

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and Risk Factors of Taste and Smell Impairment in a Nation-wide Representative Sample of the U.S. Population: a Cross-sectional Study
AUTHORS	Liu, Gang; Zong, Geng; Doty, Richard; Sun, Qi

VERSION 1 - REVIEW

REVIEWER	Joaquim Mullol Professor of Research in Otorhinolaryngology Director, Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic Head, Laboratory of Clinical & Experimental Respiratory Immunoallergy Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) Universitat de Barcelona Villarroel 170, 08036 Barcelona Catalonia, Spain
REVIEW RETURNED	20-Jul-2016

GENERAL COMMENTS	<ul style="list-style-type: none"> • Abstract. <ul style="list-style-type: none"> - (page 2, line 57) In the conclusion, please provide the differentiated prevalences for smell and taste dysfunctions since an overall prevalence (28.6%) can be confusing for the readers. - (page 3, lines 4-7) In addition to specific risk factor for taste dysfunction, also specific risk factors for smell dysfunction should be listed (instead of “a number”). • Introduction. It would recommend to the authors to summarize the main objectives of the study in the final sentence of the introduction section instead of widely summarizing the findings. • Methods. <ul style="list-style-type: none"> - (page 5, line 54) Why only the population ≥ 40 years old and was studied? - (page 5, line 42) Why the studied population for smell (N=3,519) was different from the studied population for taste (N= 3,114)? • Results. <ul style="list-style-type: none"> - (pages 10-11) Supplementary Figure 1 (smell+taste) is not referred nor commented in the results section. • Discussion. <ul style="list-style-type: none"> - (page 14, line 16) The study in reference 8 investigated 4 but not 5 odorants. A different reference should be cited here. - (page 15, lines 16-42) Potentially the factors “family income/poverty”, “educational level”, or both may be linked to ethnicity (non-Hispanic Blacks and Mexican-Americans). Concerning
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	<p>smell or taste impairment, have the authors compared the impact of different levels of incomes and education between different ethnicities (i.e. non-Hispanic Whites) to investigate if the main factor is ethnicity or poverty? If not, please discuss.</p> <ul style="list-style-type: none"> - (page 16, lines 19-24) Even protection of smell recognition / memory has been reported (reference 8) in smokers? Please comment. <ul style="list-style-type: none"> • Conclusion. <ul style="list-style-type: none"> - (page 19, lines 24-31) As in the abstract, please list also the risk factors for smell dysfunction (instead of “a multitude of”). • Figures. <ul style="list-style-type: none"> - Figure 1 (page 27). Please, identify the different graphs (A,B,C,D) as well as in the figure legend. - Supplementary Figure 1 (page 33). Please, identify the different graphs (A,B) as well as in the figure legend. The presence of statistical comparisons (by symbols) would help to understand the figures (i.e. women vs man; different ethnicities vs non-Hispanic White for each age group). - Supplementary Figure 2 (page 34). The presence of statistical comparisons (by symbols) would help to understand the figures (i.e. different age groups vs 40-49yo for each specific odor). • Tables. <ul style="list-style-type: none"> - Table 1 (pages 28-29). Please define abbreviations (BMI, CVD) as footnotes. In a number of outcomes (from line 48 and below) the word “yes” in the left column is not needed since there is already an identifying column. All values “out” and “in” should be identified in the left column [i.e. mean (SD)]. - Table 2 (page 30) and Table 3 (page 31). Please define abbreviations (CVD) as footnotes. OR for Odds ratio could be defined on the title. - Supplementary Table 1 (page 35). How many patients from the current cohort were tested with the whole UPSIT test? If these data belongs to population values from another manuscript, please reference. • STROBE checklist. <ul style="list-style-type: none"> - The objectives of the study are not well addressed (page 5). - The setting is not defined (pages 5-6). - The category of the study (participants) should be clearly presented (pages 5-6). - Study size is not clearly presented (different for smell and taste) (page 5). - Part of the items in the statistical methods are not addressed (pages 9-10). - Summarizing of key results is not done at the beginning of the discussion section (page 13) but only in the conclusion (page 19). - Contribution of L. Doty in the study should be defined (page 20).
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REVIEWER	Jayant Pinto University of Chicago, USA
REVIEW RETURNED	10-Aug-2016

