trait (drug injection and drinking) also is associated with greater nicotine addiction is neither surprising nor does it help with any therapy decision for the individual smoker!

We have seen that never smokers tend to be older. I also argued that this seems to be a general phenomenon when smoking rates are increasing. When initiation age of smoking is rather constant (which it appears to be), then older people are smoking for a longer period of time, have also a longer history of heroin abuse, and eventually also a longer history of methadone therapy. If this is true (I find it highly plausible), then any association between smoking risk and MMT duration etc. is simply a natural function of age.

Response: Thank you very much for your comments. We totally agree with you that age as well as other socio-economic factors are important predictors for the smoking habit. Therefore, in our multivariate models, we included age variables (age of patient, age at smoking initiation, age of drug use, age of drug injection) and other socio-economic factors in order to adjust the confounding effects and identify other factors that might be clinically associated with current smoking. These factors will be used to individualized the intervention messages for MMT patients in further studies.

The added value of this study is not only the importance of providing smoking cessation services for methadone maintenance patients, but also the importance of understanding that patients on longer duration of MMT might have lower nicotine dependence. We would like to emphasize this point in the context of expanding MMT services in large injection-driven HIV epidemics like Vietnam. Ideally, the comprehensive intervention packages for this group should include behavioral interventions for substance abuse. However, this part is missing or has not been well implemented or follow-up. In addition, one might think that MMT patients may take cigarettes since they are craving and this is somehow neglected as smoking is quite popular among general population. We have shown that this might not be the case, and the reduced nicotine dependence can be an indication of other substance abuse over the course of MMT. Overall, this suggests follow-up behavioral interventions for MMT patients to improve patients compliance and outcomes of MMT services.

Internationally, we found that smoking cessation intervention depends on patient group and contextualized factors. There are many widely used theories applied for smoking cessation intervention, such as behavioral theory (e.g. Health Belief Model, Social Cognitive Theory, and the Trans-theoretical Model of Health Behavior Change) or pharmacotherapies (nicotine replacement therapies - NRT). We need to identify characteristics and factors of each target group for tailored cessation intervention. Our study indicated that MMT patients with other substance abuse were the prior group for specific quitting smoking strategy to sustain methadone treatment adherence. In general population, the smoking rate is much lower than in the MMT population. They do need smoking cessation for general smokers such as quitline, school-based cessation or m-health…but our study suggest that the clinical doctors should consider when and who should be provide smoking cessation first.

5. One last remark regarding the statistics, but I assume this is a typing error only: Table 4 depicts p<0.05 according to the foot-note with ** and p<0.01 with *. The latter must be wrong because all confidence ranges that are indicated with one * include the null (Coefficient) or 1 (OR). Therefore p must be larger than 0.05. Maybe on * indicates a "trend" (p<0.1)?
Response: We had fixed errors in the manuscript (* indicates p<0.1).

REVIEWER	Joseph Guydish University of California, San Francisco, USA
REVIEW RETURNED	23-May-2017

| GENERAL COMMENTS | This paper reports on smoking status and Fagerstrom Nicotine Dependence (FTND) scores, and factors associated with these measures, in a sample of 1,016 persons recruited from methadone maintenance treatment (MMT) clinics in Northern Vietnam. Findings are that smoking prevalence is high among persons in MMT, and that being on MMT longer and being HIV positive were both associated with lower likelihood of smoking. The revision has addressed most concerns raised on the prior review.

1. The Measures subheading called "Smoking related variables" offers that the primary outcome was smoking status, categorized into current, former and never smokers. The first paragraph of "Statistical Analysis" also says "regarding smoking status (never, former, and current smokers.)" However Table 1 provides columns only for Current Smokers (Yes/no). So I think the primary outcome should be described as current smoking (y/n) with explanation that the No category collapses both former and never smokers. I believe this was raised on prior review, but the methods still appear out of step with the results reported.

2. The narrative reporting on Table 2 may contain multiple minor errors. The narrative says "average monthly income was …" while the table reports "Annual income…" The narrative says average length of MMT as 16.5 months (SD = 11.1), while the Table gives SD = 11.0. The percentage of non-smokers is 12.5% in the narrative and 12.8% in the "No" column of the table.

