Author’s response to reviews

Title: Road Traffic Noise and Registry Based Use of Sleep Medication

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Author’s response to reviews:

We are thankful for the opportunity to resubmit our manuscript. The editor and reviewers have provided us with constructive feedback, which we have carefully considered and responded to point by point. The line numbers refer to the redline copy.

Associate editor

COMMENT: Both reviewers see merit in your paper, but have a series of comments mostly related to outcome definition that require new analyses. Expand the issue of self-reported (sleep disturbances) versus medication data. The conclusion can be shorter and you need to document the impact of confounder adjustment by including unadjusted or age-sex only adjusted effect estimates (table 1 suggests a crude trend).

RESPONSE: As suggested, we have expanded the issue of self-reported sleep disturbances vs. medication use. More specifically, we have calculated the proportion of sleep medication users among individuals reporting sleep disturbances. These proportions are presented in the Results
section page 15-16, line 351-355. We have also added a section on sleep medications vs. sleep disturbances in the Discussion (page 19, line 436-449).

Furthermore, we have shortened and edited the conclusion. Some of the text that previously was in the conclusion has been moved to the section in the Discussion mentioned above.

Regarding the impact of confounder adjustment, all age and sex adjusted results are already included in Additional file 1: Table S1. However, if it is found necessary, we can move this table to the main text.

Reviewer #1

This is a well-written paper addressing an important topic. The methods, analyses and interpretation are generally appropriate. I do however have some major comments regarding the outcome definition and inclusion of self-reported sleep disturbances information (see below).

COMMENT: Page 5: Outcome definition (sleep medication use). One prescription of sleep medication is not much - please add also a more strict outcome of "two or more prescriptions"! Also, the authors should consider excluding persons who had two or more prescriptions of sleep medication in 2008, but no prescriptions in 2009, at least as a sensitivity analysis!

RESPONSE: We have added an outcome of two or more prescriptions. This is now described in the manuscript on page 9, line 220-222 in the Methods section. The results of these analyses are presented on page 15, line 329-335. These results are also mentioned in the discussion on page 17, line 386-391.

The reviewer has not explained why we should exclude the participants who had filled two or more prescriptions in 2008, but none in 2009. We assume the rationale behind this has something to do with consistency in sleep medication use over time; however, we are not quite sure. We still performed analyses excluding these participants (n=204) and found that the main results did not change. For that reason, have not included these analyses in the paper, but we can include them if the reviewer and editor find it necessary.

COMMENT: Page 6 line 147-149. It is unclear how this (END mapping) relates to what was described above (line 132-146)? Did the authors use the END mapping data or did they estimate noise themselves?

RESPONSE: We used END mapping data and have modified the section describing this (page 7, line 166-169).
COMMENT: DAG (additional figure): I miss a direct arrow between SES and sleep medication use, as low SES has been associated with higher rates of sleep complaints (not necessarily going through lifestyle)!

RESPONSE: Thank you for your interesting input. Although SES factors have been associated with sleep complaints, there may not necessarily be a direct link between SES and sleep medication use, which is likely to represent the most severe sleeping problems. We did, however, test how a direct link from SES (education, income, employment status) to sleep medication use would affect the main DAG (www.dagitty.net/mAeotvC) and ended up with an adjustment set containing the variables age, sex, income, and population density. The adjustment set we have used so far is highly focused on lifestyle factors, which are important for the association between traffic noise and sleep. We have also added the variables income and education in order to account for SES and find that an adjustment set containing both SES and lifestyle factor is appropriate for the present study.

COMMENT: I recommend deleting people with night-shift work from the analyses - sleep patterns in this group is very different compared to the other participants!

RESPONSE: In our previous paper on the same study population examining the association between traffic noise and insomnia symptoms (Evandt et al., 2017), we performed sensitivity analyses where we excluded people having worked regular night-shifts for a period of one year or more. Very little difference in the estimates was found compared to those estimated for the total study population. A problem, however, with the data on night-shift work is that we, unfortunately, have no information on when the night-shift work had taken place. If it was many years ago, it might not be relevant for the present study. Still, we performed the analyses excluding night-shift workers (n=2,038). By excluding the night-shift workers, we observed only a slight decrease in the effect estimate compared with the total study population both for one year in total (OR = 0.99; 95% CI: 0.95, 1.03) and for the summer season (OR = 1.03; 95% CI: 0.97, 1.09). Due to the small difference in the effect estimates and the limitations in the data on night-shift work, we find that these results do not add any substantial information. Thus, we have chosen not to include it in the article. However, we will include it if reviewer and editor find it necessary.