GENERAL COMMENTS	This paper treats an important topic- chemosensory impairment in US adults- and utilizes an excellent and new dataset in which to address prevalence and risk factors for smell and taste impairment.
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	<p>This is an important topic and the results provide nice national estimates and demonstrate the burden of these diseases.</p> <p>The main issues with the work are imprecision in language and lack of clarity about the statistical analysis and results. How were the models constructed, exactly what covariates were used, etc., should be clear in the abstract and the text. How were the tests scored (was intensity rating used for test or not)? Why were 2 smell tests used? Basic information about NHANES is not provided. These problems make it hard to follow and limits our understanding of the importance of the results and how relevant/justified they are.</p> <p>The paper is missing some relevant references and fails to emphasize the main strength, which is the inclusion of younger adults (most work is in older adults). As the data set is large, they should include smell and taste impairment plots by age group to mimic what one of the authors did in his landmark paper in 1984 (something that could be done with the modeled data). Examining the 40-60 years more clearly would be an advance in the field. Other key nuggets are buried and not well addressed (effects of alcohol, for example). What are the strengths of NHANES and how does that inform the results?</p> <p>Finally, overall the writing is not crisp and therefore detracts from the work. Careful editing for clarity and precision would improve the work. Suitably revised, the work could be reconsidered after major improvements.</p> <p>Specific Comments Abstract-</p> <p>Be clear about scoring of both outcome measures (smell and especially taste). Results: as written, not clear what models are being presented nor which covariates are included. Are the initial results, univariate? There are no analytic methods described.</p> <p>Conclusion: how is the survey 'complex'? Define 'large' here and 'multitude' in the strengths and limitations.</p> <p>Introduction The work is missing references for other longitudinal studies of olfaction. Some of the references that refer to the general population are not representative (and it's not clear what is meant by general population- be specific).</p> <p>Similarly, be clear that NHANES is representative of those 40 years or older, not the population overall.</p> <p>'was suggestive of' – rephrase.</p> <p>Methods</p> <p>Some background on the NHANES is warranted- at least a summary of its design, how it is representative, etc. This would help explain why the mean age is 57.</p> <p>Race categories are not standard NIH- please provide context why Mexican Americans are pulled out.</p>
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	<p>Please explain 'largely derived' and 'primarily' under smell and taste tests. Please provide a reference for how this protocol is validated against the full UPSIT and its categories. Why were 2 smell tests employed? Please justify.</p> <p>'In addition, a replication of the whole mouth test was conducted with a salt solution'- unclear- do you mean another taste test was done with salt?</p> <p>How were the intensity ratings for taste used (or not used)—unclear.</p> <p>Stats Analysis-</p> <p>'Complex' design- what do you mean?</p> <p>What is PROC SURVEYFREQ, etc? are these SAS commands? Providing them is ok, but explain. I'd rather have you describe the actual tests performed and give the commands in a supplement. What do you mean 'weights were used wherever possible'?</p> <p>Results Do Blacks have worse taste or not- conflicting statements.</p> <p>Please explain the results so people can directly understand the associations. Please don't give OR ranges- provide for each variable.</p> <p>Taste was better in older subjects?</p> <p>Figure 2- not sure how AUC is useful here- please explain.</p> <p>Conclusions</p> <p>The complexity of comparing surveys with different testing methods of smell and taste may explain different findings. Thus, the conclusions of new and critical risk factors warrants tempering. You have not proven face validity of this protocol.</p> <p>These are identification test which could require a cognitive component.</p> <p>Not sure you can explain away race differences- there are missing references here.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Joaquim Mullol

Institution and Country: Professor of Research in Otorhinolaryngology, Director, Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic

Head, Laboratory of Clinical & Experimental Respiratory Immunoallergy, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)

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Competing Interests: NONE DECLARED

- Abstract.

- (page 2, line 57) In the conclusion, please provide the differentiated prevalences for smell and taste dysfunctions since an overall prevalence (28.6%) can be confusing for the readers.

Response: We thank the reviewer for his comments. We have revised the conclusion accordingly. "Based upon a nationally representative multistage probability survey among the U.S. population aged 40 years and older, smell and taste dysfunction affected approximately 20.5 million (13.5%) and 26.3 million (17.3%) individuals, respectively." (Page 2-3)

- (page 3, lines 4-7) In addition to specific risk factor for taste dysfunction, also specific risk factors for smell dysfunction should be listed (instead of "a number").

Response: We have listed the specific risk factors for smell dysfunction accordingly. "Age, gender, ethnicity, educational attainment, family income, light-to-moderate alcohol consumption, and history of asthma or cancer were significant risk factors for smell dysfunction, whereas only ethnicity, heavy alcohol consumption, and CVD history were associated with a higher prevalence of taste dysfunction." (Page 3)

- Introduction. It would recommend to the authors to summarize the main objectives of the study in the final sentence of the introduction section instead of widely summarizing the findings.

Response: We are grateful for the reviewer's comments. We have revised the objectives of the study at the end of Introduction section.