3. The Discussion states that the smoking rate among MMT patients was "nearly 90%." This is non-conservative because it overstates the observed smoking prevalence (87.2%) as "nearly 90%". If the goal is to round, then rounding down to 85% is closer than is rounding up to 90%. So I think the best strategy here is just to say the observed rate was 87.2%.

4. The same sentence suggests that the smoking rate observed (87.2%) is "three times higher than that of the Vietnamese general population (23.8%)." Smoking prevalence is quite different among men and women in Vietnam. If the smoking prevalence in this all-male sample is compared to smoking prevalence among Vietnamese men, then the comparison is 87.2% (sample) vs. 47.4% (Vietnamese men). The difference is 2 times higher, and not times higher. This initial paragraph overstates both the prevalence of smoking in the sample and how much this differs from the general population.

5. The first paragraph of the Discussion also offers that "This result might be explained by the interaction between nicotine and methadone…" This explanation ignores the relationship between smoking and opiate use, which almost certainly predates the association between smoking and methadone use. The paragraph seems to say that some relationship between smoking and methadone is responsible for high rates of smoking in the sample. The observed relationship is driven by the relationship between |

	opiate use and smoking (smoking rates are very high among opiate users or at least among those entering drug abuse treatment). There may be some additional relationship with methadone, but the fundamental relationship is between smoking and opiate use.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1:

1. The Measures subheading called "Smoking related variables" offers that the primary outcome was smoking status, categorized into current, former and never smokers. The first paragraph of "Statistical Analysis" also says "regarding smoking status (never, former, and current smokers.)" However Table 1 provides columns only for Current Smokers (Yes/no). So I think the primary outcome should be described as current smoking (y/n) with explanation that the No category collapses both former and never smokers. I believe this was raised on prior review, but the methods still appear out of step with the results reported.
Response: We have revised the Statistical Analysis in the manuscript.

2. The narrative reporting on Table 2 may contain multiple minor errors. The narrative says "average monthly income was …" while the table reports "Annual income…" The narrative says average length of MMT as 16.5 months (SD = 11.1), while the Table gives SD = 11.0. The percentage of non-smokers is 12.5% in the narrative and 12.8% in the "No" column of the table
Response: We have revised Table 2 and the narrative reporting ("monthly" instead of "annual", "11.0" instead of "11.1" and "12.8%" for "12.5%")

3. The Discussion states that the smoking rate among MMT patients was "nearly 90%." This is non-conservative because it overstates the observed smoking prevalence (87.2%) as "nearly 90%". If the goal is to round, then rounding down to 85% is closer than is rounding up to 90%. So I think the best strategy here is just to say the observed rate was 87.2%.
Response: We have revised the discussion, particularly in the first paragraph.

4. The same sentence suggests that the smoking rate observed (87.2%) is "three times higher than that of the Vietnamese general population (23.8%)." Smoking prevalence is quite different among men and women in Vietnam. If the smoking prevalence in this all-male sample is compared to smoking prevalence among Vietnamese men, then the comparison is 87.2% (sample) vs. 47.4% (Vietnamese men). The difference is 2 times higher, and not times higher. This initial paragraph overstates both the prevalence of smoking in the sample and how much this differs from the general population.

Response: Thank you for your comments. We agree that smoking prevalence is different among men (47.4%) and women (1.4%) in the Vietnamese general population. The MMT patient are a special sub-population. Most participants in our sample were male (98%) and only 13 respondents were female. This reflects the gender ratio in the utilization of MMT in the two provinces, as our response rate is very high. Only 10 female patients were smokers. This is why we do not discuss female smokers in the paper. However, after considering your advice, we have revised Table 2 with the smoking prevalence for men (87.3%) and women (76.9%) and show that it is not significantly different (p=0.26). This unexpected finding is likely due to low statistical power for the comparison between genders.

5. The first paragraph of the Discussion also offers that "This result might be explained by the interaction between nicotine and methadone…" This explanation ignores the relationship between smoking and opiate use, which almost certainly predates the association between smoking and

methadone use. The paragraph seems to say that some relationship between smoking and methadone is responsible for high rates of smoking in the sample. The observed relationship is driven by the relationship between opiate use and smoking (smoking rates are very high among opiate users or at least among those entering drug abuse treatment). There may be some additional relationship with methadone, but the fundamental relationship is between smoking and opiate use.

Response: Thank you for these comments. We have revised this paragraph with additional sentences on the relationship between smoking, opiate use and methadone.