Author’s response to reviews

Title: Association between exposure to traffic-related air pollution and pediatric allergic diseases based on modeled air pollution concentrations and traffic measures in Seoul, Korea: A comparative analysis

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Author’s response to reviews:

Reviewer #1:

This study was aimed to investigate the relationship between pediatric allergic diseases and exposure to TRAP. The authors selected the study population appropriately according to their algorithm, and recruited a large number of children. Data were analyzed appropriately in the statistical models. However, they just found the association between eczema and TRAP, and did not show the causality. There are several issues to discuss about.

Response: We appreciate the comments of the reviewer. Our responses and revised texts are provided for each comment below. Also, please note that we provided the same version of the responses with a different format including the direct comparison of the text before and after the revision as well as additional analysis results following reviewer’ suggestions in our cover letter because we were not able to upload our word file in the submission system.

1. The authors stated that annual average concentrations of air pollutants were used. Please specify the dates to start and finish assessment of individual exposures. Was it from May 1, 2010 through Oct 31, 2010 or from Jan 1, 2010 through Dec 31, 2010?
Response: We added the start and end dates to clarify the period from January to December in 2010.

Before (line: 134): To assess children’s individual exposures to NO2, PM10, and PM2.5, we predicted annual average concentrations at children’s home addresses using universal kriging and land use regression for NO2 and PM10, and PM2.5, respectively, based on regulatory monitoring data and geographic variables (Additional file 1: Figure S1).

After: To assess children’s individual exposures to NO2, PM10, and PM2.5, we predicted annual average concentrations, from January to December in 2010, at the children’s home addresses using universal kriging for NO2 and PM10, and land use regression for PM2.5, based on regulatory monitoring data and geographic variables (Additional file 1: Figure S1).

2. This study appears to be based on the assumption that all children in the study population resided at the same area since birth. However, some of them may move into the current address within a year or two. In that situation, the annual average estimates of TRAP in 2010 do not represent the true exposure amount as they grow. Therefore, TRAP may not involve the development of atopic eczema but affect the persistence of eczema symptoms. I suggest adding a sentence to say that the relationship between TRAP exposure and AD development was not clear in the present study, especially in children aged over 5 years.

Response: We agree that our exposure assessment has a limitation to evaluate the association between AD development and TRAP exposure. We added this point as one of our limitations to the Discussion.

Before (line 375): There were several limitations in this study. First, … High correlation of PM10 with road density and proximity in our study and high contribution of traffic to PM10 in a previous review study of source apportionment in Seoul [26] may support our application in a highly populated metropolitan area such as Seoul.

After: There were several limitations in this study. First, … The high correlation of PM10 with road density and proximity in our study as well as the high contribution of traffic to PM10 according to a previous review study of source apportionment in Seoul [26], may support this application in a highly populated metropolitan area, such as Seoul. Lastly, the causal relationship between TRAP exposure and allergic disease development was unclear in the present study, especially in children aged over 5 years. Because our exposure assessment was limited to 1-year averages in 2010 and did not incorporate previous exposures such as information about relocation, our findings suggest a relationship with persistence of allergic diseases rather than their development. Future studies based on birth cohorts should investigate the impact on incidence or development of allergic diseases.

3. In this study, skin prick test was not conducted, and therefore the presence of sensitization to common allergens at individual levels was not elucidated. Although the exposure to allergens, inhalant or food, is more important risk factor than air pollutants in
children with atopic eczema, this confounder was not adjusted. This is one more limitation that should be emphasized in the manuscript.

Response: We agree that non-availability of the information on exposure to common allergens is another limitation of our study. We clarified this point in the Discussion.

Before (line 375): There were several limitations in this study. First, … Second, we did not include other potential confounders such as smoking status and educational attainment of parents, and presence of other allergen including companion animals and chemicals house-dust in children’s homes. Especially, absence of genetic predisposition should be considered in future studies.

After: There were several limitations in this study. First, … Second, we did not include other potential confounders such as family characteristics and indoor environments, which were unavailable in our study. Future studies should include family characteristics related to smoking status, allergic history, and educational attainment of parents, and the presence of other identified allergens based on companion animals, chemicals, or house dust in children’s homes, preschools, and/or schools. As the Seoul Atopy Friendly School Project Survey did not include a skin prick test, information on the presence of sensitization to common allergens was also unavailable in this study. Further studies including information of sensitization and important allergens should be conducted to confirm our findings. The absence of genetic predisposition should be also considered in future research.

