

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	An investigation on the use of snus and its association to respiratory and sleep related symptoms: A cross sectional population study.
AUTHORS	Gudnadóttir, Arna Yr; Olafsdottir, Inga Sif; Middelveld, Roelinde; Ekerljung, Linda; Forsberg, Bertil; Franklin, Karl; Lindberg, Eva; Janson, Christer

VERSION 1 - REVIEW

REVIEWER	Karl Erik Lund Norwegian Public Health Institute
REVIEW RETURNED	04-Jan-2017

GENERAL COMMENTS	<p>This manuscript address the association between the use of snus and respiratory and sleep related symptoms. With a large study population, the authors are able to investigate these associations in subgroups of tobacco users, such as never-smokers who currently and formerly have used snus. As far as I know, this has not been studied before which then provide the paper with novelty. The data is self-reported (not validated by bio-markers) and the study is cross-sectional, which means that the authors should be very careful to use any language implying causality. However the title of the study gives an impression that this is a study with ambitions of causality "Snus has an adverse impact on asthma, respiratory symptoms and snoring". This must be changed</p> <p>The associations are adjusted for some important confounders (BMI, age, sex, education, physical activity), but the questionnaire did not address the probably most important confounder – alcohol use. A lot of studies have reported increased alcohol intake by snus users compared to non-users of tobacco and also compared to cigarette smokers. In a revised version, I suggest the authors should dig into this literature (snus use and alcohol) and then perhaps come up with a more thorough discussion regarding the confounding issue and a more modest conclusion. However, the authors discuss some possible bio-physiological mechanisms that might explain the associations. This reviewer is in no position to assess whether these are plausible or not.</p> <p>Some minor things. In the introduction, the authors claim: "Compared with smoking, it has been suggested that the addiction to snus use is stronger, due to a lower cessation rate and reports of greater experience of nicotine dependence". This a highly debatable topic, and not consistent with other nicotine product-specific assessments of dependence that take into consideration mode of use, sensory stimulation, duration of use, speed of uptake, absorption of nicotine, difficulty quitting and social elements (see Fagerström and Eissenberg 2012 for a revision of the literature). Towards the end, the authors become activists when discussing</p>
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	(turning down) the role of snus in smoking cessation. This fine paper would benefit from not entering into this discussion. They also have to take into consideration that snus also seem to appeal to a segment of (hardcore) smokers without any strong intentions to quit smoking, becomes an alternative and harm-reducing device for nicotine uptake for these persons and eventually leads to 'accidental quitting'. It's not all negative.
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REVIEWER	Julian Crane University of Otago New Zealand
REVIEW RETURNED	06-Jan-2017

GENERAL COMMENTS	<p>This is an interesting study suggesting that oral snus may be associated with obstructive respiratory tract symptoms and sleep disorders. The data comes from a postal questionnaire used in Sweden as part of the global allergy and asthma European network. Use of snus is largely restricted in many countries and is most prominently used in Scandinavia. The manuscript is well written and clearly sets out what has been done and what has been found.</p> <p>The large dataset has allowed the authors to explore snus associations with asthma symptoms independent of previous tobacco smoking which of course would be the obvious confounding factor. However, I'm not quite as convinced as the authors. The definition of current asthma is rather odd being either an attack or medication use in the last 12 months. I wonder if things would change if they used other definitions such as a doctor's diagnosis plus wheezing symptoms or medication use in the last 12 months. Presumably given that this was an asthma and allergy study they would have this information and could look at it. Asthma appears to be associated with snus users but not smokers or dual users, which is quite difficult to explain.</p> <p>The response rate to the questionnaire is low and this always raises the issue, as the authors suggest, of how representative the respondents are of the population. It would have been quite useful to see the unadjusted values as well as the adjusted and this might be included in a supplementary table.</p> <p>The authors do not control for passive smoking amongst non-smoking snus users and this is likely to be quite high, and should at least be discussed. It is also presumably possible that never smoking snus users may partially represent a group who were unable to tolerate smoking, possibly because of sensitive airways and a prior history of asthma and thus opted to use snus alone. This would be impossible to unravel unless they have data on asthma prior to any tobacco use, again this might usefully be discussed.</p> <p>The authors mention a follow-up study on page 17 but following up this population is not going to provide robust evidence of causality. This would require either a very large cohort study or a randomised trial and neither seem very likely. The authors do not speculate on possible causal mechanisms for their results. This might lead to alternative ways to explore the possible airway effects especially given that the effects seem to require current snus use. For example acute effects of snus on FeNO, airway hyperresponsiveness, sputum cellularity and cough reflex. Nicotine is certainly aversive to</p>
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	<p>the airway. Does snus make pre-existing asthma worse?</p> <p>Minor issues include no bolding in table 4 at least in my copy, some rather odd language that could be tightened up on page 15 such as "retrograde effect on asthma" and "distracting agents"..... I am not sure what these mean and they should be more clearly explained.</p> <p>In general I think this is an interesting paper but the authors might be more cautious in their interpretation and discuss the alternative non-causal possibilities in more detail</p>
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REVIEWER	Dr John Burgess Allergy and Lung Health Unit School of Population and Global Health The University of Melbourne
REVIEW RETURNED	16-Jan-2017

