PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and associations of behavioral risk factors with blood lipids profile in Lebanese adults: findings from the WHO STEPwise NCD cross-sectional Survey
AUTHORS	Mansour, Megali; Tamim, Hani; Nasreddine, Lara; EL Khoury, Christelle; Hwalla, Nahla; Chaaya, Monique; Farhat, Antoine; Sibai, Abla

VERSION 1 – REVIEW

REVIEWER	Erkki Vartiainen National Institute for Health and Welfare, Finland
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	Alcohol intake is not measured adequately for this type of analyses. BMI is missing from the analyses. You may consider to live out alcohol intake and add BMI. At least you should have BMI as a covariate in the models. Add number of participant in tables 2a and 2b in smoking, physical activity and alcohol intake categories.

REVIEWER	Alan Ducatman WVU School of Public Health, United States
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	Review of bmjopen-2018-026148 entitled "Prevalence and associations of behavioral risk factors with blood lipids profile in Lebanese adults: findings from the WHO STEPwise NCD Survey" for BMJ Open Abstract and overview: The abstract is clearly written, as are associated strengths and limitations. The most important finding (an association of lipids to smoking) does not appear novel, but the data come from a place where there are many barriers to public health research, and it is important to encourage research that articulates whether or not known findings pertain to specific populations. Therefore, publication is encouraged. The methodological approach to alcohol should be justified or altered. Details: Introduction: the list of modifiable risk factors is truncated. The Introduction reasonably mentions modifiable risk factors related to modernization, and then omits diet from the specific list on p5 lines 31-34. Diet should be added to the list. It is understood that diet is not addressed in the paper. This is an introduction, not the methods, and the sentence is about modifiable risk factors. The introduction (or the methods) might include a brief mention of the reasons that diet is not addressed, except as an adjustment for

	caloric intake (which is not even mentioned in the introduction or the abstract). Alternatively, the value of the paper increases if diet can be added as part of the investigation in more detail. Methods: It is usually fine to simply refer to the previously published details of an existing survey dataset, as this study does. However, there is one clarification that should be provided, especially for a survey as small as this one. We learn that 1,331 adults participated in phase 1 of the survey, and that 363 of these agreed to participate in biochemical assessment (27.3% response rate). This response rate should be clearly stated as a per cent. However, we are not provided with data how many were invited to participate in phase 1 (how many accepted and how many refused), so the 27.3% may be inflated and misleading. That should be rectified. The methods do not clearly state that all biological testing is done on fasting samples of some minimum hours of duration. Clarification of this point is essential. The authors should explicitly discuss whether they adjusted for BMI and if not, why that choice was made. Caffeine has known impact on lipids, and there is more to learn. If caffeine data are available, that is an opportunity area. The choice of alcohol consumption as a yes/no dichotomous variable is one way to evaluate the effect alcohol. Most studies take a different approach and evaluate subgroups with different levels of consumption, and there are ample examples of how this is generally done, and there are also many reasons why those who consume a little alcohol such as one glass per week are not like those who consume moderately or heavily . If there is a reason to stratify as yes/no, that reason should be provided. The selection of 1 drink per week as a yes in a dichotomous circumstance creates an investigation that is physiologically limited. (Are there any precedent studies which identify 1 drink per week as physiologically important?) This choice may be based upon a relatively less common consumption of alcohol in a Muslim majority country, but it should either be defended as useful with a citation from strong precedent literature or reconsidered to a more helpful approach. The presence of a marriage variable provides the opportunity to investigate if there is a differential effect of single status vs married. Interesting data on this were found in single and married women (advantage single in Algeria) and married and divorced women (advantage married) in Israel. The data may provide a cultural comparison of the effect of being single on lipids. This is mentioned as an opportunity area, and not a requirement. Similarly, socioeconomic status has been repeatedly shown to relate to lipid levels. Are data on SES available? The survey did obtain biochemical data. Was serum or urine cotinine measured? If so, there is an opportunity for improved reporting. Results: the results that are presented in a reasonable way with one possible exception. Where a relationship is seen, but is not statistically significant, such as (and not limited to) the relationship of cigarette smoking and VLDL, the authors appear to use wording that discounts the relationship at lower dose. More properly, the sample size is the issue. In addition, the results presented are limited by the absence of consideration of potentially influential variables (see methods). In addition, it is reiterated that it is difficult to tell if the alcohol results have meaning since it is not clear how many of those who

