Title: Air ions and mood outcomes: A review and meta-analysis

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Author's response to reviews: see over
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Dr. Deesha Majithia
Executive Editor
BMC Psychiatry

Dear Dr. Majithia:

The manuscript we submitted to BMC Psychiatry titled “Air ions and mood outcomes: A review and meta-analysis” is the first structured literature review to examine the potential effects of exposure to negative and positive air ions on psychological measures of mood and emotional state. Our review included a meta-analysis using data from five studies of negative air ionization and depression symptom severity as measured using the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders, and 27 other studies published between 1957 and 2012.

We have received comments on our manuscript from two reviewers and have provided our responses here.

All authors have participated in preparing the manuscript, responses to the reviewers’ comments, and have reviewed and approved the current submitted version.

We look forward to your response.

Sincerely,

Vanessa Perez, PhD, MS
Senior Scientist/Epidemiologist
Response to Catherine Harmer (Reviewer)

All text below that is underlined has been newly added to our manuscript. Italicized text comes from the manuscript.

Essential revisions classified as minor

- The abstract concludes that negative ion exposure may improve depression at its 'highest' exposure level - this might be clearer for the reader if high and low density ion exposure was introduced earlier in the abstract.

**Response:** We have added additional text in the ‘methods’ and ‘results’ sections of the abstract for clarity (track marked). In the ‘methods’ section of the abstract, the following was added: “Five studies on negative ionization and depression (measured using a structured interview guide) were evaluated by level of exposure intensity (high vs. low) using meta-analysis. In the ‘results’ section of the abstract, the following was added: "In contrast, meta-analysis results showed that negative ionization, overall, was significantly associated with lower depression ratings, with a stronger association observed at high levels of negative ion exposure (mean summary effect and 95% confidence interval (CI) following high- and low-density exposure: 14.28 (95% CI: 12.93-15.62) and 7.23 (95% CI: 2.62-11.83), respectively).”

- The meta-analysis of depression scores is clear and well presented. However, I found the review section of the results difficult to follow. This is presented as a list of studies and results, but it would be more useful to provide a more critical analysis or way of sub-grouping these results - there are likely for example to be key differences between effects in an ill group compared to healthy controls. In addition, the effects of exposure duration and different scales were not raised in the results section but which may have affected outcome. I think this is important since the conclusion that negative ion exposure does not affect subjective state is based on these papers in the absence of a formal process of comparison and this needs therefore to be more compelling and organized.

**Response:** Regarding the organization of our ‘results’ section and given the number of studies we evaluated, we chose to organize the studies by outcome and then by ascending year of publication and last name (we have added text in track changes to clarify this for the reader). We reported the main findings of each study in our narrative review, along with a description of the study design and details regarding the exposure measurement and assessment. The majority of studies evaluated healthy individuals, except for six non-depression studies (Silverman and Kornbleuh (1957) (10 healthy adults and 2 additional subjects with chronic stationary neurologic conditions); Yaglou (1961) (6 arthritic patients); Assael (1974) (10 healthy participants and 10 subjects receiving tranquilizers); Dantzler...
(1983) (9 subjects with bronchial asthma); Misiaszek (1987) (8 manic patients), and Gianinni (2007) (24 manic male patients)). Studies including depressed subjects are those discussed separately within the Depression section in our results (all subjects evaluated had some form of depression). The six non-depression studies involving subjects that were not healthy did not have disparate findings from those studies that included only healthy subjects. Hence, we feel that subgrouping by ill and non-ill subjects (aside from the depression studies) will not enhance the organization of our results section. We have, however, raised this in our ‘results’ section to address the reviewer’s comment (track marked). We now state: “Apart from the studies that evaluated ion effects on patients with some form of depression, six studies (Silverman and Kornbleuh (1957), Yaglou (1961), Assael (1974); Dantzler (1983); Misiaszek (1987), Gianinni (2007)) also evaluated the influence of ions on mood states of persons with varying health conditions. Collectively, the findings from these six studies did not provide contrasting results from those studies that included only healthy subjects.”

In response to the reviewer’s comment regarding the effects of exposure duration not being raised in the results section, we would like to highlight that we did mention a consideration of exposure duration among studies included in our meta-analysis and in the overall review. We reported the following in our ‘results’ section: “Sensitivity analyses were performed by removing the Terman and Terman [6] study since the data were presented in a figure and not explicitly reported. These analyses showed no alteration in the findings. An additional assessment of exposure duration (hours), within high- and low-density air ion levels, and each study’s score mean difference indicated no evidence of a dose-response relationship.” We further mention in our ‘discussion’ that “A causal basis for this finding, however, was not presumed as the durations of exposure and depression scores were not dose-related.” We also raise in the discussion the following: “However, when hours of exposure were considered as a surrogate for dose within the high- and low-density analyses, repeated or longer exposure durations to negative air ions failed to produce a greater effect on depression scores than did shorter durations.”