4. The present conclusion needs to be revised. This study simply provides one additional evidence that TRAP exposure is association with high prevalence of eczema, but does not prove either the causal relationship or biological mechanism. The last 2 sentences (As people tend to ~ children living in large cities) are not based on the present study results.

Response: Following the reviewer’s comment, we revised our conclusion to clarify our findings based on prevalence and a future research topic for the causal relationship

Before (line 393): In this study, we found the evidence of the association between traffic-related air pollution and atopic eczema in children based on a large and representative population in a highly urbanized city with a major pollution source of traffic. In particular, consistent findings using both traffic measures and air pollution concentrations reassured the association. As people tend to live near busy and large roads for easy access to transportation in a megacity, the affected children and the amount of risks would be enormous. Our results suggest appropriate policy consideration to minimize adverse health effects of traffic-related air pollution particularly for children living in large cities.

After: In this study, we found evidence of the association between traffic-related air pollution and prevalence of atopic eczema in children, based on a large and representative population in a highly urbanized city in which traffic is a major pollution source. In particular, consistent findings observed using both traffic measures and air pollution concentrations confirmed the association. As people in megacities tend to live near large, busy roads for easy access to transportation, the number of the affected children and the level of risk would be enormous.
Future studies based on extended data including early air pollution exposure and exposure to common allergens should further investigate the associations with the incidence and development of allergic diseases, and provide policy recommendations to minimize the adverse health effects of traffic-related air pollution particularly for children living in large cities.

5. The authors should follow the styles of the Journal according to the instructions.

Response: We made edits over the entire manuscript to meet the required journal styles.

6. I would recommend to get assistance for English translation before publication.

Response: We have had a native English speaker edit the entire manuscript to improve the quality of English writing.

Reviewer #2:

This is an interesting large study investigating the association of childhood prevalence of asthma and allergic disease with long-term exposure to PM and NO2 in Seoul, therefore a large densely populated Asian city, where traffic is a (the) prominent source.

So far European and North American-studies seem to be predominant, so an Asian study would be a welcome addition.

The manuscript is overall clearly and well written, although English needs some polishing in several places.

Response: We appreciate the positive comment of the reviewer. We have had a native English speaker edit the entire manuscript to improve the quality of English writing. Our responses and revised texts are provided for each comment below. Also, please note that we provided the same version of the responses with a different format including the direct comparison of the text before and after the revision as well as additional analysis results following reviewer’s suggestions in our cover letter because we were not able to upload our word file in the submission system.

A strength is the information of school exposure; and data on SES as potential confounders, while a certain weakness is the absence of other potential confounders: no ETS, indoor air pollution sources, dampness, parental allergy, (older) siblings, day care (?) - I guess these were not available.

Response: We added other characteristics suggested by the reviewer as our limitations for potential confounders.
There were several limitations in this study. First, measurement errors in outcome might have affected our findings. The data obtained from self-reported questionnaire would produce over- or under-estimated prevalence, as we observed relatively high prevalence...
of allergic rhinitis in our study. However, consistent findings between symptom and doctor-diagnosis indicate that the impact of misclassification could be negligible.

After: There were several limitations in this study. First, measurement errors of outcome might have affected our findings. The data obtained from the self-reported questionnaires could overestimate prevalence. Recent validation studies of the ISAAC questionnaires in South Korea reported overestimated prevalence for allergic rhinitis (Kim et al, 2018) and atopic eczema (Choi et al, 2012). In particular, this overestimation could have been greater as the questions regarding symptoms are not allergy-specific. However, consistent findings with respect to the association with TRAP in our study between symptoms and doctor-diagnoses based on allergic-specific questions indicate that the impact of misclassification could be negligible.

Another interesting addition would be to investigate asthma in children with other allergic disease as done in a Canadian study (Dell et al., reference 17): test rhinitis and also rhinoconjunctivitis which is more indicative of allergy, similarly flexural eczema: more specific than eczema. Indeed, Asthma has a large non-allergic component, and it would be worthwhile to investigate whether the relation of asthma with air pollution is modified by rhinitis or excema as it has been done in (Dell et al). Although number of children in the analysis will decrease, it will still be comparable to the numbers in the Canadian study where a clear effect was found.

Response: Following the suggestion of the reviewer, we conducted additional analysis to investigate the association between air pollution and asthma in the children restricted to those having diagnosis of rhinitis and eczema. Additional table 1 and 2 shows no associations which is consistent with our previous result for all children. We added our approach, findings, and interpretation for this additional analysis to the Methods, Results and Discussion.