GENERAL COMMENTS	<p>General comments-</p> <p>The authors have used data from the GA2LEN study to examine the association between snus use and asthma and asthma symptoms and some sleep symptoms. The authors report an association between snus use and asthma in both smokers and non-smokers as well as an association between snus use and asthmatic symptoms and between snus use and bronchitis, rhino-sinusitis and some sleep related symptoms. This is an interesting subject area which has not been studied previously to any degree. it is important in that snus has been promoted as an alternative to tobacco smoking in relation to the well known harmful effects of the latter. Any additional information on possible harms from snus use are welcome.</p> <p>Specific comments-</p> <p>(1) This is an observational study and like most such studies, is plagued by possible unmeasured confounding and reverse causation, particularly the latter. The authors do not specifically comment on the former in their discussion and I think this should be at least mentioned. The issue of reverse causation has been addressed albeit briefly in the discussion (page 15, lines 35-40) and without actually using this term. This issue could be addressed if the authors used information on age at onset of asthma and age when snus was first used if these are available. If it were shown that snus use began before asthma started then reverse causation is ruled out.</p> <p>(2) The analysis included several potential confounders amongst which was "centre". Was "centre" simply included in the multivariate model as another covariate or was a mixed model used with "centre" as a random effect?</p> <p>(3) A large number of comparisons has been done and no mention is made of adjusting for multiple comparisons in the analysis. Was this considered?</p> <p>(4) In the discussion (page 15), the authors have used two terms that I do not understand- "retrograde effects" (line 29) and "distracting agent". Could alternative terms be used?</p> <p>(5) Page 15 (lines 40-44) offers an attempt at an explanation for the mechanism that could explain the association between snus use and asthma but the suggested mechanism is vague and lacks biological plausibility. Could the authors offer a more detailed explanation of possible mechanisms to account for the observed association drawing on any known biological effect of snus on airway function?</p> <p>(6) Page 5, definition of chronic rhino-sinusitis, the authors have</p>
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	used the term "discoloured snot". Most native English speakers would be a bit taken aback by the term "snot". Could I suggest that the word be changed to "nasal secretions"?
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Karl Erik Lund

Institution and Country: Norwegian Public Health Institute, Norway Competing Interests: None

This manuscript address the association between the use of snus and respiratory and sleep related symptoms. With a large study population, the authors are able to investigate these associations in subgroups of tobacco users, such as never-smokers who currently and formerly have used snus. As far as I know, this has not been studied before which then provide the paper with novelty. The data is self-reported (not validated by bio-markers) and the study is cross-sectional, which means that the authors should be very careful to use any language implying causality. However the title of the study gives an impression that this is a study with ambitions of causality "Snus has an adverse impact on asthma, respiratory symptoms and snoring". This must be changed

A: The title has now been changed (see above)

The associations are adjusted for some important confounders (BMI, age, sex, education, physical activity), but the questionnaire did not address the probably most important confounder – alcohol use. A lot of studies have reported increased alcohol intake by snus users compared to non-users of tobacco and also compared to cigarette smokers. In a revised version, I suggest the authors should dig into this literature (snus use and alcohol) and then perhaps come up with a more thorough discussion regarding the confounding issue and a more modest conclusion. However, the authors discuss some possible bio-physiological mechanisms that might explain the associations. This reviewer is in no position to assess whether these are plausible or not.