COMMENT: Page 9, effect modifications. The authors include a number of relevant effect modification analyses. I strongly recommend also adding an analysis stratified on noise annoyance.
RESPONSE: Following your recommendation, we have performed analyses stratified on noise annoyance. Surprisingly, the results showed a negative, however not statistically significant association between noise and sleep medication use among the very and extremely annoyed (two highest categories on the five items noise annoyance scale) both for the year in total (OR = 0.94; 95% CI: 0.80, 1.11) and for the summer season (OR = 0.91; 95% CI: 0.77, 1.09). Among those not slightly, or rather annoyed, the effect estimate was similar to the total study population with an OR of 0.99 (95% CI: 0.95, 1.03) for the year in total. For the summer season, the OR for the not annoyed was 1.04 (95% CI: 0.98, 1.10). Since the study is cross sectional, we cannot know whether the noise annoyance precedes the medication use. This could contribute to explain these surprising results. We find these results hard to interpret and due to the limitations in the study design, we have decided not to present the results in the paper. It would have been interesting to see how the results turned out in a prospective where we knew that the noise annoyance preceded the sleep medication use.

COMMENT: Please add information in the result section on the distribution of your outcome - how many filled in 1, 2, 3, 4 etc. prescriptions.

RESPONSE: We have created a new table (Table 1) where we have presented this information and referred to this table on page 11, line 266-267.

COMMENT: The minimum noise level estimated is 7.6 dB. This is far below the background level of noise (a very silent bedroom is around 20 dB) and therefore unrealistic (especially considering that this is outdoor levels!!). This potential misclassification may be important for the linear analysis. A standard approach used in most paper on noise is to use a "lowest detectable level of noise". I recommend 35 dB for night-time noise. The author should apply this in all analyses!

RESPONSE: We are aware that many papers on noise and health use a cut off in order to account for background noise. (We also know that the modelled noise exposure at lower levels are more uncertain than at higher noise levels, however, it might still be that the ranking of the lower levels is reasonable). The question is, is it still more correct to assign all respondents below Lnight 35 to Lnight=35 dB? After several discussions in our research group, also including acousticians, we consider it more correct to use the full range of modelled noise levels. First, the exposure variable in the present paper is road traffic noise, which is the only noise source included in the noise model. Lnight is an annual average noise descriptor and e.g. Lnight 20 dB from road traffic noise is not directly comparable to a continuous background sound pressure level of 20 dB. Second, by increasing the lowest calculated noise levels to a level of background noise, e.g. Lnight 35 dB, we would also probably introduce a misclassification of exposure. This would in turn increase the mean exposure level in the study population and the
association with sleep medication use could be overestimated. That is our experiences for the analyses of previous studies where we have performed the analyses both with and without a cut off (Oftedal et al. 2015; Evandt et al. 2017). A cut off would also mean that some of the variance in the exposure is lost. Thus, the accuracy of the analytic model is reduced. Furthermore, in the analytic model, we have adjusted for population density. This variable is likely to account for, at least, some of the background noise.

We have added a section regarding this issue to the Discussion on page 20, line 457-466.

COMMENT: Page 13. Please add the estimates for the stratified analyses on sex (instead of just writing the interaction p-value).

RESPONSE: We have included the results from the sex-stratified analyses in Additional file 1: Table S1 and have written in the Methods section that we have performed these analyses (page 11, line 252-253). Furthermore, we refer to Additional file 1: Table S1 regarding these results on page 16, line 358-359.

COMMENT: The authors have information on self-reported sleep (both medication and disturbance) for this cohort: https://www.ncbi.nlm.nih.gov/pubmed/28364487 - in this paper the authors find that traffic noise was associated with difficulties falling asleep and waking up too early. It would be highly relevant for the present publication to know the degree of association between the prescription data used and information on self-reported sleep? Also, this should be addressed in the discussion (which at present only discusses previous studies on sleep medication) - I find it highly important that the different estimates of sleep are compared and discussed (in these few unique cohorts that has information on both self-reported sleep and sleeping medication prescriptions)!