"In the present study, based on a larger sample size from the NHANES 2013-2014 survey among U.S. population aged 40 years and older, we aimed to estimate the prevalence of both olfactory and taste dysfunction in the U.S. population, and explore potential risk factors for these conditions." (Page 5)

- Methods.

- (page 5, line 54) Why only the population ≥ 40 years old and was studied?

Response: To assess the health and nutritional status of adults and children in the United States, NHANES examines a nationally representative sample of about 5,000 people each year. The taste and smell examination was a new health examination component which was performed among participants aged 40 and older only. We have added more information on NHANES and current study population.

"NHANES is a cross-sectional survey designed to assess the health and nutritional status of adults and children in the United States. Each year, the survey examines a nationally representative sample of about 5,000 people who are located in 15 counties randomly selected across the country. The taste and smell examination was a new health examination component which was performed among participants aged 40 years and older. A total of 3708 men and women were enrolled in the taste and smell examination." (Page 5)

- (page 5, line 42) Why the studied population for smell (N=3,519) was different from the studied population for taste (N= 3,114)?

Response: Based on the exclusion criteria, not all the participants were eligible to take both the smell and taste tests. For example, some participants were excluded if they were allergic to quinine or

unable to correctly rate the brightness of three lights in an LED luminescence panel. We finally included 3,519 eligible participants for the smell test and 3,114 eligible participants for the taste test.

- Results.

- (pages 10-11) Supplementary Figure 1 (smell+taste) is not referred nor commented in the results section.

Response: Thank you for the comment. We have included the results of Supplementary Figure 1 in the Results section accordingly.

“Supplementary Figure 1 shows mean (SE) NHANES Pocket Smell Test™ scores according to age and gender.” (Page 11)

- Discussion.

- (page 14, line 16) The study in reference 8 investigated 4 but not 5 odorants. A different reference should be cited here.

Response: Sorry for this error. It should be reference 9 here. We have revised the reference accordingly.

“Other studies have set this criterion at 62.5% for either 8 or 16 odorants, 6, 14, 21 and 40% for 5 odorants.” (Page 14-15)

- (page 15, lines 16-42) Potentially the factors “family income/poverty”, “educational level”, or both may be linked to ethnicity (non-Hispanic Blacks and Mexican-Americans). Concerning smell or taste impairment, have the authors compared the impact of different levels of incomes and education between different ethnicities (i.e. non-Hispanic Whites) to investigate if the main factor is ethnicity or poverty? If not, please discuss.

Response: We appreciate the reviewer’s insightful comments. We have conducted additional analyses to estimate the prevalence of smell and taste impairment according to different ethnicities, educational level, and family income (see the supplementary table below). For smell impairment, compared with non-Hispanic White, the prevalence was higher in non-Hispanic Blacks and Mexican-Americans, especially in the groups of low family income or low educational level. In addition, compared with high family income or high education level, the prevalence of smell impairment was higher in the groups of low family income or low education level in different ethnicities. Therefore, ethnicity, family income, and education level were all risk factors for smell impairment. In contrast, for taste impairment, the prevalence was only higher in non-Hispanic Blacks, compared with non-Hispanic Whites. Education level and family income were not associated with the prevalence of taste impairment. We have added the Supplementary Table 2 in the text and revised the Discussion section accordingly.

“In the current study, other potential socioeconomic risk factors for smell impairment that are independent of ethnicities were also identified, including low educational attainment and low family income.” (Page 16)

Supplementary Table. Prevalence of smell and taste impairment according to different ethnicities, educational level, and family income (please see attached response letter)

- (page 16, lines 19-24) Even protection of smell recognition / memory has been reported (reference

8) in smokers? Please comment.

Response: Thank you for the comment. We have cited this paper and discussed it in the Discussion section accordingly.

“Accumulating evidence has suggested that smoking may exert an adverse effect on smell function,^{8,17,41} although some studies did not observe such a link.^{11,20,42} In another cross-sectional population-based study, Mullol et al. reported that smoking and exposure to noxious substances were even mild protective factors for smell recognition.⁹ These mixed findings may reflect the cross-sectional nature of these studies, as well as the lack of detailed assessments of smoking dose and duration, which are often more informative than dichotomous smoking status.”(Page 17)

• Conclusion.

- (page 19, lines 24-31) As in the abstract, please list also the risk factors for smell dysfunction (instead of “a multitude of”).

Response: We are grateful for the reviewer’s suggestion. We have listed the risk factors for smell dysfunction in the Conclusion section.

“As shown in the NHANES study, age, gender, ethnicity, educational attainment, family income, light-to-moderate alcohol consumption, and history of asthma or cancer were potential risk factors for smell dysfunction.” (Page 20)

• Figures.

- Figure 1 (page 27). Please, identify the different graphs (A,B,C,D) as well as in the figure legend.