Before (line 220, method): Our sensitivity analysis included the analysis using an alternative individual-level exposure metric that incorporated air pollution exposure at children’s schools or kindergartens. We predicted annual average concentrations at schools using the same prediction methods to those used for homes. We recomputed individual air pollution concentrations by averaging predicted concentrations at homes and schools using the ratio of 2 to 1, because the average operating hour of kindergartens was reported as 7 hours and 34 minutes [42] and elementary school students stayed at their schools for 8 hours on average [43].

After: Our sensitivity analysis included analysis using an alternative individual-level exposure metric that incorporated air pollution exposure at the children’s schools or kindergartens. We predicted annual average concentrations at school addresses using the same prediction methods as those used for homes. We recomputed individual air pollution concentrations by averaging the predicted concentrations at homes and schools using a ratio of 2:1 because the average operating hours of kindergartens are reported as 7 hours and 34 minutes [42] and elementary school students remain at school for 8 hours, on average [43]. As another sensitivity analysis, we examined the association of asthma by presence of allergic and non-allergic diseases, as the prevalence of asthma comprises a large proportion of non-allergic cases and the association of TRAP was modified by presence of allergic diseases (Dell et al. 2014). We conducted our analysis for asthma in children with a diagnosis of allergic rhinitis or atopic eczema and compared the results with those in children who did not have these diagnoses.
Before (Line 289 results): When we recomputed children’s exposures to TRAP by including air pollution concentrations at schools in addition to homes, we found the associations of NO2 with atopic eczema symptom and diagnosis. ORs slightly decreased (Model 3 OR = 1.06, 95% CI = 1.01–1.12; 1.07, 1.01–1.13) compared to those based on children’s home addresses only in the main analysis (Additional file 5: Figure S4). ORs of PM10 were positive but showed marginal significance (1.05, 0.99-1.11; 1.05, 0.99-1.12).

After: When we recomputed children’s exposures to TRAP by including air pollution concentrations at their schools in addition to their homes, we found associations of NO2 with atopic eczema symptom and diagnosis; ORs for these (model 3 OR = 1.06, 95% CI = 1.01–1.12; 1.07, 1.01–1.13) were slightly lower than ORs based on children’s home addresses only in our main analysis (Additional file 5: Figure S4). ORs for PM10 were positive but showed marginal significance (1.05, 0.99-1.11; 1.05, 0.99-1.12, respectively). In the analysis for asthma using children with and without a diagnosis of allergic rhinitis or atopic eczema, effect estimates were mostly close to the null and non-significant, without any clear pattern of differences between the two groups.

Before (Line 347 discussion): We did not find the association for asthma and allergic rhinitis. A recent review study showed associations between outdoor NO2 and pediatric asthma development and symptoms of wheezing [50], and experimental evidences also supported the relationship between PM and asthma [51]. While further investigations are needed to elucidate these contradictory relationships, various etiology of asthma other than exposure to air pollution may explain the discrepancy [52]. Especially genetic predisposition and secondary smoking which were not adjusted in this study, would act as confounders and lead to different results.

After: We did not find significant associations for asthma and allergic rhinitis. A recent review study showed associations between outdoor NO2 and pediatric asthma development and symptoms of wheezing [50]; experimental evidences has also supported the relationship between PM and asthma [51]. Although further investigations are needed to elucidate these discrepancies, various etiologies of asthma other than exposure to air pollution may explain these discrepancies [52]. Particularly genetic predisposition and/or secondary smoking, which were not included in this study, could act as confounders and may lead to different results without adjustment. In addition, non-allergic components of asthma possibly included in the asthma prevalence in our study might have affected the results of no association. Previous studies showed higher effect estimates of TRAP in people diagnosed with allergic diseases than in those who were never diagnosed (Dell et al 2014) and significant estimates only in individuals with allergic asthma (Lindgren et al 2009). However, our sensitivity analysis restricted to children diagnosed with allergic rhinitis or eczema also showed no associations.

The authors emphasize the findings on eczema which are statistically significant, but also positive associations that are only nearly statistically significant should receive more attention (rhinitis and PM2.5).

Response: We added our findings of positive associations between PM2.5 and rhinitis to the Results and Discussion.
Before (Line 277, results): There were no associations of asthma and allergic rhinitis for all three pollutants and two types of allergic diseases

After: There were no associations of asthma and allergic rhinitis for all three pollutants and two types of allergic diseases. However, allergic rhinitis based on both symptom and diagnosis was marginally associated with PM2.5 (1.04, 0.99–1.09; 1.04, 0.98–1.10, respectively).