	are included as consuming alcohol are really seldom or only occasional drinkers (1 drink/week). The response rate (27.3% or likely much less) should be clarified as the first line in the results. If there are known social differences between those who provided and decided not to provide blood samples, these should be presented briefly. Discussion: The response rate and its relationship to study weakness deserves mention. Either a BMI adjustment is worth doing if needed variables are present (as either result or sensitivity test), or else the evident importance of not doing one should be discussed. The discussion of cigarette smoking is partially misleading as it emphasizes only highest dose in (p11 line 28). The authors show a dose response for VLDL, and the absence of statistical significance appears to reflect sample size. The rest of the discussion of this topic is more reasonable. The discussion of alcohol is not justified. I do not know what the authors expected to see when 1 drink per week is included as part of a dichotomous variable. Whether or not alcohol has benefits at very low exposure levels (most recent literature suggests possibly not, purported benefits are probably confounded by education and other markers of SES and behavior), there is no reason to treat its presence like a cancer or a gunshot wound.

VERSION 1 – AUTHOR RESPONSE

Comments	Reply
Reviewer 1: Erkki Vartiainen National Institute for Health and Welfare, Finland	
Alcohol intake is not measured adequately for this type of analyses. You may consider to live out alcohol intake and add BMI. At least you should have BMI as a covariate in the models. BMI is missing from the analyses.	We thank the reviewer for the comments and feedback. We agree with the reviewer regarding the need to include BMI, as a covariate in the models. We have revised the analyses adjusting for BMI. Results did not change appreciably. For alcohol and based on the second reviewer suggestion regarding the categorization of the exposure, kindly note that we had altered the grouping of alcohol and it is now based on “ever drinking” compared to “never drinking”. With the relatively low levels of alcohol drinking in our context and communities, this categorization is less prone to misclassification error. A positive significant association was observed between ever drinking and LDL-C.

Add number of participants in tables 2a and 2b in smoking, physical activity and alcohol intake categories.	Kindly note that these are listed in table 1. Adding the numbers again in tables 2a and 2b would be redundant.

Reviewer 2: Alan Ducatman WVU School of Public Health, United States	
Abstract and overview: The abstract is clearly written, as are associated strengths and limitations. The most important finding (an association of lipids to smoking) does not appear novel, but the data come from a place where there are many barriers to public health research, and it is important to encourage research that articulates whether or not known findings pertain to specific populations. Therefore, publication is encouraged. The methodological approach to alcohol should be justified or altered.	We thank the reviewer for the thoughtful comments and feedback, these have greatly improved our letter. We also are thankful for the opportunity to revise and resubmit.
Introduction:	
The list of modifiable risk factors is truncated. The Introduction reasonably mentions modifiable risk factors related to modernization, and then omits diet from the specific list on p5 lines 31- 34. Diet should be added to the list. It is understood that diet is not addressed in the paper. This is an introduction, not the methods, and the sentence is about modifiable risk factors. The introduction (or the methods) might include a brief mention of the reasons that diet is not addressed, except as an adjustment for caloric intake (which is not even mentioned in the introduction or the abstract). Alternatively, the value of the paper increases if diet can be added as part of the investigation in more detail.	We agree with the reviewer and have revised the introduction to include reference to dietary habits. Also, in accordance with the suggestions below, we revised the analyses and added dietary intakes as part of the investigation details and considered them as independent variables in the revised analyses. As such, we have assessed the dietary intake of energy, fat, saturated fat, carbohydrates, sugar and protein. A significant association between saturated fat with TC and LDL-C was observed. There were no significant associations with other dietary variables. The manuscript, including abstract, introduction, methods, results and discussion sections were revised accordingly. Furthermore, we took into consideration BMI as a co-variate and adjusted for it. With these additions and changes, we agree with the reviewer that the value of the paper has been enhanced.