Additionally, the duration of exposure in each study is shown in Table 2 of our paper and is already discussed in the ‘results’ section as follows: “Air ion intensities and duration are summarized in Table 2. Air ion intensities were reported in 29 studies (range: 1000 ions/cm³ (ambient levels) to 27,500,000 ions/cm³). Air ionization duration ranged from 10 minutes at a single time point, to daily treatment periods administered for multiple days, to successive weeks at a time where air ion generators were switched on continuously. Collectively, many studies reported a mood-related response after exposure to ionized air; however, considerable variation by outcome, statistical significance testing, and degree of precision across the reported data was noted.”

We further state the following in our ‘discussion’ section: “Based on our review, there is no scientific basis for concluding that air ions have a beneficial or adverse effect on measures
of anxiety, mood, relaxation/sleep, and personal comfort in the range of exposures reviewed (200-300 ions/cm$^3$ (ambient levels) to $10^6$ ions/cm$^3$). The quality of many studies, however, is low and there are several important inconsistencies across studies (e.g. differential study settings/populations, follow-up periods, exposure/outcome measurement and assessment, and unmeasured confounders such as temperature). Of particular importance is the heterogeneity observed in the frequency, duration, and intensity of air ionization evaluated. Presumably, the greater the ion concentration, combined with longer exposure durations at greater frequency, the greater the likelihood for air ion exposure to produce a biological response in exposed subjects, if in fact a real association is present. Nonetheless, our findings on the relationship between exposure duration, within high and low air ion concentrations, and depression symptom severity do not support such a relationship.”

Regarding the reviewer’s comment on the effects of different scales, we reported in our ‘discussion’ section the following, which we feel addresses the reviewer’s concern: “Additional experiments are warranted to clearly understand the impact of negative air ionization on depression severity and how findings may be influenced by variable concentration levels and different metrics for symptom measurement.”

We also reported that heterogeneity across studies, overall, was evident in the exposure/outcome measurement and assessment by stating the following: “The quality of many studies, however, is low and there are several important inconsistencies across studies (e.g. differential study settings/populations, follow-up periods, exposure/outcome measurement and assessment, and unmeasured confounders such as temperature).”

Per the reviewer’s request, however, we have added additional text (track marked) on the possible effect(s) of different scales within the ‘discussion’ section: “A disparity in the measurement and assessment of the outcomes evaluated also renders a comparison across studies difficult. In this regard, instruments other than the SIGH-SAD to measure depression severity (e.g., the Beck Depression Inventory (ref added), the Center for Epidemiological Studies Depression Scale (ref added), the Zung Self-Rating Depression Scale (ref added)) might be considered in future studies since different depression scales may vary in sensitivity and specificity for depression severity, may differ in the measurement of different construct(s) based on the inclusion of specific survey items (i.e., items may discriminate between different dimensions of depression), and may be more suited over others in specific target populations (e.g., young adults vs. elderly patients).”

- The authors examine the effect of hours of exposure but I wonder if days of exposure might be more appropriate (i.e. all day for one day may have less effect than an hour a day for 24 days)?

Response: We examined the effect of hours of exposure in our additional assessment of a possible dose-response relationship because it corresponded to the administration of treatment
in each of the individual studies evaluated. For example, Terman and Terman 1995 administered treatment for 20 days in 30 minute sessions. This corresponded to approximately 10 hours of exposure, which makes more intuitive sense than evaluating 0.42 days (i.e., less than 1 day) of exposure. Given the presentation of data within each study, we strongly believe that a more valuable metric for evaluating dose-response is on the hour scale. An analysis based on days of exposure rather than hours of exposure showed no difference in trends. We have added the plot of our assessment based on hours in the manuscript and referenced it accordingly (figure 3). As you can see, there is no evidence of a monotonic dose-response trend that is evident.

- The authors end by saying that the biological plausibility of the association needs further study. However, there are some studies which have examined potential mechanisms such as effects on the serotonin system and emotional processing which should be cited at this stage.