Response: We have revised the Figure 1 accordingly.

“A and B are the prevalence of smell and taste impairment in men and women according to each age group. C and D are the prevalence of smell and taste impairment in different ethnicities according to each age group.”

- Supplementary Figure 1 (page 33). Please, identify the different graphs (A, B) as well as in the figure legend. The presence of statistical comparisons (by symbols) would help to understand the figures (i.e. women vs man; different ethnicities vs non-Hispanic White for each age group).

Response: We thank the reviewer for his suggestion. We have revised Supplementary Figure 1 accordingly.

- Supplementary Figure 2 (page 34). The presence of statistical comparisons (by symbols) would help to understand the figures (i.e. different age groups vs 40-49 yr for each specific odor).

Response: We have revised Supplementary Figure 2 according to the reviewer’s suggestion.

• Tables.

- Table 1 (pages 28-29). Please define abbreviations (BMI, CVD) as footnotes. In a number of outcomes (from line 48 and below) the word “yes” in the left column is not needed since there is already an identifying column. All values “out” and “in” should be identified in the left column [i.e. mean (SD)].

Response: Thank you for the suggestions. We have defined the abbreviations of BMI and CVD in the footnotes, deleted “yes” in the left column, and added mean (SD) in the tables.

- Table 2 (page 30) and Table 3 (page 31). Please define abbreviations (CVD) as footnotes. OR for Odds ratio could be defined on the title.

Response: We have added this information in Table 2 and Table 3.

- Supplementary Table 1 (page 35). How many patients from the current cohort were tested with the whole UPSIT test? If these data belongs to population values from another manuscript, please reference.

Response: Sorry for the confusion. In the current study, all the participants only received the 8-item smell test. Our definition of smell impairment (i.e., <75% or 6 out of 8 items) approximately corresponds to the definition of being unable to correctly identify 29 or more of the 40 odors using the UPSIT test. Supplementary Table 1 shows the prevalence of smell impairment in UPSIT study and current study according to each age group to facilitate comparison. We have revised Supplementary Table 1 accordingly.

“Supplementary Table 1. Comparison of prevalence of smell impairment between the UPSIT study and the current study in NHANES population”

• STROBE checklist.

- The objectives of the study are not well addressed (page 5).

Response: We have revised the objectives of the study in the Introduction section.

“In the present study, based on a larger sample size from the NHANES 2013-2014 survey among U.S. population aged 40 years and older, we aimed to estimate the prevalence of both olfactory and taste dysfunction in the U.S. population, and explore potential risk factors for these conditions.” (Page 5)

- The setting is not defined (pages 5-6).

Response: we have revised this part accordingly.

“NHANES is a cross-sectional survey designed to assess the health and nutritional status of adults and children in the United States. Each year, the survey examines a nationally representative sample of about 5,000 people who are located in 15 counties randomly selected across the country.” (Page 5)

- The category of the study (participants) should be clearly presented (pages 5-6).

Response: Our study was a cross-sectional study based on data collected in NHANES 2013-2014. We have added this information to the Methods section accordingly.

“NHANES is a cross-sectional survey designed to assess the health and nutritional status of adults and children in the United States...” (Page 5)

- Study size is not clearly presented (different for smell and taste) (page 5).

Response: Thank you for the comment. Because not all of the participants had completed both the smell and taste tests in NHANES 2013-2014, we finally included 3,519 eligible participants for smell test and 3,114 eligible participants for taste test. We have revised this part accordingly.

“...A total of 3708 men and women were enrolled in the taste and smell examination.” (Page 5)

“...These exclusions left 3114 participants who completed the quinine and sodium chloride (NaCl) taste tests and 3519 participants who completed the 8-item smell test.” (Page 5)

- Part of the items in the statistical methods are not addressed (pages 9-10).

Response: We have added more information on statistical methods.

“To minimize sample reduction due to missing covariates, indicator variables were used for missing categorical variables” (Page 10)

“In sensitivity analyses, we defined taste impairment as failing to correctly identify quinine (both tongue tip and whole mouth test) or NaCl (both tongue tip and whole mouth test).” (Page 8)

- Summarizing of key results is not done at the beginning of the discussion section (page 13) but only in the conclusion (page 19).

Response: We thank the reviewer’s comment. We have summarized the key results at the beginning of the Discussion section.

“In this most current nation-wide representative sample of U.S. men and women aged 40 years and older, a significant number of U.S. adults were found to experience smell or taste problems. The overall estimated prevalence of smell and taste impairment was 13.5% and 17.3%, respectively...” (Page 13-14)

- Contribution of L. Doty in the study should be defined (page 20).

Response: We have defined the contribution of R. L. Doty in detail.

