

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Tobacco stained fingers: a clue for smoking related disease or harmful alcohol use? A case-control study.
AUTHORS	John, Gregor; Pasche, Séphora; Rothen, Nicole; Charmoy, Alexia; Delhumeau-Cartier, Cecile; Genne, Daniel

VERSION 1 - REVIEW

REVIEWER	Lina Zgaga Associate Professor in Epidemiology Trinity College Dublin Ireland
REVIEW RETURNED	26-Jun-2013

RESULTS & CONCLUSIONS	Conclusions are generally a bit overstated, it would be better to keep them closer to study findings (eg. "study suggests a link between this tar-stained fingers and addictive behavior or concomitant high alcohol consumption"
GENERAL COMMENTS	<p>In abstract:</p> <ol style="list-style-type: none"> 1. Conclusion is vague and needs to be modified, maintaining the focus on the study findings. 2. Giving OR and 95% CI for non-significant results in Abstract/Results is unnecessary; other more meaningful results could be presented instead. 3. Abstract/Objective: objective was to investigate association between tobacco stains and: (1) tobacco related disease and (2) behavioral and environmental characteristics. Currently objective 2 suggests only harmful alcohol use (" or of harmful alcohol use, independent ...") so this should be expanded to clarify to the reader what was the scope of the study. <p>Article summary</p> <ol style="list-style-type: none"> 1. First key message is unclear -- should be rephrased so that it is informative even for a reader who did not read the whole paper 2. Additional limitation is that study only includes only hospital population. <p>Introduction</p> <ol style="list-style-type: none"> 1. Paragraph 2, line 9: "...and is a reliable marker of concurrent disease" -- not clear <p>Methods</p> <ol style="list-style-type: none"> 1. Give full name for DSM-IV criteria 2. Details on occupation were collected, but this variable was not used in the present analysis (other than unemployment)? 3. power is calculated for 50 case-control pairs, but 49 were used in the analysis. This should be commented on. <p>Discussion</p>

	<p>1. clarify what does "A tar stained finger gives clue for a tobacco related conditions four times out of five" mean.</p> <p>2. lack of an association with other investigated tobacco related illnesses could arise from insufficient power of the study</p> <p>3. To address - Could peripheral circulation affect tar deposition or removal, or rate of skin cell regeneration?</p> <p>4. At its current form conclusion that "yellow staining is rather a proxy of the consequences of tobacco: its presence in itself seems to identify high/risk smokers due to the tobacco exposure, rather than a specific increased susceptibility" is overstating the results. Either explain better or keep conclusions closer to results.</p> <p>Results show association to PAD -- avoid generalization to association with tobacco related illnesses as only PAD was significant</p> <p>Table 4. It seems 50% of cases have harmful alcohol use and 67% are on psychotropic medication. Are these overlapping? Since association between harmful alcohol use is one of the main take home messages of the study, maybe additional analyses could clarify the associations.</p>
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REVIEWER	Mark Gold, MD Distinguished Professor & Chairman University of Florida College of Medicine Gainesville, FL USA
REVIEW RETURNED	13-Jul-2013

- The reviewer completed the checklist but made no further comments.

VERSION 1 – AUTHOR RESPONSE

Referee 1:

We thank referee 1 for her attentive lecture of our manuscript.

- "Conclusions are generally a bit overstated, it would be better to keep them closer to study findings (eg. "study suggests a link between this tar-stained fingers and addictive behavior or concomitant high alcohol consumption")"

We agree that we used a rhetoric style to enhance the study conclusions, mainly in the discussion section. We therefore decided to change abstract (as suggested) and most of the discussion section. We try to state clearly which sentences reflect our ideas and reduce the deductions.

In abstract:

- "Conclusion is vague and needs to be modified, maintaining the focus on the study findings."

We changed the conclusion in the abstract to better fit the results observed and to do minimal hypothesis.

- "Giving OR and 95% CI for non-significant results in Abstract/Results is unnecessary; other more

meaningful results could be presented instead.”
We took out the non-significant results.

- “Abstract/Objective: objective was to investigate association between tobacco stains and: (1) tobacco related disease and (2) behavioral and environmental characteristics. Currently objective 2 suggests only harmful alcohol use (“, or of harmful alcohol use, independent ...”) so this should be expanded to clarify to the reader what was the scope of the study.”
We totally agree and change the objective of the abstract to fit the objectives stated in the introduction session (main manuscript). The initial formulation in the abstract was chosen because it was shorter, but it doesn’t show the complete scope of the study.

In article summary:

- “First key message is unclear -- should be rephrased so that it is informative even for a reader who did not read the whole paper.”
We changed the first key message to explain what we consider to be tobacco related disease and expressed in percent the proportion of cases with those diseases.

- “Additional limitation is that study only includes only hospital population”
This limitation was added in this section.

