

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Psychosocial factors and indoor environmental quality in respiratory symptom reports of pupils: A cross-sectional study in Finnish schools
<b>AUTHORS</b>	Savelieva, Kateryna; Elovainio, Marko; Lampi, Jussi; Ung-Lanki, Sari; Pekkanen, Juha

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Diaba Silva Faculty of Medicine of Porto University, Portugal
<b>REVIEW RETURNED</b>	01-Mar-2020

<b>GENERAL COMMENTS</b>	<p>This is a cross-sectional study with a large population of pupil's reports addressing the association of psychosocial factors and reported respiratory symptoms related to indoor environment quality. The authors were able to show that psychosocial factors can interfere with respiratory symptoms reports related to indoor air environment in schools. The main limitation of this study is the lack of objective measures in the evaluation of respiratory symptoms, but also on the evaluation of indoor air quality, like physical parameters (like temperature and humidity) or measurement of chemical or biological indicators. Individual characteristics regarding asthma, atopic rash and hay fever were not specified how were measured (was this reported medical diagnosis?) .</p> <p>The following point should also be addressed:</p> <ul style="list-style-type: none"> <li>• The term “individual characteristics” should be better specified as most characteristics are associated with allergic diseases, perhaps it should be stated “Individual and allergic characteristics” or “demographic and allergic characteristics”;</li> <li>• It could be considered the use of a flow diagram regarding participants selection, as supplementary file to follow more comparatively the rate of response between groups and the participants exclusion. This is included in the text however the presence of a supplementary table or flow-chart might increase comprehensibility</li> <li>• Respiratory symptoms were assessed only by questionnaire, further these questionnaires were different between primary and secondary pupils and parents. How was the questionnaire changed? Was there performed any pilot trial?</li> <li>• Regarding the psychosocial factors and satisfaction with school environment could these answers be associated with academic success/scholar achievement. Was the evaluation performed during exam season? This could also interfere with the school environment reported satisfaction</li> <li>• Within the psychosocial factors worry about indoor environment is expressed on table 1 as mean (SD), most of the values were</li> </ul>
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	<p>low, is there any minimal important difference defined? Why is low school satisfaction presented as mean (SD) and home satisfaction as a percentage. Similar data presentation could help to improve results interpretation.</p> <ul style="list-style-type: none"> <li>• Line 222: How were asthma, hay fever and atopic rash defined? What “atopic rash” includes, atopic dermatitis, urticaria? In table 2 only the word rash was include.</li> <li>• Models characterization should be included in table 3-5 to improve comprehensibility</li> <li>• In the limitation section (line 388) it should be included that the study cross-section design limits the ability to establish causality</li> <li>• In the conclusion section (line 391) it should be considered that an intervention on psychosocial outcomes might interfere with the children perception of indoor environment associated with school.</li> </ul>
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<b>REVIEWER</b>	Jonas Miller Stanford University, USA
<b>REVIEW RETURNED</b>	29-Apr-2020

<b>GENERAL COMMENTS</b>	<ol style="list-style-type: none"> <li>1. I think it would be helpful to provide some brief examples what is meant by “poor psychosocial work environment” on page 4 of the introduction.</li> <li>2. The introduction needs to provide more justification for considering the question of “how much variance between schools in symptom reporting is explained by” psychosocial and individual characteristics. Currently, it is hard for me to understand how individual differences in psychosocial factors might explain differences in reporting across schools.</li> <li>3. Are there prior studies indicating why reporting on symptoms in relation to a specific environment might be moderated by psychosocial factors? I’m wondering if the introduction can provide additional information about what led the authors to ask the following question on page 5 and why it is meaningful: “When symptoms are reported in relation to specific environment, the responses may be influenced by various psychosocial factors, such as worry about IEQ, overall satisfaction with school environment, and interactions with teachers and peers, although this has not been yet addressed.”</li> <li>4. As the authors report in their manuscript, there is a lot of missing data for parent-report measures. Please clarify whether any of the models included parent-reported symptoms as the outcome and child-reported psychosocial factors as the predictor. One strength of this approach is that it does not rely on a single reporter. On the other hand, there is a lot missing data for parent-report measures. Are there issues of missingness that violate any of the assumptions of the analysis (e.g., missing completely at random)?</li> <li>5. How many schools were included in each latent class?</li> <li>6. Report the Cronbach’s alpha for the measure of satisfaction with home environment as is currently done for the measure of satisfaction with school environment.</li> <li>7. What is the interpretation of the finding that worry about IEQ reported by school principals was not associated with respiratory symptoms in any of the samples?</li> </ol>
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	<p>8. The variance between schools was very low for respiratory symptoms. Could the authors show whether variances were statistically significant? In other words, were there meaningful differences between schools that were even worth probing?</p> <p>9. The interpretation for the association between symptom reporting and negative affectivity is that these individuals are more likely to pay attention to, monitor, and accurately report on somatic states. My understanding is that there is little support for the perspective that there are meaningful individual differences in the ability to report on somatic states (e.g., interoception). Thus, I think it would be helpful to briefly talk about the potential impact of negative affective states on biology related to symptoms.</p> <p>10. What does it mean that women may report more symptoms and describe changes in health “more easily” than men?</p> <p>11. Much of the discussion is spent summarizing the findings and then commenting on whether findings fit with prior studies. I would like a little more attention devoted to discussing what the authors think the findings mean.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewers' Comments to Author:

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**Reviewer: 1**

Reviewer Name: Diaba Silva

Institution and Country: Faculty of Medicine of Porto University, Portugal

Please state any competing interests or state 'None declared': None declared

**Comment 1.** This is a cross-sectional study with a large population of pupil's reports addressing the association of psychosocial factors and reported respiratory symptoms related to indoor environment quality. The authors were able to show that psychosocial factors can interfere with respiratory symptoms reports related to indoor air environment in schools. The main limitation of this study is the lack of objective measures in the evaluation of respiratory symptoms, but also on the evaluation of indoor air quality, like physical parameters (like temperature and humidity) or measurement of chemical or biological indicators. Individual characteristics regarding asthma, atopic rash and hay fever were not specified how were measured (was this reported medical diagnosis?).

**Response 1.** We agree with the reviewer that the lack of objective measurements of respiratory health is a limitation of our study. This is acknowledged in the Limitation section (lines 419-420), as well as in the article summary (lines 57-58). Please see our response to your comment #4 for more details on this issue.

Regarding the assessment of indoor environmental quality, the strength of the study was that IEQ was expert-evaluated and not based on the reports from pupils or parents. However, neither specific measures of IEQ (e.g., CO2 levels, oxides of sulfur and nitrogen) nor special visits to the school buildings were done, as the reviewer has pointed out. To validate the expert assessment of IEQ, moisture and mold damage was also assessed in a subsample of 43 school buildings by two independent inspectors, and a substantial agreement was found between the experts' and inspectors' assessment of moisture and mold damage in schools. We have previously extensively discussed the strengths and limitations of the expert assessment of IEQ used in our previous study (Savelieva et al. Associations between indoor environmental quality in schools and symptom reporting in pupil-administered questionnaires. *Environ Heal.* 2019;18:115) and have summarized it in the current study. Please see lines 185-192; 424-429 for details.

As for the pupils' allergic characteristics, we have now provided a more detailed description of asthma, hay fever, and atopic dermatitis to the Method section (lines 238-242). The information on medical diagnosis is only available for asthma. Please see also our response to your comment # 7 for details.

The following point should also be addressed:

**Comment 2.** The term "individual characteristics" should be better specified as most characteristics are associated with allergic diseases, perhaps it should be stated "Individual and allergic characteristics" or "demographic and allergic characteristics"

**Response 2.** Thank you for this suggestion. We are now using the term 'individual characteristics' for age, sex, and smoking, and the term 'allergic characteristics' for asthma, hay fever, and atopic dermatitis everywhere in the manuscript.

**Comment 3.** It could be considered the use of a flow diagram regarding participants selection, as supplementary file to follow more comparatively the rate of response between groups and the participants exclusion. This is included in the text however the presence of a supplementary table or flow-chart might increase comprehensibility

**Response 3.** As suggested, we have now added a flow diagram to the Supplementary Materials which describes how the school buildings and participants in three samples were selected for the study. We have also added a table with a response rate of participants. Please see Supplementary Table 1 and Supplementary Figure 1.

**Comment 4.** Respiratory symptoms were assessed only by questionnaire, further these questionnaires were different between primary and secondary pupils and parents. How was the questionnaire changed? Was there performed any pilot trial?