“R. L. Doty contributed to results interpretation, statistical analysis, and critical revision of the manuscript.” (Page 21)

Reviewer: 2

Reviewer Name: Jayant Pinto

Institution and Country: University of Chicago, USA

Competing Interests: None Declared

This paper treats an important topic--chemosensory impairment in US adults--and utilizes an excellent and new dataset in which to address prevalence and risk factors for smell and taste impairment. This is an important topic and the results provide nice national estimates and demonstrate the burden of these diseases.

Response: We appreciate the reviewer’s comments.

The main issues with the work are imprecision in language and lack of clarity about the statistical analysis and results. How were the models constructed, exactly what covariates were used, etc., should be clear in the abstract and the text. How were the tests scored (was intensity rating used for

test or not)? Why were 2 smell tests used? Basic information about NHANES is not provided. These problems make it hard to follow and limits our understanding of the importance of the results and how relevant/justified they are.

Response: We are grateful for the reviewer's comments. We have revised the statistical analysis and results section as much as we can. An 8-item "scratch and sniff" test was used for the smell test. We used backward stepwise logistic regression to examine the risk factors for smell and taste impairment. Instead of using intensity ratings, we defined taste dysfunction according to the ability to identify the tastants. We have provided more information about NHANES in the text.

"In backward stepwise logistic regression, low educational attainment, low family income, and a history of asthma or cancer were independently associated with a higher prevalence of smell impairment, whereas light-to-moderate alcohol consumption (1-3 drinks/day) was associated with a lower prevalence of such impairment."(Abstract)

"Using the NHANES Pocket Smell TestTM, smell impairment was defined as failing to correctly identify 6 or more of the 8 odors. Taste impairment was defined as failing to correctly identify quinine or sodium chloride." (Abstract)

"NHANES is a cross-sectional survey designed to assess the health and nutritional status of adults and children in the United States. Each year, the survey examines a nationally representative sample of about 5,000 people who are located in 15 counties randomly selected across the country. The taste and smell examination was a new health examination component which was performed among participants aged 40 years and older.¹⁸ A total of 3708 men and women were enrolled in the taste and smell examination." (Page 5)

The paper is missing some relevant references and fails to emphasize the main strength, which is the inclusion of younger adults (most work is in older adults). As the data set is large, they should include smell and taste impairment plots by age group to mimic what one of the authors did in his landmark paper in 1984 (something that could be done with the modeled data). Examining the 40--60 years more clearly would be an advance in the field. Other key nuggets are buried and not well addressed (effects of alcohol, for example). What are the strengths of NHANES and how does that inform the results?

Response: We appreciate the reviewer's comments. We have cited more relevant references (Schubert CR, 2011; Pinto JM, 2015; Correia C; 2016) and revised the strength of the study accordingly. In addition, we plotted the prevalence of smell test scores by age group and gender (see below). In a secondary analysis, similar results regarding the risk factors for taste and smell impairment were observed when analyses were restricted to the participants aged 40-60 years. Regarding alcohol consumption, we found that heavy drinking was associated with an increased prevalence of taste dysfunction, whereas light-to-moderate drinking was associated with a decreased prevalence of smell dysfunction, suggesting that the amount of alcohol intake may exert distinct effects on chemosensory perception. In addition, using a nationally representative sample, NHANES provides reference data for taste and smell testing for U.S. adults aged 40 and over. We have revised the text accordingly.

"Although a large literature suggests that chemosensory disorders are relatively common,^{2,8-16} there remains a lack of consensus as to the prevalence of such disorders in population-based epidemiological studies.^{8,12,17-22}" (Page 4)

"In a secondary analysis, similar results regarding the risk factors for taste and smell impairment were observed when analyses were restricted to the participants aged 40-60 years, although some of the associations did not reach statistical significance probably due to reduced power (data not shown)." (Page 13)

“The present study provides a nation-representative estimate of the prevalence of taste and smell impairment among men and women aged 40 years and above in the United States population. Most previous studies were only conducted among older adults.8,10,12,14,15” (Page 19)

Supplementary Figure 1. Mean (SE) NHANES Pocket Smell Test™ scores according to age and gender.(please see the attached response letter)

Reference:

1. Correia C, Lopez KJ, Wroblewski KE, et al. Global Sensory Impairment in Older Adults in the United States. *J Am Geriatr Soc.*2016;64:306-313.
2. Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Olfactory impairment in older adults: five-year incidence and risk factors. *Laryngoscope.*2011;121:873-878.
3. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. The Rate of Age-Related Olfactory Decline Among the General Population of Older U.S. Adults. *J Gerontol A Biol Sci Med Sci.*2015;70:1435-1441.