**Response:** We found no consistent indication in our review, overall, of mood state alterations attributed to high levels of air ion exposure. While there are some experimental studies suggesting effects of air ions on neural mechanisms (e.g., norepinephrine) none have been replicated. Some reports pertain to systems that might be thought to be relevant to neurotransmitter systems affecting mood but are not. For example, Krueger, Andriese and Kotaka (1966, 1968) report a short-lived effect of continual ion exposure on blood serotonin levels in rats. However, blood serotonin is not an indicator of central nervous system (CNS) serotonergic activity but instead reflects variations in major peripheral stores of serotonin in the gut, platelets, and respiratory tract. Regarding the respiratory tract, a separate comprehensive review and meta-analysis that has been submitted for publication and is currently under review (Alexander, et al.) did not support a beneficial role in exposure to negative air ions and respiratory function or asthmatic symptom alleviation. The review by Alexander et al. also did not find a detrimental effect of exposure to positive air ions on respiratory measures.

Charry and Bailey (1985) collected data on brain norepinephrine and dopamine systems and found that exposure of rats to high concentrations ($5.0 \times 10^5$/cm$^3$) of positive or negative air ions for periods of up to 66 hours did not significantly affect the concentration of norepinephrine or dopamine in any brain region. Similarly, no effect of exposure to air ions on the concentration or turnover of serotonin metabolism in rats was able to be identified in a separate experiment (Bailey and Charry 1987)). In these studies, no effect of ion exposure on circadian behavioral activity levels was observed either. Finally, biological plausibility is also not supported by the consideration that air ions would need an extraordinary biological potency to affect the CNS. This can be appreciated by noting that the concentrations of air ions in the range of reported biological responses in some experimental studies is associated with a range of exposure levels up to
100,000 ions/cm³, representing a vanishingly small fraction of the $10^{19}$ gas molecules in one cm³ of air. This concentration is similar to the threshold dose of botulism, one of the most toxic chemicals known (Luttrell et al., 2008). Given that our review found no consistent indication, overall, of mood state alterations attributed to high levels of air ion exposure, and that findings from experimental research do not provide replicated evidence for the notion that high levels of ion exposure impact neurotransmitters that regulate mood, we believe that the biological plausibility of the responses of humans to air ions should be demonstrated, not assumed.

We have added additional text (track marked) per the reviewer’s comment in the conclusion of our manuscript. We now state the following: “Given that longer or repeated exposures to negative air ions were not observed to strengthen the response of subjects, additional investigation of the biological plausibility is warranted. The concentrations of air ions expressed as parts per trillion are vanishingly small and well-controlled animal studies do not report changes in catecholamine neurotransmitter levels (ref added) or the levels and turnover of serotonin in the brain (ref added).”
Response to Timo Partonen (Reviewer)

Essential revisions classified as major

- Page 3. It says here that additional dose-response relationships were evaluated by plotting. Please include the plots in the manuscript.

Response: We have included the plots in the manuscript and referenced them accordingly.

- Page 14, line 3 up. It says that effect sizes were analyzed, but they are not reported. Please report.

Response: The effect sizes for each individual study are shown in our Figures 1 and 2. The weighted group mean differences generated in our forest plots (Figures 1 and 2) show the combined effect sizes associated with high- and low-density negative air ionization.

We have already reported the effect sizes in the manuscript as follows: “Utilizing the later post-baseline mean score where applicable, the weighted difference in group means when exposed to high-density air ionization was indicative of a beneficial negative air ion effect on SAD (Atypical symptom subscale mean=5.64 (95% CI: 4.44-6.85); Hamilton subscale mean=9.23 (95% CI: 8.52-9.94); composite SIGH-SAD scale mean=14.28 (95% CI: 12.93-15.62); P for heterogeneity (SIGH-SAD) < 0.0001) (Figure 1). The effect sizes for low-density ionization were statistically significant, yet smaller in magnitude than for high-density exposure (Atypical symptom subscale mean=1.98 (95% CI: 0.57-3.40); Hamilton subscale mean=4.87 (95% CI: 0.96-8.77); composite SIGH-SAD scale mean=7.23 (95% CI: 2.62-11.83); P for heterogeneity (SIGH-SAD) < 0.0001) (Figure 2).”

- Page 15, line 7 up. It says that a clustering (indicative of publication bias) was not observed but the results are not shown. Please show the graph and include it in the manuscript.