Before (Line 354, discussion): Our findings of no associations between TRAP and allergic rhinitis were also inconsistent with previous findings [53]. Rhinitis has dynamic natural course indicating that the symptoms of rhinitis were not persistent and could disappear within two years [54]. Considering the cross-sectional nature of this study, the association with allergic rhinitis could have been difficult to be captured.

After: Our findings of no association between TRAP and allergic rhinitis, although there was a marginal association for PM2.5, were also inconsistent with previous epidemiological and toxicological findings (Chen et al 2018; Li et al 2019). Rhinitis has a dynamic natural course, indicating that the symptoms of rhinitis are not persistent and could disappear within two years [54]. Considering the cross-sectional nature of this study, the association with allergic rhinitis could have been difficult to capture.

More specific comments:

Title:

The "using traffic measures and surrogate air pollutants" is a bit misleading as modelled pollutants are investigated. Also not only traffic geographic indicators are used for modelling therefore, I suggest to use the term traffic related air pollution (TRAP) in a more cautious way and mention it only in the discussion (but not as it is in the first sentence there), to contrast it to studies where explicitly only the traffic-component has been modelled.

Response: Modeled air pollution concentrations for NO2 and PM, used in this study, were considered surrogates for TRAP in previous studies, but also have the limitation as they include other emission sources than traffic as pointed out by the reviewer. To confirm the association between TRAP and allergic diseases, we compared our results using air pollution with those using direct “traffic measures”, road proximity and density, in our previous study. We revised our title to clarify this point.

Before: Associations between exposure to traffic-related air pollution and pediatric allergic diseases using traffic measures and surrogate air pollutants in Seoul, Korea

After: Association between exposure to traffic-related air pollution and pediatric allergic diseases based on modeled air pollution concentrations and traffic measures in Seoul, Korea: A comparative analysis

Abstract: (350 words)
In the Results, the positive association of rhinitis with PM2.5 should also be mentioned with ORs, and that no association was found for the others. To keep the word count the Introduction could be shortened (e.g. by deemphasizing TRAP).

Response: We added the association of PM2.5 and rhinitis to the Abstract. However, ORs were not presented given the word limit.

Before: We found the associations of symptoms and diagnoses for atopic eczema symptoms with NO2 (OR=1.07, 95% Confidence Interval=1.02–1.13; 1.08, 1.03–1.14) and PM10 (1.06, 1.01–1.12; 1.07, 1.01–1.13). ORs of PM2.5 were positive but not statistically significant (1.01, 0.96–1.07; 1.03, 0.98–1.09). We did not find any associations for asthma and allergic rhinitis.

After: Symptoms and diagnoses of atopic eczema symptoms showed an association with NO2 (OR=1.07, 95% confidence interval=1.02–1.13; 1.08, 1.03–1.14) and PM10 (1.06, 1.01–1.12; 1.07, 1.01–1.13). ORs of PM2.5 were positive but not statistically significant (1.01, 0.96–1.07; 1.03, 0.98–1.09). No association was found between asthma and allergic rhinitis, although PM2.5 showed a marginal association with allergic rhinitis.

In the conclusions: the first sentence using the formulation TRAP and its surrogates is misleading (as the title) - rather the pollutants that were investigated should be named.

Response: We revised the conclusion to clarify that we used both traffic and air pollution measures to support the association between TRAP and allergic diseases, as revised in our title. We focused on this clarification rather than providing the names of pollutants given the word limit.

Before: Our consistent findings of the association between TRAP and atopic eczema using traffic measures and surrogate air pollutants confirm the role of TRAP in children’s health. This study suggests the need of subsequent policy consideration to minimize the adverse health effects in children particularly living in a large city with a major pollution contributor of traffic.

After: Our consistent findings regarding the association between TRAP and the prevalence of atopic eczema using traffic measures and surrogate air pollutants suggested the effect of TRAP on children’s health. Follow-up studies should elucidate the causal link, to support subsequent policy considerations and minimize adverse health effects in children.

Introduction:

p4, line 79-80: should be made clear that reference 17 does not investigate this but only discusses this mechanism.

Response: We revised the sentence to imply a possible explanation.