Methods	
It is usually fine to simply refer to the previously published details of an existing survey dataset, as this study does. However, there is one clarification that should be provided, especially for a survey as small as this one. We learn that 1,331 adults participated in phase 1 of the survey, and that 363 of these agreed to participate in biochemical assessment (27.3% response rate). This response rate should be clearly stated as a per cent. However, we are not provided with data how many were invited to participate in phase 1 (how many accepted and how many refused), so the 27.3% may be inflated and misleading. That should be rectified.	We agree with the reviewer. We are providing further details on outcome of phase 1 (total number and response rate). Kindly note that our earlier publications using this same data set of the NCD-Risk Factor Survey have addressed the issue of response rates. We provide references to these in the manuscript. We also provided further assessments of the differences between respondents and non-respondents in the discussion section of the manuscript.
The methods do not clearly state that all biological testing is done on fasting samples of some minimum hours of duration. Clarification of this point is essential.	Participants must have been fasting for at least 8 hours. This detail is included in the revised manuscript.
The authors should explicitly discuss whether they adjusted for BMI and if not, why that choice was made.	Thank you for this comment, we agree with the reviewer. We have revised the analyses adjusting for BMI. Results did not change appreciably.
Caffeine has known impact on lipids, and there is more to learn. If caffeine data are available, that is an opportunity area.	We do not have caffeine intake as a variable in our dataset.
The choice of alcohol consumption as a yes/no dichotomous variable is one way to evaluate the effect of alcohol. Most studies take a different approach and evaluate subgroups with different levels of consumption, and there are ample examples of how this is generally done, and there are also many reasons why those who consume a little alcohol such as one glass per week are not like those who consume moderately or heavily. If there is a reason to stratify as yes/no, that reason should be provided. The selection of 1 drink per week as a yes in a dichotomous circumstance creates an investigation that is physiologically limited. (Are there any precedent studies which identify 1 drink per week as physiologically important?) This	We agree with the reviewer that the choice of categories of alcohol consumption varies in the literature and this may affect the findings. The effect of alcohol consumption on the risk of these diseases is complex, as there are beneficial and detrimental effects depending on volume and patterns of alcohol consumption Within our context, alcohol consumption is relatively uncommon compared to western communities. Hence, the categorization of alcohol –related variable was altered. We revised the manuscript opting to categorize the study participants based on “ever drinking” compared to “no drinking”. This categorization is less prone to misclassification error and allows comparison with the international literature. A positive significant association was observed between ever drinking and LDL-C.

choice may be based upon a relatively less common consumption of alcohol in a Muslim majority country, but it should either be defended as useful with a citation from strong precedent literature or reconsidered to a more helpful approach.	
The presence of a marriage variable provides the opportunity to investigate if there is a differential effect of single status vs married. Interesting data on this were found in single and married women (advantage single in Algeria) and married and divorced women (advantage married) in Israel. The data may provide a cultural comparison of the effect of being single on lipids. This is mentioned as an opportunity area, and not a requirement. Similarly, socioeconomic status has been repeatedly shown to relate to lipid levels. Are data on SES available	We thank the reviewer for this comment and for the suggestion to consider social (e.g. marriage) and socioeconomic variables (e.g. education) as other main independent variables. However, we believe that this requires more in-depth and separate analysis. For example, studies have shown that 'relationship quality' rather than marital status per se affects CVD risk factors, and this may be modified by gender. With the addition of dietary habits as suggested by the reviewer, we believe the focus need to remain on behavioral risks including diet, with martial and SES variables considered as control variables.
The survey did obtain biochemical data. Was serum or urine cotinine measured? If so, there is an opportunity for improved reporting.	We did not conduct this assessment and urine cotinine is not available in our dataset.
Results	
The results are presented in a reasonable way with one possible exception. Where a relationship is seen, but is not statistically significant, such as (and not limited to) the relationship of cigarette smoking and VLDL, the authors appear to use wording that discounts the relationship at lower dose. More properly, the sample size is the issue.	We agree with the reviewer; the sample size may have been an issue for the lack of statistical significance. The text has been revised taking into consideration the magnitude of the association, where it exists.
In addition, the results presented are limited by the absence of consideration of potentially influential variables (see methods).	As noted above, BMI was added to the list of confounders and analyses were adjusted for BMI. Also, as mentioned earlier, dietary intakes including total and saturated fat intake, carbohydrates, sugar and protein are considered as other variables of interest and examined as independent variables.
In addition, it is reiterated that it is difficult to tell if the alcohol results have meaning since it is not clear how many of those who are included as consuming alcohol are really seldom or only occasional drinkers (1 drink/week).	Kindly, see our response above regarding alcohol.