A: We agree that not having data on alcohol use is a drawback. We have now expanded the discussion on this limitation in the discussion. We also suggest that part of the association between snoring and snus could be associated with alcohol use (page 17, para 2).

Some minor things. In the introduction, the authors claim: "Compared with smoking, it has been suggested that the addiction to snus use is stronger, due to a lower cessation rate and reports of greater experience of nicotine dependence". This a highly debatable topic, and not consistent with other nicotine product-specific assessments of dependence that take into consideration mode of use, sensory stimulation, duration of use, speed of uptake, absorption of nicotine, difficulty quitting and social elements (see Fagerström and Eissenberg 2012 for a revision of the literature).

Towards the end, the authors become activists when discussing (turning down) the role of snus in smoking cessation. This fine paper would benefit from not entering into this discussion. They also have to take into consideration that snus also seem to appeal to a segment of (hardcore) smokers without any strong intentions to quit smoking, becomes an alternative and harm-reducing device for nicotine uptake for these persons and eventually leads to 'accidental quitting'. It's not all negative.

A: We have modified the text according to these suggestions and also included the suggested reference (page 3, para 1).

Reviewer: 2

Reviewer Name: Julian Crane

Institution and Country: University of Otago, New Zealand Competing Interests: None

This is an interesting study suggesting that oral snus may be associated with obstructive respiratory tract symptoms and sleep disorders. The data comes from a postal questionnaire used in Sweden as part of the global allergy and asthma European network. Use of snus is largely restricted in many countries and is most prominently used in Scandinavia. The manuscript is well written and clearly sets out what has been done and what has been found.

The large dataset has allowed the authors to explore snus associations with asthma symptoms independent of previous tobacco smoking which of course would be the obvious confounding factor. However, I'm not quite as convinced as the authors. The definition of current asthma is rather odd being either an attack or medication use in the last 12 months. I wonder if things would change if they used other definitions such as a doctor's diagnosis plus wheezing symptoms or medication use in the last 12 months. Presumably given that this was an asthma and allergy study they would have this information and could look at it. Asthma appears to be associated with snus users but not smokers or dual users, which is quite difficult to explain.

A: This is a good idea. Unfortunately, there was no question included on doctor's diagnosed asthma, but we have asked the participants the question: Have you ever had asthma? If we combine a positive answer to this question and the question on wheeze we find a prevalence of 9.9% in those in snus users and 6.6% in the non-snus users when limiting the analysis to never-smokers. The corresponding adjusted OR (95% CI) is 1.45 (1.17-1.80). This is very similar to what we report in table 4.

The response rate to the questionnaire is low and this always raises the issue, as the authors suggest, of how representative the respondents are of the population. It would have been quite useful to see the unadjusted values as well as the adjusted and this might be included in a supplementary table.

A: Yes we agree that the response rate is a problem. We have now added a supplementary table on the unadjusted values presented in table 2 – table S1

The authors do not control for passive smoking amongst non-smoking snus users and this is likely to be quite high, and should at least be discussed. It is also presumably possible that never smoking snus users may partially represent a group who were unable to tolerate smoking, possibly because of sensitive airways and a prior history of asthma and thus opted to use snus alone. This would be impossible to unravel unless they have data on asthma prior to any tobacco use, again this might usefully be discussed.

A: We know from previous studies that the prevalence of passive smoking is very low in Sweden (<10%) Janson C et al Eur Respir J 2006; 27: 517–524, so we do not think that this has influenced our results (page 17, para 2). In order to investigate the possible effect of childhood asthma we made a sensitivity analyses where we excluded those that reported having asthma that started before they were teenagers (page 5, para 2). This exclusion had a fairly limited effect on our results (page 11, para 1)

The authors mention a follow-up study on page 17 but following up this population is not going to provide robust evidence of causality. This would require either a very large cohort study or a randomised trial and neither seem very likely.

A: We agree and have modified this sentence (page 17, para 2)

The authors do not speculate on possible causal mechanisms for their results. This might lead to alternative ways to explore the possible airway effects especially given that the effects seem to require current snus use. For example acute effects of snus on FeNO, airway hyperresponsiveness, sputum cellularity and cough reflex. Nicotine is certainly aversive to the airway. Does snus make pre-existing asthma worse?