Before (Line 78): NO2 could modify immune responses to various allergens [15, 16] by acting as an adjuvant for sensitization or potentiating inflammatory effects of allergen challenge [17].
After: NO2 can modify immune responses to various allergens [15, 16] possibly by acting as an adjuvant, leading to sensitization or potentiation of inflammatory effects on an allergen challenge as discussed in a previous study [17].

p.5. line 105-112: this paragraph seems not very consequential in its logical argumentation. I think it would be more stringent to omit (or place elsewhere) the 2nd and 3rd sentence and the "Thus" of the fourth sentence. It would be also helpful to introduce here which of the "surrogate pollutants" the authors expect to be most strongly to be associated with traffic - generally this is NO2 and much less PM, esp. PM2.5 - similar in Seoul?

Response: We revised the paragraph to clarify our intention of using two TRAP metrics and then to provide the traffic conditions of Seoul including previous findings for each traffic-related air pollutant.

Before (Line 105): Our recent epidemiological study assessed TRAP using road proximity and density measurements in a largely populated and highly polluted city, Seoul, Korea, and found the association with atopic eczema in about 15,000 children [25]. Although a major source to PM air pollution in Seoul was indicated as traffic [26], people tend to live near arterial roads with large congestion for easy access to transportation [25]. The average of road density within 300m from children’s residences in this study was 7,200m2. Thus, comparison of health analysis findings using original traffic estimates with those using concentrations of traffic-related air pollutants will reassure the health effect of TRAP exposure.

After: A study using both direct traffic measures and air pollution concentrations can enhance our understanding in the association between TRAP and allergic diseases. Our recent epidemiological study assessed TRAP using road proximity and density measurements in a heavily populated and highly polluted city, Seoul, Korea. We found an association between TRAP and atopic eczema in our study, which included approximately 15,000 children [25]. Using the same study population, exposure to TRAP could be assessed by modeled air pollution concentrations, instead of traffic measures. The comparison of two sets of health analysis results from two different measures for TRAP can provide strong evidence of the association between TRAP and allergic diseases. In particular, traffic conditions and related air pollution characteristics in Seoul provide a unique opportunity to investigate the association of TRAP. People in Seoul tend to live near arterial roads with heavy congestion for easy access to transportation; the average of road density within 300m from children’s residences in our previous study was 7,200m2 [25]. NO2 and PM, suggested as traffic-related air pollutants in previous studies, also showed their relationships with traffic in Seoul. There was high correlation between traffic volume estimates and NO2 concentrations in Seoul (Kim and Guldmann. 2011; Kim and Guldmann. 2015). A previous review of source apportionment studies indicated that a major source of PM10 and PM2.5 in Seoul is traffic (Ryou et al, 2018).

Methods:

Study population and Fig1: numbers should be checked - they do not add up correctly in Fig1 and do not correspond to the 16,962 mentioned in the text
Response: Corrected.

Before (Line 126): We excluded 16,962 children who did not meet the inclusion criteria [25] (Figure 1).

After: We excluded 16,386 children who did not meet the inclusion criteria [25] (Figure 1).

Allergic diseases: please check the wordings of the questions given: they are not the same as in the ISAAC questionnaire and not the same as in the corresponding Korean publication (reference 27: Hong et al, and ref 56). Were the questions backtranslated into English for a check as it was done in the ISAAC-study?

Response: We presented back-translated questions from the questions translated in Korean in a previous study (Hong et al 2012); these Korean-translated questions were previously validated (Choi et al 1998). We revised our back-translation to English based on the original English questions.

REFERENCES


Before (Line 177): “Has your child wheezed in the last 12 months?”; “Has your child shown nasal stuffiness, runny nose, or sneeze in the last 12 months?”; and “Has your child had itchy rash at any time in the last 12 months?” We also used the following specific questions to define three doctor-diagnosed allergic outcomes: “Has your child ever been diagnosed as asthma by a medical doctor?”; “Has your child ever been diagnosed as allergic rhinitis by a medical doctor?”; and “Has your child ever been diagnosed as atopic eczema by a medical doctor?”.

After: “Has your child had wheezing or whistling in the chest in the past 12 months?”; “In the past 12 months, have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu?”; and “Has your child had an itchy rash at any time in the past 12 months?”. We also used the following specific questions to define three doctor-diagnosed allergic outcomes: “Has your child ever been diagnosed with asthma by a medical doctor?”; “Has your child ever been diagnosed with allergic rhinitis by a medical doctor?”; and “Has your child ever been diagnosed with atopic eczema by a medical doctor?”.

p.9. line 186-187: Were breastfeeding and adiposity the only individual characteristics assessed? Is there no information on additional potential(ly) important confounders such as indoor air
pollution sources, dampness in the home, pets, parental allergic disease? Was BMI reported or measured? Was breastfeeding exclusive? Or with other foods added?