The response rate (27.3% or likely much less) should be clarified as the first line in the results. If there are known social differences between those who provided and decided not to provide blood samples, these should be presented briefly. The response rate and its relationship to study weakness deserves mention.	We have added this limitation in the discussions and provided additional data on differences between respondents and non-respondents, as below. The proportion of participants who gave fasting blood samples was relatively small (27.3%); however, theses responders were comparable to non-responders on several socio-demographic characteristics except for marital status (61% of responders vs. 50% of non-responders were married). Also, we had earlier documented comparable dietary data between respondents and non-respondents based on factor loading matrices on patterns of food groups intake [4] . We also mention this issue in the bulleted points under subheading: Strengths and limitations, as below. • Low response rate (27.3%) for those who consented and gave fasting blood samples. Yet, differences between responders and non-responders were not significant on a number of socio-demographic characteristics.
Discussion	
Either a BMI adjustment is worth doing if needed variables are present (as either result or sensitivity test), or else the evident importance of not doing one should be discussed.	We have revised the analyses and adjusted for BMI
The discussion of cigarette smoking is partially misleading as it emphasizes only highest dose in (p11 line 28). The authors show a dose response for VLDL, and the absence of statistical significance appears to reflect sample size. The rest of the discussion of this topic is more reasonable.	Our observation of the largest effect of cigarette smoking on lipid parameters being seen in those who are heavy smokers is consistent with the literature (Chen et al. 2008). Yet we agree with the reviewer, there is a need to put less emphasis on statistical significance and embrace findings showing a positive association at lower levels of statistical significance. As mentioned earlier, the sample size may have been an issue for some categories. We revised the discussion taking into consideration the magnitude of the association, where it exists.
The discussion of alcohol is not justified. I do not know what the authors expected to see when 1 drink per week is included as part of a dichotomous variable. Whether or not alcohol has benefits at very low exposure levels (most recent literature suggests possibly not, purported benefits are probably confounded by education and	We agree with the reviewer. Kindly see our response above in the comment of alcohol.

other markers of SES and behavior), there is no reason to treat its presence like a cancer or a gunshot wound.	

VERSION 2 – REVIEW

REVIEWER	Erkki Vartiainen National Institute for Health and Welfare Finland
REVIEW RETURNED	03-Apr-2019

GENERAL COMMENTS	Authors have done the changes I proposed.