Finally, overall the writing is not crisp and therefor detracts from the work. Careful editing for clarity and precision would improve the work. Suitably revised, the work could be reconsidered after major improvements.

Response: We are grateful for the reviewer’s comments. We have polished the writing for this manuscript and hope the current revision is now suitable for publication.

Specific Comments

Abstract---

Be clear about scoring of both outcome measures (smell and especially taste). Results: as written, not clear what models are being presented nor which covariates are included. Are the initial results, univariate? There are no analytic methods described. Conclusion: how is the survey ‘complex’? Define ‘large’ here and ‘multitude’ in the strengths and limitations.

Response: We thank the reviewer’s helpful comment. We have revised the outcome measurements with more details. Regarding results, backward stepwise logistic regression was used, and we have added more information in the abstract. In addition, we have revised the description of NHANES, which is a nationally representative multistage probability survey. Instead of using “large” and “multitude”, we have listed the detailed risk factors accordingly.

“Using the NHANES Pocket Smell Test™, smell impairment was defined as failing to correctly identify 6 or more of the 8 odors. Taste impairment was defined as failing to correctly identify quinine or sodium chloride.” (Abstract)

“In backward stepwise logistic regression, low educational attainment, low family income, and a history of asthma or cancer were independently associated with a higher prevalence of smell impairment, whereas light-to-moderate alcohol consumption (1-3 drinks/day) was associated with a lower prevalence of such impairment.” (Abstract)

“Based upon a nationally representative multistage probability survey among the U.S. population aged 40 years and older...” (Abstract)

“Age, gender, ethnicity, educational attainment, family income, light-to-moderate alcohol consumption, and history of asthma or cancer were significant risk factors for smell dysfunction, whereas only ethnicity, heavy alcohol consumption, and CVD history were associated with a higher prevalence of taste dysfunction.” (Abstract)

“This study demonstrates associations of age, gender, ethnicity, educational attainment, family

income, alcohol consumption, and history of asthma, cancer, or CVD with chemosensory disorders on a nation-wide scale.” (Strengths and limitations of this study)

Introduction

The work is missing references for other longitudinal studies of olfaction. Some of the references that refer to the general population are not representative (and it’s not clear what is meant by general population--be specific). Similarly, be clear that NHANES is representative of those 40 years or older, not the population overall. ‘was suggestive of’ – rephrase.

Response: We are grateful for the helpful comments. We have cited more studies of olfaction (Schubert CR, 2011; Pinto JM, 2015; Correia C; 2016) in the Introduction section. Instead of using “general population”, we revised it as “population-based epidemiological studies”. We have revised the reference and the description of NHANES. In addition, “was suggestive of” was rephrased as “reported a...”.

“Although a large literature suggests that chemosensory disorders are relatively common,2,8-16 there remains a lack of consensus as to the prevalence of such disorders in population-based epidemiological studies.8,12,17-22” (Page 4)

“In the present study, based on a larger sample size from the NHANES 2013-2014 survey among U.S. population aged 40 years and older, we aimed to estimate the prevalence of both olfactory and taste dysfunction in the U.S. population, and explore potential risk factors for these conditions.” (Page 5)

“An evaluation of the olfactory data collected during the first year of this survey (2012) reported a 12.4% prevalence for smell dysfunction in the sampled population...” (Page 5)

Reference:

1. Correia C, Lopez KJ, Wroblewski KE, et al. Global Sensory Impairment in Older Adults in the United States. *J Am Geriatr Soc.*2016;64:306-313.
2. Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Olfactory impairment in older adults: five-year incidence and risk factors. *Laryngoscope.*2011;121:873-878.
3. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. The Rate of Age-Related Olfactory Decline Among the General Population of Older U.S. Adults. *J Gerontol A Biol Sci Med Sci.*2015;70:1435-1441.

Methods

Some background on the NHANES is warranted--at least a summary of its design, how it is representative, etc. This would help explain why the mean age is 57.

Response: We thank the reviewer for his comments. We have added more information about NHANES in the Methods section.

“NHANES is a cross-sectional survey designed to assess the health and nutritional status of adults and children in the United States. Each year, the survey examines a nationally representative sample of about 5,000 people who are located in 15 counties randomly selected across the country. The taste and smell examination was a new health examination component which was performed among participants aged 40 years and older.18 A total of 3708 men and women were enrolled in the taste and smell examination.” (Page 5)

Race categories are not standard NIH-- please provide context why Mexican Americans are pulled

out.

Response: In NHANES survey, race was categorized as Mexican Americans, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race (Niskar AS et al, 1998). We have provided more information in the text accordingly.