Response: Individual covariates we included in the model 3 were sex, age, breast feeding, and BMI reported by participants or guardians. Other individual covariates such as diet and indoor environments were not available. We added this limitation to the Discussion

Before (Line: 375): There were several limitations in this study. First, … Second, we did not include other potential confounders such as smoking status and educational attainment of parents, and presence of other allergen including companion animals and chemicals house-dust in children’s homes. Especially, absence of genetic predisposition should be considered in future studies.

After: There were several limitations in this study. First, … Second, we did not include other potential confounders such as family characteristics and indoor environments, which were unavailable in our study. Future studies should include family characteristics related to smoking status, allergic history, and educational attainment of parents, and the presence of other identified allergens based on companion animals, chemicals, or house dust in children’s homes, preschools, and/or schools. As the Seoul Atopy Friendly School Project Survey did not include a skin prick test, information on the presence of sensitization to common allergens was also unavailable in this study. Further studies including information of sensitization and important allergens should be conducted to confirm our findings. The absence of genetic predisposition should be also considered in future research.

p.10. lines 205 to 209: random effect: why was adjustment not for the 25 districts but 8 "district areas" - generally random effects modelling performs better with more level2 units - unless they are too numerous to affect convergence, which would surprise me in this case. And how was it determined which adjacent districts should be aggregated? Was also adjusted for regional income?

Response: We used the 8 district areas instead of 25 districts, because the number of participating schools and participants was largely heterogeneous across districts. For example, there were some districts that have much smaller numbers of participants than in other districts, which could have affected our analyses. Thus, the previous study (Yi et al. 2017) that we compared our results with also used these 8 district areas. Furthermore, we performed additional analysis using 25 districts and found almost identical effect estimates with similar AIC values as shown in Additional Table 3.

Reference

Before (Line 205): In model 3 as our primary model, we added a random effect at the residential district area to adjust for unmeasured area-level confounding and to account for correlation of children’s allergic disorders within the same residential district area. For the residential district area, we categorized all 25 districts in Seoul into eight areas by aggregating 2-4 districts nearby.

After: In model 3 we added random effects at the school and residential district area, to adjust for unmeasured area-level confounding and to account for correlation of children’s allergic disorders within the same school and residential district area. For the residential district area, we categorized all 25 districts in Seoul into eight areas by aggregating 2-4 nearby districts. We determined residential district areas via combining of the 25 districts in this way because some districts consist of much smaller numbers of schools and children than others.

p.11 line 219: what is meant by "consistent" data?

Response: We revised the sentence for further clarification.

Before (Line 219): This comparison was performed based on the consistent data and health analysis models including identical covariates.

After: This comparison was done based on the same input data and health analysis models including identical covariates.

Results:

I suggest to give the results of Fig 2 (which are the main results) in a Table to avoid emphasis on statistically significant values which are given in the text and to facilitate future potential meta-analyses. This Table could also contain additional useful information such as the number of children in each analyses.

Response: We added a supplementary table (Table S2) that includes effect estimates shown in Figure 2.

In addition, it would be nice to show there also the results of the sensitivity analysis taking into account school/kindergarten addresses (model 3 only). Where do children typically spend more time outdoors? At home or kindergarten?

Response: We revised our text to clarify that we repeated our main analyses by incorporating exposures at school/kindergarten addresses along with the description for the hours spending at schools/kindergartens.

I miss a Table which reports the prevalence estimated by asking for the diagnosis.
Response: We clarify that Table 1 is for symptom and added a supplemental table (Table S1) to provide the summary for diagnosis prevalence.

Before (Line 259): Children from low-income households showed higher prevalence of atopic eczema (17.9%) and asthma (8.6%) than children from high-income households (13.9 and 7.6%), whereas children living in high SES regions showed higher prevalence (17.3% and 9.2%) than in low SES regions (15.1 and 6.1%). The means of predicted annual average concentrations of NO2, PM10, and PM2.5 across children’s homes were 35.99 ppm, 49.67 μg/m3, and 25.30 μg/m3, respectively (Table 2).