REVIEWER	Alan Ducatman WVU School of Public Health
REVIEW RETURNED	08-Mar-2019

GENERAL COMMENTS	The authors have addressed many of the concerns in the initial review. And, they are correct that there is a need for confirmatory research in the Middle East. And, they have improved upon the understanding of participation rate as requested. This reviewer continues to advocate that the paper deserves a place in the literature. However, a critical recommendation about the weakness of methods concerning alcohol has not been followed, and it is consequential. I The results about alcohol continue to be presented in a misleading and unwarranted way, and that is a concern because the findings are also different than the findings of most studies. What does it mean when a group with "ever alcohol" consumption differs from "never alcohol" consumption in a society when this is a consequential decision about lifestyle? . What does "ever alcohol" (defined in the previous submission as one drink) mean in terms of exposure? The authors hypothesize that there is a genetic susceptabilty locus. While this is possible, and certainly deserves study, it is more likely that the breadth of the definition is responsible. Are there unmenasured and important differences in "Western" acculturation and possibly other unmeasured and unreported aspects of SES that are very well known to be associated with lipid profiles, induding but not limited to urban/rural differences, job categories, and much more? Addressing this problem with a single phrase which is hooked to another topic in the discussion is not adequate to the problem. Here is the phrase about this topic. ("Whilst this may have been problematic in the case of alcohol consumption that lacked detailed data on type of alcohol consumed".....) This is the only attmpet of the authors to adddress the gap between alcohol methods and the numerous statemetns about alcohol and LDL.

	Before publication, this reviewer hopes that the editor will ask the authors to to describe far more honestly that not much can be made of the exposure characteristics of "ever" alcohol and it is not knowable from the data presented if the association is due to chance, social factors not measured in the survey, or allelic variants from the rest of the world as the authors has hypothesized. . The survey weakness of the method about alcohol was likely unadvoidable. It is not a "fault." However, the weakness should be mentiuoned when pointing out the assocation to lipids each time it comes up in the discussion.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer's comment:

Comment:

The authors have addressed many of the concerns in the initial review. And, they are correct that there is a need for confirmatory research in the Middle East. And, they have improved upon the understanding of participation rate as requested. This reviewer continues to advocate that the paper deserves a place in the literature.

However, a critical recommendation about the weakness of methods concerning alcohol has not been followed, and it is consequential.

The results about alcohol continue to be presented in a misleading and unwarranted way, and that is a concern because the findings are also different than the findings of most studies. What does it mean when a group with "ever alcohol" consumption differs from "never alcohol" consumption in a society when this is a consequential decision about lifestyle? . What does "ever alcohol" (defined in the previous submission as one drink) mean in terms of exposure? The authors hypothesize that there is a genetic susceptibility locus. While this is possible, and certainly deserves study, it is more likely that the breadth of the definition is responsible. Are there unmeasured and important differences in "Western" acculturation and possibly other unmeasured and unreported aspects of SES that are very well known to be associated with lipid profiles, including but not limited to urban/rural differences, job categories, and much more? Addressing this problem with a single phrase which is hooked to another topic in the discussion is not adequate to the problem. Here is the phrase about this topic. ("Whilst this may have been problematic in the case of alcohol consumption that lacked detailed data on type of alcohol consumed".....) This is the only attempt of the authors to address the gap between alcohol methods and the numerous statements about alcohol and LDL.

Before publication, this reviewer hopes that the editor will ask the authors to describe far more honestly that not much can be made of the exposure characteristics of "ever" alcohol and it is not knowable from the data presented if the association is due to chance, social factors not measured in the survey, or allelic variants from the rest of the world as the authors has hypothesized.

The survey weakness of the method about alcohol was likely unavoidable. It is not a "fault." However, the weakness should be mentioned when pointing out the association to lipids each time it comes up in the discussion.

Response:

We thank the reviewer for this comment.

To address the reviewer's recommendation, we have given more space to this issue and added further statements to the discussion section indicating the bias introduced owing to the way alcohol was measured in the questionnaire and appeared in the data:

"Alternatively, this discrepancy may be due to the definition of alcohol exposure adopted in our study which was based on a dichotomous variable (ever vs never), and thus does not capture alcohol intake in terms of frequency, intensity, types and pattern of alcohol consumed. It is important to also acknowledge that alcohol consumption may be subject to reporting bias in the Lebanese society due to cultural or religious norms. The observed association between alcohol and lipid profile should therefore be interpreted with caution, as it may have been the artifact of other social or lifestyle factors that were not measured in our study.

We have also added the following to the limitations section:

"This may have been particularly problematic in the case of alcohol consumption, given that our definition based on a dichotomous variable of "ever" vs "never" does not allow for the assessment of drinking frequency and patterns or the type of alcohol consumed.

Thank you.