**Response 4.** We agree with the reviewer that having objective measurements of respiratory health would have strengthened our study design. To make any conclusions about the role of psychosocial factors, the results of our study should be, therefore, replicated with objective measurements of respiratory health. It should be noted, however, that the main aim of the survey of indoor air quality and symptoms conducted in all schools in Helsinki was to study how pupils' themselves report their symptoms related to indoor air quality, as well as perceive indoor air quality in schools. Given that reported symptoms have a major influence on the authorities' conclusions concerning the severity of indoor air problems in specific schools and the need for renovation or other actions, we wanted to study what other factors (e.g., psychosocial factors) may influence symptom reporting of pupils.

The main difference between the questionnaires for primary pupils versus secondary pupils and parents is that the questionnaire for primary pupils was simplified, contains pictures of a child experiencing the symptom, and has less response options (0 = "never", 1 = "sometimes", 2 = "almost every day" for primary pupils versus 0 = "never", 1 = "sometimes", 2 = "every week", and 3 = "almost every day" for secondary pupils/parents). A pilot study was conducted in ten primary schools, and parents were asked to filled-in questionnaires for their children (Ung-Lanki S, Lampi J, Pekkanen J. Analyzing symptom data in indoor air questionnaires for primary schools. *Indoor Air*. 2017;27:900-8, doi: 10.1111/ina.12378). We have also examined the repeatability of the questionnaires in pupil- and parent-administered questionnaires (Lampi J, Ung-Lanki S, Santalahti P, Pekkanen J. Test-retest repeatability of child's respiratory symptoms and perceived indoor air quality - comparing self- and parent-administered questionnaires. *BMC Pulm Med*. 2018;18:32. doi: 10.1186/s12890-018-0584-x). The questionnaire used in the present study was developed based on the results of the pilot studies.

**Comment 5.** Regarding the psychosocial factors and satisfaction with school environment could these answers be associated with academic success/scholar achievement. Was the evaluation performed during exam season? This could also interfere with the school environment reported satisfaction

**Response 5.** The questionnaire survey was conducted in all schools during winter (both in 2017 and 2018), therefore we do not think that the exam time could interfere with pupils' satisfaction with school environment. We cannot, however, eliminate the possibility that pupils' academic achievements may influence their perception of the school environment, but, unfortunately, this information was not available in the present study.

**Comment 6.** Within the psychosocial factors worry about indoor environment is expressed on table 1 as mean (SD), most of the values were low, is there any minimal important difference defined? Why is low school satisfaction presented as mean (SD) and home satisfaction as a percentage. Similar data presentation could help to improve results interpretation.

**Response 6.** We are not aware of any meaningful cut-off points for these psychosocial factors, therefore we have treated pupil- or parent-reported worry, school-principal-reported worry, and school satisfaction as continuous variables in the analyses and reported means (SD) for these variables in table 1. Also, pupil- or parent-reported worry is related to respiratory symptoms in a dose-response manner and we have now shown this in Supplementary Table 2.

Home satisfaction, as well as having friends to spend time with, were highly skewed and we therefore categorized them into three groups to facilitate the interpretation of the results (0 = “always or often”, 1 = “quite often”, 2 = “occasionally, quite rarely, and rarely or never”). That is why we presented prevalence estimates for these three groups for home satisfaction and having friends in Table 1. This is now described in the manuscript on lines 214-223.

**Comment 7.** Line 222: How were asthma, hay fever and atopic rash defined? What “atopic rash” includes, atopic dermatitis, urticaria? In table 2 only the word rash was include.

**Response 7.** Asthma, allergic rhinitis or hay fever, and atopic rash were self-reported by the survey participants who were asked whether they had the following diseases during the last 12 months. Secondary school pupils and parents of primary school pupils were further asked whether asthma was diagnosed, and the majority responded that yes (i.e., 72% for secondary school pupils and 85% for parents of primary school pupils).

Atopic rash includes atopic dermatitis, and we have now corrected this everywhere in the manuscript.

**Comment 8.** Models characterization should be included in table 3-5 to improve comprehensibility

**Response 8.** We have now specified the models for tables 3-5 (see pages 28-32).

**Comment 9.** In the limitation section (line 388) it should be included that the study cross-section design limits the ability to establish causality

**Response 9.** We have now added the following to the Limitation section (lines 414-419): *“First, as we have discussed earlier in length<sup>26</sup>, a cross-sectional design of this study does not allow to determine the direction of the associations between psychosocial factors, especially worry, and respiratory symptoms: we cannot state whether it is psychosocial factors that increases respiratory symptom reporting or whether experiencing symptoms induces psychosocial factors. Therefore, further studies with prospective study design are needed to investigate this issue.”*

**Comment 10.** In the conclusion section (line 391) it should be considered that an intervention on psychosocial outcomes might interfere with the children perception of indoor environment associated with school.