After: Children from low-income households had higher prevalence of eczema (17.9%) and asthma (8.6%) than those from high-income households (13.9% and 7.6%, respectively), whereas children living in high SES regions had higher prevalence of these allergic diseases (17.3% and 9.2%) than in low SES regions (15.1% and 6.1%). For children with prevalent allergic diseases based on a doctor’s diagnosis, the patterns of individual characteristics were generally consistent with those with children who had symptoms (Table S1). One exception was that much fewer children aged ≤ 6 years had asthma and allergic rhinitis. This indicates the possibility of overestimated prevalence among young children based on questions addressing symptoms, justifying our restriction of the analyses to children aged ≥ 6 years. The means of predicted annual average concentrations of NO2, PM10, and PM2.5 at children’s homes were 35.99 ppm, 49.67 μg/m3, and 25.30 μg/m3, respectively (Table 2).

Paragraph on SES, line 287 onwards: while I can support the 1st sentence to some extent, I think the following lines become more and more speculative based on differences in effect estimates that have largely overlapping confidence intervals and seem to be oversimplifying a complex and uncertain pattern. In this context it is very unfortunate that the reader cannot instantly crosscheck with the figures as they are given in the online supplement. Overall, I suggest to deemphasize this part of the study.

Response: We revised the text to avoid misleading and to clarify no statistically meaningful differences between SES groups.

Before: In the stratified analysis by regional and household SES jointly, the highest OR for atopic eczema was found in the low regional and middle household SES and in the high regional and low household SES across all pollutants. Whereas ORs were generally low in the high regional and household SES, the low regional and household SES did not always provide higher ORs than in the other groups. ORs for atopic eczema and allergic rhinitis tended to increase in children with high to low household SES for all pollutants in the middle and high regional SES groups (Additional file 6, 7, and 8: Figure S5, S6, and S7). Also, there was an increasing trend of ORs from the high to low regional SES group in the middle household SES group. Although no association was found for PM2.5 with all three allergic diseases, children from the middle household and low regional SES group showed the association with symptom and diagnosis of allergic rhinitis (1.23, 1.07–1.40; 1.20, 1.03–1.39).
After: In the stratified analysis by regional and household SES jointly, the highest ORs for atopic eczema were found for low regional and middle household SES and for high regional and low household SES, across all pollutants. Whereas ORs were generally low in the group with high regional and high household SES for all three allergic diseases, low regional and low household SES did not always yield higher ORs than in the other groups. In addition, we found statistically significant associations of PM2.5 with both symptom and diagnosis of allergic rhinitis (1.23, 1.07–1.40; 1.20, 1.03–1.39) in children from the group of middle household and low regional SES. These high effect estimates possibly resulted in the marginal association of PM2.5 with allergic rhinitis for all children.

Line 295: add "statistically" in front of the significant, in fact there is already an increased OR for rhinitis in relation to PM2.5 (the exact magnitude and CIs one would be able to see from a Table rather than the Fig).

Response: Revised.

Discussion:

Line 309: what is meant by "different severities"? Which data is that?

Response: We revised the sentence for further clarification.

Before (Line 309): Our results confirmed the association between TRAP and atopic eczema by using different forms of exposure and outcomes with different severities

After: Our results confirmed the association between TRAP and atopic eczema, using two different forms of exposure to TRAP and two types of outcomes including symptom and diagnosis.

Line 319: rather write "symptom prevalence"

Response: Revised

Line 335: reference(s) for studies that did not find this association with PM2.5 should be given

Response: We revised the sentence as below

Before (Line 335): Previous epidemiological findings also suggested that NO2 and PM10 could affect development and exacerbation of atopic eczema [13, 47] but did not find the association for PM2.5. No association between PM2.5 and atopic eczema was further confirmed in a prospective birth cohort study without clear explanation [48].
After: Previous epidemiological findings have also suggested that NO2 and PM10 could affect development and exacerbation of atopic eczema [13, 47]. However, no association was found between PM2.5 and atopic eczema in a prospective birth cohort study [48].

Line 344: I suggest to amend the sentence to: which were not adjusted FOR in this study, COULD would act as confounders and MAY lead to different results

Response: Revised

Line 350-352: Reference 55 gives a rather limited view on worldwide rhinitis, it is better to look e.g. at the world wide ISAAC study in particular Björkstén et al 2008, and compare it to the respective outcome: it can be seen there that a prevalence of rhinitis (which is the equivalent to the question in this article i.e. not reflecting allergic rhinitis) above 40% occurs in several regions of the world, therefore the data here are not that outstanding. Also the argumentation is not stringent: 1) the prevalence in other countries is typically also given by questionnaire response (and it is not necessarily higher in South Korea) and 2) the authors highlight earlier that the consistence between the effect estimates "indicating that the influence of potential misclassification would be minimal" (line322) - and this consistence is also given for rhinitis.