“The in-home questionnaire obtained information on age, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, and other race),26...” (Page 8)

Reference:

1. Niskar AS, Kieszak SM, Holmes A, Esteban E, Rubin C, Brody DJ. Prevalence of hearing loss among children 6 to 19 years of age: the Third National Health and Nutrition Examination Survey. *JAMA*.1998;279:1071-1075.

Please explain ‘largely derived’ and ‘primarily’ under smell and taste tests. Please provide a reference for how this protocol is validated against the full UPSIT and its categories. Why were 2 smell tests employed? Please justify.

Response: An 8-item “scratch and sniff” test was used for the smell test. According to a recent validation study, Rawal S et al. reported that the NHANES taste and smell protocol had moderate-to-good test–retest reliability (Rawal S, 2015). A convenience sample of 73 adults underwent the NHANES protocol at baseline, 2 weeks and 6 months. For smell function, participants received both the Pocket Smell Test™ (PST, eight-item odor identification test) and the 40-item olfactometer-generated identification test (Rawal S, 2015). Olfactory function classification from PST and olfactometer agreed for 94.5% of participants. In the current study, our definition of smell impairment (i.e., <75% or 6 out of 8 items) approximately corresponds to the definition of being unable to correctly identify 29 or more of the 40 odors using the UPSIT test. Supplementary Table 1 shows the comparison of prevalence of smell impairment between the UPSIT study and the current study in NHANES population. We have deleted the unclear expression of “largely derived” and “primarily”, and revised this sentence accordingly.

“For smell testing, the two 4-item versions (A & B) of the NHANES Pocket Smell Test™ (Sensonics International, Haddon Heights, NJ), developed in conjunction with the NIH, were sequentially administered, resulting an 8-item “scratch and sniff” test.23” (Page 6)

“A recent validation study demonstrated moderate-to-good test–retest reliability of the NHANES smell protocol (intraclass correlations were 0.82 and 0.69 for 2-week and 6-month intervals, respectively).23 Of note, the eight odorants used in NHANES test are components of the 40-item University of Pennsylvania Smell Identification Test (UPSIT).24” (Page 6)

“Our definition of smell impairment approximately corresponds to the definition of being unable to correctly identify 29 or more of the 40 odors using the UPSIT test (Supplementary Table 1).” (Page 6-7)

Reference:

1. Rawal S, Hoffman, H.J., Honda, M., et al. The taste and smell protocol in the 2011–2014 US National Health and Nutrition Examination Survey (NHANES): test–retest reliability and validity testing. *Chemosensory Perception*. 2015;8:138-148.

‘In addition, a replication of the whole mouth test was conducted with a salt solution’--- unclear--- do you mean another taste test was done with salt? How were the intensity ratings for taste used (or not used)—unclear.

Response: As a replication test, a whole month taste test for salt was performed at the end of the chemosensory test. The participants were randomized to receive either a 0.32 M NaCl or a 1 M NaCl salt solution. In our analysis, instead of using the intensity ratings, we defined taste dysfunction according to the ability to identify the tastants. We have revised the text accordingly.

“As a replication test, another whole month taste test for salt was performed at the end of the chemosensory test. The participants were randomized to receive either a 0.32 M NaCl or a 1 M NaCl salt solution.” (Page 7)

“Thus, in our study, instead of intensity ratings, failing to correctly identify quinine in the whole mouth test was used to define taste dysfunction.” (Page 8)

Stats Analysis--

‘Complex’ design--what do you mean? What is PROC SURVEYFREQ, etc? Are these SAS commands? Providing them is ok, but explain. I’d rather have you describe the actual tests performed and give the commands in a supplement. What do you mean ‘weights were used wherever possible’?

Response: The NHANES survey uses a complicated multistage sampling method to obtain the nationally representative sample. (http://www.cdc.gov/nchs/data/series/sr_02/sr02_162.pdf) As a SAS statement, PROC SURVEYFREQ is usually used to analyze sample survey data. According to the NHANES analytic guidelines, the sample weights were required to be used to analyze the taste and smell exam data. (http://www.cdc.gov/Nchs/Nhanes/2013-2014/CSX_H.htm#SEQN) We have revised the text accordingly.

“Due to the NHANES sampling design, the sample weights were incorporated into the analysis whenever possible” (Page 9)

“A SAS procedure—PROC SURVEYFREQ—was used to estimate the weighted prevalence of taste and smell disorders in the total population as well as within subgroups of the population.” (Page 9)

Results

Do Blacks have worse taste or not--conflicting statements. Please explain the results so people can directly understand the associations. Please don’t give OR ranges-- provide for each variable. Taste was better in older subjects? Figure 2-- not sure how AUC is useful here-- please explain.