**Response 10.** This is a good suggestion and we agree that intervention on psychosocial factors might be important in children perception of school indoor environment. However, we are not discussing intervention on psychosocial factors in this study because it is beyond the scope of the paper.

**Reviewer: 2**

Reviewer Name: Jonas Miller

Institution and Country: Stanford University, USA

Please state any competing interests or state 'None declared': None declared

**Comment 1.** I think it would be helpful to provide some brief examples what is meant by “poor psychosocial work environment” on page 4 of the introduction.

**Response 1.** As suggested, we have now briefly explained what is meant under poor psychosocial work environment (lines 72-73):

*“Several studies in office buildings have shown that poor psychosocial work environment (characterized by high job demands, low work control, and low support at work)...”*

**Comment 2.** The introduction needs to provide more justification for considering the question of “how much variance between schools in symptom reporting is explained by” psychosocial and individual characteristics. Currently, it is hard for me to understand how individual differences in psychosocial factors might explain differences in reporting across schools.

**Response 2.** Thank you for pointing this out. We have now added the explanation to the Introduction section. Please see it in the revised manuscript on lines 82-88 and below.

*“It is also possible that pupils’ reporting of symptoms differs between schools due to school IEQ or due to psychosocial characteristics of pupils (e.g., worry and school satisfaction), suggesting potential clustering of schools. Previous studies on perceived indoor air quality have shown that both pupil- and school-level psychosocial factors explained part of the variance between schools on perceived indoor air quality<sup>27</sup>. However, it has not been addressed how much variance in symptom reporting between*

*schools is explained by psychosocial, and individual and allergic characteristics of pupils in addition to school IEQ.”*

**Comment 3.** Are there prior studies indicating why reporting on symptoms in relation to a specific environment might be moderated by psychosocial factors? I'm wondering if the introduction can provide additional information about what led the authors to ask the following question on page 5 and why it is meaningful: "When symptoms are reported in relation to specific environment, the responses may be influenced by various psychosocial factors, such as worry about IEQ, overall satisfaction with school environment, and interactions with teachers and peers, although this has not been yet addressed."

**Response 3.** To the best of our knowledge, no previous studies have examined associations between psychosocial factors and symptoms reported in general versus in relation to a specific environment. We have now revised the paragraph on page 5 and better explained our motivation for studying this question.

*Lines 91-102: "The indoor air questionnaires sometimes ask whether symptoms are related to a certain indoor environment or even get worse in a certain environment<sup>28</sup>. It is difficult for some respondents to assess this<sup>29</sup>, and symptoms that are attributed to a specific environment may also produce responses more related to this environment<sup>26</sup>, although this has not been studied. We have previously found that the associations between school IEQ and pupils' symptoms were stronger in magnitude when symptoms were reported in relation to the school environment compared to symptoms reported without such relation<sup>29</sup>. However, it has not been addressed whether the associations between psychosocial factors and symptom reporting differ when symptoms are asked in relation to being in school and when symptoms are experienced in general (i.e., without relation to any specific environment). Based on previous studies<sup>25,26</sup>, it might be possible that pupils who are more worried about school IEQ, less satisfied with the school environment, or have higher neuroticism would report more symptoms, especially in relation to the school environment."*

**Comment 4.** As the authors report in their manuscript, there is a lot of missing data for parent-report measures. Please clarify whether any of the models included parent-reported symptoms as the outcome and child-reported psychosocial factors as the predictor. One strength of this approach is that it does not rely on a single reporter. On the other hand, there is a lot missing data for parent-report measures. Are there issues of missingness that violate any of the assumptions of the analysis (e.g., missing completely at random)?