A: We have written a short paragraph on possible biological mechanisms (para 16, page 4)

Minor issues include no bolding in table 4 at least in my copy, some rather odd language that could be tightened up on page 15 such as “retrograde effect on asthma” and “distracting agents”..... I am not sure what these mean and they should be more clearly explained.

A: There is bolding in table 4 in the original file

The sentence including retrograde and distracting has been rewritten (page 15 , para 3).

In general I think this is an interesting paper but the authors might be more cautious in their interpretation and discuss the alternative non-causal possibilities in more detail

A: This has been done. See also answers to reviewer 1.

Reviewer: 3

Reviewer Name: Dr John Burgess

Institution and Country: Allergy and Lung Health Unit, School of Population and Global Health, The University of Melbourne, Australia Competing Interests: None declared

General comments-

The authors have used data from the GA2LEN study to examine the association between snus use and asthma and asthma symptoms and some sleep symptoms. The authors report an association between snus use and asthma in both smokers and non-smokers as well as an association between snus use and asthmatic symptoms and between snus use and bronchitis, rhino-sinusitis and some sleep related symptoms. This is an interesting subject area which has not been studied previously to any degree. It is important in that snus has been promoted as an alternative to tobacco smoking in relation to the well known harmful effects of the latter. Any additional information on possible harms from snus use are welcome.

Specific comments-

(1) This is an observational study and like most such studies, is plagued by possible unmeasured confounding and reverse causation, particularly the latter. The authors do not specifically comment on the former in their discussion and I think this should be at least mentioned. The issue of reverse causation has been addressed albeit briefly in the discussion (page 15, lines 35-40) and without actually using this term. This issue could be addressed if the authors used information on age at onset of asthma and age when snus was first used if these are available. If it were shown that snus use began before asthma started then reverse causation is ruled out.

A: We now include the term reversed causation (page 15, para 3).

We have no information on when the subjects started to use snus, but we have now included a sensitivity analysis where we excluded all that had asthma before being teenagers. See also answer to comments from reviewer 2

(2) The analysis included several potential confounders amongst which was "centre". Was "centre" simply included in the multivariate model as another covariate or was a mixed model used with "centre" as a random effect?

A: Yes centre was simply one of the independent variables in the model. We have, however, now included meta analyses to look for centre heterogeneity (Data analysis and results page 11, para 2).

(3) A large number of comparisons has been done and no mention is made of adjusting for multiple comparisons in the analysis. Was this considered?

A: We did not adjust for multiple comparisons as most association were in the same direction and the p-values were usually quite low.

(4) In the discussion (page 15), the authors have used two terms that I do not understand- "retrograde effects" (line 29) and "distracting agent". Could alternative terms be used?

A: Yes this has been done (see also answer to reviewer 2)

(5) Page 15 (lines 40-44) offers an attempt at an explanation for the mechanism that could explain the association between snus use and asthma but the suggested mechanism is vague and lacks biological plausibility. Could the authors offer a more detailed explanation of possible mechanisms to account for the observed association drawing on any known biological effect of snus on airway function?

A: We have added a short paragraph on this (see answer to reviewer 2)

(6) Page 5, definition of chronic rhino-sinusitis, the authors have used the term "discoloured snot". Most native English speakers would be a bit taken aback by the term "snot". Could I suggest that the word be changed to "nasal secretions"?

A: This has been done

Once again many thanks for these valuable comments we look forward hearing from you

VERSION 2 – REVIEW

REVIEWER	Karl Erik Lund Norwegian Institute of Public Health
REVIEW RETURNED	28-Feb-2017

GENERAL COMMENTS	The MS has improved
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REVIEWER	Julian Crane University of Otago New Zealand
REVIEW RETURNED	22-Feb-2017

GENERAL COMMENTS	The authors have appropriately addressed the issues that I raised. In general they have modified some of their statements and usefully expanded on the limitations of the study.
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REVIEWER	John Burgess Allergy and Lung Health Unit, School of Population and Global Health, The University of Melbourne, Australia.
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	The authors have addressed the comments from the reviewers satisfactorily. I have no further comments.
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