Response: Thank you for the comments and suggestions. Overall, non-Hispanic Black Americans had a higher prevalence of taste impairment than that in other ethnic groups (22.9% for non-Hispanic Black, 17.1% for non-Hispanic White, 15.6% for Mexican American, and 13.9% for other race). We have revised this sentence and provided OR values for each variable. Regarding taste impairment, the unexpected inverse association of taste dysfunction with age suggested that the relatively high concentrations of tastants used by NHANES may not be discriminating enough to capture age-related declines in taste function. We have discussed it in the Discussion section. To examine the capacity of selected risk factors in predicting smell and taste impairment, we plotted a receiver operating characteristic (ROC) curve and calculated a sample-weighted area under the ROC curve (AUC).

“Overall, non-Hispanic Black Americans had a higher prevalence of taste impairment than that in other ethnic groups (22.9% for non-Hispanic Black, 17.1% for non-Hispanic White, 15.6% for Mexican American, and 13.9% for other race).” (Page 11)

“In backward stepwise selection, older age, male gender, ethnic minorities (including non-Hispanic Black and Mexican American), low family income, low educational attainment, and a history of asthma or cancer remained in the model and were independently associated with an increased prevalence of

smell impairment (OR and 95% CI was 1.37 [1.30, 1.45] for age, 1.68 [1.27, 2.22] for men, 1.91 [1.36, 2.67] for non-Hispanic Black, 1.45 [1.04, 2.01] for low family income, 1.33 [1.17, 1.52] for low education attainment, 1.38 [1.05, 1.83] for cancer, and 1.39 [1.02, 1.89] for asthma; all P<0.05)...” (Page 12)

Conclusions

The complexity of comparing surveys with different testing methods of smell and taste may explain different findings. Thus, the conclusions of new and critical risk factors warrants tempering. You have not proven face validity of this protocol. These are identification test which could require a cognitive component. Not sure you can explain away race differences-- there are missing references here.

Response: We are grateful for the reviewer’s comments. Regarding the conclusions of new and critical risk factors, we have revised the sentence accordingly. Although a recent study by Rawal S et al. demonstrated that the NHANES taste and smell protocol had moderate-to-good test–retest reliability (Rawal S, 2015), the face validity of the protocol was not proven, which could require a cognitive component. We have added it as a limitation in the Conclusion section. Regarding race differences, we have cited more relevant references and revised the discussion accordingly.

“In the National Social Life, Health, and Aging Project study, Pinto et al. also demonstrated that older African Americans and Hispanics had worse olfactory function.³¹ In taste perception, Williams et al. observed significant differences between Hispanics, African Americans, and non-Hispanic Whites.³² While a subtle difference was noted by Doty et al. between White and Black Americans in a large, albeit convenience, sample,²⁴ another study observed equivalent UPSIT scores in White and Black American populations and relatively higher scores in Korean American populations.³³ The discrepant results may reflect differences in population characteristics, testing methods, and definitions for smell impairment.” (Page 16)

“In addition, although a recent study demonstrated that the NHANES taste and smell protocol has moderate-to-good test–retest reliability,²³ the face validity of the protocol was not proven. Furthermore, the impact of cognitive function on the validity of assessments of smell and taste functions cannot be evaluated in this investigation.” (Page 19)

Reference:

1. Rawal S, Hoffman, H.J., Honda, M., et al. The taste and smell protocol in the 2011–2014 US National Health and Nutrition Examination Survey (NHANES): test–retest reliability and validity testing. *Chemosensory Perception*. 2015;8:138-148.
2. Pinto JM, Schumm LP, Wroblewski KE, Kern DW, McClintock MK. Racial disparities in olfactory loss among older adults in the United States. *J Gerontol A Biol Sci Med Sci*.2014;69:323-329.
3. Williams JA, Bartoshuk LM, Fillingim RB, Dotson CD. Exploring Ethnic Differences in Taste Perception. *Chem Senses*.2016;41:449-456.

VERSION 2 – REVIEW

REVIEWER	Joaquim Mullo Hospital Clínic - IDIBAPS. Spain
REVIEW RETURNED	18-Sep-2016
GENERAL COMMENTS	The authors have done an important effort to providing appropriate answers and doing pertinent changes in the manuscript after the comments and questions raised by this reviewer. However, the following two issues still need to be amended. 1st) Since the concept “race” is quite controversial in sociology and

	<p>has a low level of scientific support, I would delete this word all over the manuscript (text, figures, and tables) while keeping the words “ethnicity” or “ethnic”.</p> <p>2nd) I don't see the new “Supplementary Table 2” comparing different levels of family income to poverty, educational level for both smell and taste in the revised manuscript. To avoid any misunderstanding, I consider this table should definitively be included in the manuscript.</p>
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