**Response 4.** The original analyses were conducted in all three samples separately (i.e., primary school pupils, secondary school pupils, and parents of primary school pupils); therefore, no models included parent-reported symptoms as outcomes and child-reported psychosocial factors as predictors. However, this is a good suggestion and we agree with the reviewer that building such model will eliminate a single reporter bias. Therefore, we conducted additional analyses in the combined sample for primary school pupils and their parents (n=1606) using parent-reported symptoms as outcomes and child-reported psychosocial factors as predictors. But given the very low response



rate in parental data (less than 20%) which may involve the risk of sampling bias, we have conducted multiple imputation to minimize bias and examine the potential impact of missing data on the findings. For this, we built a model using all the available information on primary school pupils (e.g., pupils' individual and allergic characteristics, their reports of symptoms, psychosocial factors, as well as schools' IEQ) to impute parent-reported respiratory symptoms reported in general and in relation to school environment. Multiple imputation was done under fully conditional specification in Stata 15 using *mi impute* command. The statistical analyses were conducted using the pooled estimates of 20 imputed data sets. We reported the results in imputed sample (n=8775) and in original sample (complete cases, n=1606) for comparison (Supplementary Table 3). This is now described in Statistical analysis section on lines 276-281.

The results are described on lines 323-327 in the manuscript: *"In the combined sample of parent-child pairs, pupil-reported worry was related to higher respiratory symptoms reported by parents for their children both in relation to the school environment and without such relation; school principal-reported worry was also related to respiratory symptoms, but only when reported in relation to the school environment (Supplementary Table 3). The results in the imputed and original sample were largely the same."*

**Comment 5.** How many schools were included in each latent class?

**Response 5.** The distribution of school buildings per each latent class was the following: (a) Good IEQ (n = 62 school buildings, 46%), (b) Moderate IEQ (n = 54, 40%), and (c) Poor IEQ (n = 19, 14%). This is now mentioned in the manuscript on lines 195-196.

**Comment 6.** Report the Cronbach's alpha for the measure of satisfaction with home environment as is currently done for the measure of satisfaction with school environment.

**Response 6.** The measure of satisfaction with home environment is based only on one question – "It is nice being at home". It is, therefore, not possible to estimate the Cronbach's alpha, a measure of internal consistency which shows how closely a set of items are related as a group, for this variable. Another variable mentioned together with the satisfaction with home environment is the measure of whether a pupil has friends – "I have friends with whom to spend time". This measure is not combined with satisfaction with home environment and used separately in the analyses. We have now clarified the description of these two measures in the Method section (lines 214-223).

**Comment 7.** What is the interpretation of the finding that worry about IEQ reported by school principals was not associated with respiratory symptoms in any of the samples?

**Response 7.** Worry about IEQ reported by school principals was associated with higher respiratory symptoms, but only in models not including pupil- or parent-reported worry. ORs from these models (additionally adjusted for individual and allergic characteristics) were the following: ORs for primary school pupils were 1.10 [1.02, 1.19] and 1.22 [1.08, 1.38] (reported in general and in relation to the school environment, respectively); ORs for secondary school pupils were 1.21 [1.05, 1.40] and 1.65 [1.37, 1.99], respectively; ORs for parents were 1.37 [1.16, 1.61] and 2.08 [1.62, 2.68], respectively. However, when including pupil- or parent-reported worry to the model, the associations between school principals' reported worry and respiratory symptoms attenuated and became nonsignificant (these associations are shown in tables 3-5). We have now clarified this in the manuscript on lines 311-318.

These results suggest that principal-reported worry does not have any independent effects on respiratory symptoms beyond pupil- or parent-reported worry. Worry reported by school principals could to some extent reflect the situation with IEQ in school, because it could be based on reports of indoor air quality assessment or of any repair works done in schools. Principal-reported worry strongly correlates with school IEQ ( $r=0.68$ ) in our data. Pupil- or parent-reported worry, on the other hand, could reflect a more subjective evaluation of IEQ situation in schools. When including both principal-reported worry and pupil- or parent-reported worry to the model, it seems that principal-reported worry does not bring any new information to the association between pupil- or parent-reported worry and respiratory symptoms. Also, given that symptoms are reported by pupils or parents, it is more likely that pupil- or parent-reported worry is related to symptom reporting rather than principal-reported worry.

**Comment 8.** The variance between schools was very low for respiratory symptoms. Could the authors show whether variances were statistically significant? In other words, were there meaningful differences between schools that were even worth probing?

**Response 8.** Thank you for this comment. The variance in respiratory symptoms between schools was indeed very low but statistically significant. We have now reported in the Results section the intraclass correlation coefficients and their statistical significance based on the null model which includes only random intercept.