In the introduction section

- “Paragraph 2, line 9: “...and is a reliable marker of concurrent disease” -- not clear.”
First description of this sign was done in a confuse patient presenting a stroke. Knowing the speed of nail growth, the delimitation between stained nail and newly growing part could estimate the onset of neurologic deficit. We changed the sentence for “The latter is seen after an acute illness that causes cessation of cigarette consumption resulting in a bi-colour nail (the distal end is cigarette stained contrasting the newly growing proximal part)”.

In the method section

- “Give full name for DSM-IV criteria.”
It has been added.

- “Details on occupation were collected, but this variable was not used in the present analysis (other than unemployment)?”
We did collect information on occupation and resumed them according to the National Statistics Socio-Economic Classification six-class version. However the number of participants in each category was small. We choose not to show those results and to use only the binary variable (unemployment) in the analyses.

- “Power is calculated for 50 case-control pairs, but 49 were used in the analysis. This should be commented on. ”
The matching was difficult, especially for young smokers with heavy cigarette consumption, for whom it was not possible to find control without stain. Of the 63 patients evaluated that presented one or more tar staining on the hand, 9 refused to participate and five could not be matched, resulting into 49 cases. We agree that this is affecting the statistic power. However the power size calculation was

done with the hypothetically Odd ratio of 3. The main result (any tobacco related disease) had OR of 1.3, 30% discordant pairs. The sample size that would be needed to explore a statistical significance of that magnitude would be 1530 participants. Similarly, the highest secondary result (BPCO) had an OR of 2.2, and also 30% of discordant pairs, requiring 187 participants. We added a note in the weakness section of the article, adjacent to the sample size considerations.

In the discussion section

- "Clarify what does "A tar stained finger gives clue for a tobacco related conditions four times out of five" mean."

The sentence has been changed to be more understandable.

- "lack of an association with other investigated tobacco related illnesses could arise from insufficient power of the study"

This sentence has been added in the article.

- "To address - Could peripheral circulation affect tar deposition or removal, or rate of skin cell regeneration?"

We are grateful for this suggestion and we added a new paragraph to expose those possible explanations for tar stained in heavy smokers (paragraph 2)

- "At its current form conclusion that "yellow staining is rather a proxy of the consequences of tobacco: its presence in itself seems to identify high/risk smokers due to the tobacco exposure, rather than a specific increased susceptibility" is overstating the results. Either explain better or keep conclusions closer to results."

We agree that it could be misleading. We changed to make the sentence clearer, and to state that it is an opinion.

- "Results show association to PAD -- avoid generalization to association with tobacco related illnesses as only PAD was significant."

Association with PAD is considered in the new second paragraph

- "Table 4. It seems 50% of cases have harmful alcohol use and 67% are on psychotropic medication. Are these overlapping? Since association between harmful alcohol use is one of the main take home messages of the study, maybe additional analyses could clarify the associations."

We are grateful for this observation. 26/35 (74%) of alcoholic patients are taking medication against only 27/63 (43%, $p = 0.003$). In fact alcohol consumption is linked to psychotropic medication use. Most of the in hospital patients known to have risky alcohol intake, are receiving benzodiazepine to prevent delirium tremens (depending on CIWA score). Furthermore, alcohol is linked to depressive mood and behaviour disorders. In the other side, substance dependence is a known complication of many psychiatric conditions. We could only use few variables to construct the final model, because of the number of case-control pairs. We choose to show harmful alcohol use in the final model, because it was the most strongly associated, and many medication "used" were those prescribed in the hospital (unlikely to be anterior of the stain development). We did a conditional logistic regression with the two variable to test the interaction: there was no interaction.

. xi: clogit cas antidepbenzoneuroepi OH_etude i.OH_etude*i.antidepbenzoneuroepi , group(paire)or
i.OH_etude _IOH_etude_0-1 (naturally coded; _IOH_etude_0 omitted)

i.antidepbenz~i _lantidepbe_0-1 (naturally coded; _lantidepbe_0 omitted)

i.OH_~e*i.a~b~i _IOH_Xant_#_# (coded as above)

note: _IOH_etude_1 omitted because of collinearity

note: _lantidepbe_1 omitted because of collinearity
 Iteration 0: log likelihood = -28.226258
 Iteration 1: log likelihood = -28.15896
 Iteration 2: log likelihood = -28.158701
 Iteration 3: log likelihood = -28.158701
 Conditional (fixed-effects) logistic regression Number of obs = 98
 LR chi2(3) = 11.61
 Prob > chi2 = 0.0088
 Log likelihood = -28.158701 Pseudo R2 = 0.1709

cas	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
antidepbenzoneuroepi	1.875208	1.037426	1.14	0.256	.6340704 5.545768
OH_etude	2.667003	2.14995	1.22	0.224	.5493448 12.94798
_IOH_etude_1	1				(omitted)
_lantidepbe_1	1				(omitted)
_IOH_Xant_1_1	1.216294	1.319606	0.18	0.857	.1450563 10.1986

Referee 2:

We thank the referee for his agreement.

We are looking forward to hearing from you in the near future and thank you for considering our manuscript for publication.