RESPONSE: Regarding the degree of association between the prescription data used and information on self-reported sleep, we have included the proportion having filled a prescription of sleep medications in 2009 among the participants having reported any of the sleep problems difficulties falling asleep, awakenings during the night, and waking up too early. This is described in the Methods section on page 10, line 242-248; the proportions are presented in the Results section on page 15-16, line 351-355. Furthermore, we have a section on this issue to the Discussion on page 19, line 436-449.

Minor

COMMENT: Typo at page 7 line 156 - were should be corrected to where.
Reviewer #2

This paper is a cross-sectional study looking at potential associations between night-time road-traffic noise and use of sleep medication in Oslo, Norway. The study is very well designed and methods sound.

The authors had information on window opening and closing habits as well as bed room facing road; aspects which are often major limitations in this type of studies.

The use of a DAG to identify confounders is also commendable.

Overall, I only have minor comments, as listed below.

My main concern is with the outcome under study.

COMMENT: Why do the authors focus on registry based use of sleep medication? It is not clear why the authors used a proxy to account for sleep disturbance, annoyance, etc. Did they not have such information available? Using prescription sleep medication seems to me to be more associated with severe pre-existing health conditions, e.g. people suffering from pain use sleep medication but also people suffering mental health conditions. Use of over-the-counter sleep medication seems to me more indicative of annoyance related sleep problems. Is there any data on this? Could the authors please provide a better rational for why they focus on sleep medication use and expand on the limitations on this? Some aspects have been mentioned in the discussion but I think these needs more explanations and though in order to make this a meaningful outcome.

RESPONSE: In a previous paper using the same study population, we assessed the association between traffic noise and self-reported sleep disturbances and self-reported sleep medication use (https://www.ncbi.nlm.nih.gov/pubmed/28364487). In that paper, we found that road traffic noise was associated with difficulties falling asleep and waking up too early. In the present paper, we are following up by using registry data on sleep medications as the outcome. We have edited the Introduction and elaborated on the rationale for using this outcome on page 4, line 81-95. Furthermore, we refer to our reply to Reviewer #1’s comment regarding the association between self-reported sleep disturbances and sleep medication use.
A few minor issues:

COMMENT: Can you please provide a bit more information on why you considered some covariates, e.g. physical activity? How is this related to road-traffic noise? Also, why do you adjust for rail-way noise? Have you considered a sensitivity analysis which excludes all people exposed to rail-way noise?

RESPONSE: In the present study, we used a DAG in order to identify which variables to adjust for in the analyses. The DAG includes factors that are relevant for the pathway from road traffic noise to sleep medication use. Physical activity was included in the DAG because it can be affected by SES (SES may affect lifestyle). Furthermore, SES can affect exposure to road traffic noise since it may affect whether you live in a noise exposed area or not. Physical activity can also affect sleep. We included rail traffic noise in the DAG because it is connected to road traffic noise via SES and population density (areas close to rail networks including trams, subways, and trains are often more densely populated than other areas). Rail traffic noise may also affect sleep. The connections between each variable included in the DAG are shown both in the full version of the DAG, which can be accessed at [www.dagitty.net/mAeotvC](http://www.dagitty.net/mAeotvC). A simplified version of the DAG is presented in Additional file 1: Figure S1.

We find it too comprehensive for the present paper to include detailed descriptions for why we considered each variable for the DAG, however, if the reviewer and editor find it necessary, we can describe the variables the reviewer thinks need a more detailed description.

We did not initially consider a sensitivity analysis excluding participants exposed to rail traffic noise. However, based on the reviewer’s suggestion we performed such analyses both for sleep medication use during the year in total, which gave an OR of 0.99 (95% CI: 0.94, 1.04) and during the summer season (OR = 1.05; 95% CI: 0.98, 1.13). These results only deviated slightly from the main analyses. Thus, we do not find that these sensitivity analyses add substantial information to the present paper. However, if the reviewer and editor find it necessary, we will include them.

COMMENT: The authors have information on sleeping with windows open or closed as well as bedroom facing road. Where does this information come from? This is not quite clear? How was sleeping with window open defined? On average over year, on average in summer/winter? Could you please provide a bit more information on this?

RESPONSE: We obtained information on window opening/closing and bedroom location from the HELMILO questionnaire and have now edited the section in Statistical analysis describing these analyses (page 9-10, line 223-233)