Lines 333-339: *“Based on the results from the null model including random intercept, the variance between schools was statistically significant but very low for respiratory symptoms reported in general (ICC = 0.6%,  $p=0.010$  for primary school pupils; ICC = 1.4%,  $p < 0.001$  for secondary school pupils; and ICC = 1.3%,  $p = 0.016$  for parents of primary school pupils) and slightly higher for respiratory symptoms reported in relation to the school environment (ICC = 0.6%,  $p=0.013$  for primary school pupils; ICC = 2.4%,  $p < 0.001$  for secondary school pupils; ICC = 2.2%,  $p < 0.001$  for parents of primary school pupils).”*

We have now mentioned this in the Abstract: *“The variance between schools in respiratory symptoms was low (ICC = 0.6-2.4%).”* (lines 35-36).

In the Results section, we have also shortened our description of how much variance between schools is explained by psychosocial and individual factors (lines 339-342). Based on the changes of ICC, it seems that psychosocial factors, and especially worry about IEQ, explained more of the variance between schools in respiratory symptoms than IEQ in the reports by secondary school pupils and parents (Supplementary Table 4). Individual and allergic characteristics explained much less variance between schools in symptom reporting (Supplementary Table 5).

While discussing these results, we make sure to remind our readers that although psychosocial factors explained much of the variance between schools in respiratory symptoms, the variance between schools was low to begin with (see, for example, lines 361-366; 435-437).

**Comment 9.** The interpretation for the association between symptom reporting and negative affectivity is that these individuals are more likely to pay attention to, monitor, and accurately report on somatic states. My understanding is that there is little support for the perspective that there are meaningful individual differences in the ability to report on somatic states (e.g., interoception). Thus, I think it would be helpful to briefly talk about the potential impact of negative affective states on biology related to symptoms.

**Response 9.** Thank you for this comment. Several mechanisms have been proposed that may explain the associations between neuroticism / negative affectivity and increased symptom reporting. We have rewritten that paragraph and included more explanations for the associations between neuroticism and symptom reporting.

Lines 390-402: *“Among personality traits, higher neuroticism, which is characterized by a tendency to experience negative emotional states, was associated with increased respiratory symptom reporting in the present study. This accords with previous studies on high negative affectivity (a mood-related disposition similar to neuroticism) which is known to correlate with virtually all measures of symptoms<sup>20,40</sup>. One line of explanations suggests that attentional processes and biases in the interpretation of bodily sensations may contribute to the relationship between neuroticism and increased symptom reporting<sup>24,41</sup>. Another line of explanations is that people with high neuroticism have a higher sensitivity to negative experiences and poorer abilities in adapting to difficult situations<sup>42,43</sup>, which results in higher psychosocial stress leading, for example, to elevated blood pressure, increased migraines, and neck pains<sup>44</sup>. Alternative explanations are also possible suggesting that health problems can cause distress and lead to personality changes (such as higher neuroticism) which, in turn, are related to higher symptom complaints<sup>41</sup>.”*

**Comment 10.** What does it mean that women may report more symptoms and describe changes in health “more easily” than men?

**Response 10.** We have now revised this part of the manuscript and improved interpretation of our findings that female sex was associated with higher symptom reporting.

Lines 407-413: *“In line with previous studies showing that women tend to report indoor air problems and symptoms more often than men <sup>21,28,45,46</sup>, we found that female sex was associated with higher respiratory symptom reporting among pupils. It has been suggested that males and females rely on different sources of information to interpret bodily states, and females are particularly sensitive to external environmental cues <sup>24</sup>. Although speculative, this could partly explain the findings that women consistently report greater symptom levels in, for example, sick building syndrome or multiple chemical sensitivity <sup>24</sup>.”*

**Comment 11.** Much of the discussion is spent summarizing the findings and then commenting on whether findings fit with prior studies. I would like a little more attention devoted to discussing what the authors think the findings mean.

**Response 11.** We have now substantially revised Discussion and focus on interpretation of our findings. See, for example, the revised paragraphs 2-4 in Discussion (pages 16-18).

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Diana Silva Faculty of Medicine of Porto University, Portugal
<b>REVIEW RETURNED</b>	12-Jun-2020
<b>GENERAL COMMENTS</b>	All reviewer comments and suggestions have been fully addressed by the authors.
<b>REVIEWER</b>	Jonas Miller Stanford University, USA
<b>REVIEW RETURNED</b>	24-Jun-2020
<b>GENERAL COMMENTS</b>	I commend the authors on their job revising their manuscript. I have no further comments.