Response: A validation study in South Korea (Kim et al, 2018) revealed that there was over-estimation for ISAAC questionnaire measurement for allergic rhinitis. However, we agree that the effect of the over-estimation on the association would be minimal, since our analyses using diagnosis outcomes showed similar results. We deleted the referred sentence to avoid confusion.

Reference


Before (line 350): Also, the higher prevalence of allergic rhinitis in our study compared with those in other countries [55], suggests the possibility of over-estimation resulting from questionnaire data [56]. This misclassification could have contributed to the null association

After: (deleted)

Line 357: what does this imply that it is the centroid: what area is covered by that? And in how much would this be different from the spatial resolution for the childrens' homes? This would be useful to mention.

Response: We revised the sentence to clarify that the spatial scale of schools is much wider than homes.
Before (Line 357): In addition, most geocoded addresses of schools were their centroids which may result in exposure misclassification and affect subsequent health effect estimation.

After: In addition, most geocoded addresses of schools were the centroids of relatively large areas that included school buildings, playgrounds, and other facilities. This may have resulted in exposure misclassification and affected subsequent health effect estimation.

Line 359 onwards: It should be mentioned that this is very speculative as confidence intervals are widely overlapping and pattern not very consistent across pollutants.

Response: We clarified that our effect estimates are uncertain.

Before (Line 359): We found that probability of having allergic diseases tended to be high in the children with low household or regional SES when combined with middle household or high regional SES, respectively. Effect estimates were even higher than those found in the low regional and household SES. This pattern indicates the possibility of the interactive impact of deprivation at the household and regional levels. The higher risk estimate in the children of lower income families was consistent with previous findings [57], which can be explained by co-existing risk factors in lower income groups, such as lower quality of diet and stress-related environment [57].

After: We found that the probability of having allergic diseases tended to be high in children with low household or low regional SES when combined with middle household or high regional SES, respectively, although effect estimates were not statistically different. Effect estimates in these groups were even higher than those found in the group of low regional and low household SES. This pattern indicates the possibility of an interactive impact of deprivation between household and regional levels. The higher risk estimates found in children from lower-income families was consistent with previous findings [57], which can be explained by co-existing risk factors in lower-income groups, such as low quality diet and living in a stressful environment [57].

Line 369-70: "high prevalence of allergic rhinitis" see comment above

Response: We cited the Korean validation study to clearly show the overestimation of allergic rhinitis, although the effect of the over-estimation would be minimal as we described in the following sentence.

Before (Line 375): There were several limitations in this study. First, measurement errors in outcome might have affected our findings. The data obtained from self-reported questionnaire would produce over- or under-estimated prevalence, as we observed relatively high prevalence of allergic rhinitis in our study. However, consistent findings between symptom and doctor-diagnosis indicate that the impact of misclassification could be negligible.
After: There were several limitations in this study. First, measurement errors of outcome might have affected our findings. The data obtained from the self-reported questionnaires could overestimate prevalence. Recent validation studies of the ISAAC questionnaires in South Korea reported overestimated prevalence for allergic rhinitis (Kim et al, 2018) and atopic eczema (Choi et al, 2012). In particular, this overestimation could have been greater as the questions regarding symptoms are not allergy-specific. However, consistent findings with respect to the association with TRAP in our study between symptoms and doctor-diagnoses based on allergic-specific questions indicate that the impact of misclassification could be negligible.

Line 375-376: ?? PM10 reflects better the larger particles, PM2.5 would be preferable for smaller particles!

Response: We revised the text for further clarification.

Before (line 375): As vehicles largely produce fine exhaust particles such as ultra-fine particles, our inclusion of PM10 to TRAP could be an extended application

After: Third, as motor vehicles largely produce fine exhaust particles such as ultra-fine particles and PM2.5, our inclusion of PM10 in TRAP might be uncommon. However, relatively large particles attributed to rising dust from vehicles travelling on roads may also contribute to children’s allergic symptoms. The high correlation of PM10 with road density and proximity in our study as well as the high contribution of traffic to PM10 according to a previous review study of source apportionment in Seoul [26], may support this application in a highly populated metropolitan area, such as Seoul.