Response: We have included the plots in the manuscript and referenced them accordingly. We have added the following text for clarity: “Publication bias was examined visually with funnel plots, which allow for a visual assessment of the estimated intervention effects from the individual studies plotted against a measure of effect size. Separate plots were done for SIGH-SAD composite scores and SIGH-SAD subscales combined since Terman and Terman [6] reported estimates by subscale only and Terman et al. [8] reported estimates for the composite scale only. A clustering indicative of publication bias was not observed (Figure 4) (i.e., no marked asymmetry was evident). Statistical evidence of publication bias was not found (Begg
rank correlation \( p=0.71 \); Egger regression \( p=0.37 \). These findings were supported by those observed when combining the Atypical and Hamilton subscales.”

Essential revisions classified as minor

- Abstract, Results, line 3. It reads: mean "summary" effect. Please clarify the term "summary" or reword.

Response: The term “summary” is standard terminology taken to indicate, within the context of our research, the ‘weighted mean difference’ observed when pooling the study results. Each study reported the mean depression severity score before and after ion exposure, resulting in each study reporting a ‘difference in means’ (i.e., the study effect size). Our meta-analysis therefore combined these observed effect sizes using a random effects model to produce an overall effect (i.e., a summary effect or weighted difference in means). Also note that a weight is assigned to each study in the meta-analysis based on that study’s precision. As the “mean summary effect” is well-known terminology, we believe that leaving the text as is in the abstract will be in line with the language in the current literature.

Of note, the random effects model allows for both within- and between-study heterogeneity (e.g., sources of heterogeneity can be various exposure durations across studies, different sample sizes). The studies included in our meta-analysis are assumed to be a random sample of the relevant distribution of effects, and the combined effect size (i.e., the weighted mean difference) estimates the mean effect in this distribution.

- Abstract, Results, line 5. Please indicate for which patients the treatment had the effects, i.e. those with winter depression or dysthymia.

Response: The high-density negative air ion exposure was reported to produce an effect in all patients (i.e., those with seasonal depression and those with chronic depression). The low-density negative air ion exposure produced an effect in patients with seasonal depression only (note, Goel et al., 2005 did not find a significant effect among patients with chronic depression). We have modified the text in our ‘abstract’ per the reviewer’s comment (track marked). We now state: “Consistent ionization effects were not observed for anxiety, mood, relaxation/sleep, and personal comfort. In contrast, meta-analysis results showed that negative ionization, overall, was significantly associated with lower depression ratings, with a stronger association observed at high levels of negative ion exposure (mean summary effect and 95% confidence interval (CI) following high- and low-density exposure: 14.28 (95% CI: 12.93-15.62) and 7.23 (95% CI: 2.62-11.83), respectively). The response to high-density ionization was observed in patients with seasonal or chronic depression, but an effect of low-density ionization was only observed in patients with seasonal depression. However, no relationship between the duration or frequency of ionization treatment on depression ratings was evident.”
• Page 2, line 10 up. It says here that identical search strings were used. Are the search strings noted in the parentheses? If yes, fine. If not, please write them down. Please confirm.

**Response:** Yes, the search strings are given in the parentheses.

• Page 14, lines 6 to 7 up. It reads: the "weighted" difference in group means. Please clarify in the methods how the means were weighted.

**Response:** In the ‘methods’ section we currently state the following: “Forest plots from random effects modeling [23] were generated to estimate weighted group mean differences in depression scores, 95% confidence intervals (CIs), and corresponding p-values for heterogeneity.”

We have added the following text (track marked) per the reviewer’s comment to provide clarity to the reader. We now state the following: “Forest plots from random effects modeling [23] were generated to estimate weighted group mean differences in depression scores, 95% confidence intervals (CIs), and corresponding p-values for heterogeneity. Of note, using the random effects analysis, the weighted mean is defined as the sum of each study effect size multiplied by its weight (i.e., the inverse of the within-study variance plus the between-studies variance) divided by the sum of the weights. The variance of the weighted group mean difference is defined as the reciprocal of the sum of the weights.”

• Page 15, line 6. It reads: the group "summary estimate". Please clarify what do you mean by the summary estimate or reword.

**Response:** We have reworded (track marked) this to say the “weighted group mean difference.” See responses to previous comments that are related to this topic.

• Page 19, line 7. You may want to add to the text a comment that the references #4 and #7 which reported a significant relationship are the two most recent ones.

**Response:** We have modified accordingly (track marked).

_Discretionary Revisions_

Page 19, lines 8 to 12 up. These lines describe the situation in the USA only and may be too specific to report here. Please consider omitting.

• **Response:** We strongly believe that it is important to provide some framework of the public...
health consequences. Since we mostly provide this context for U.S. populations, we have added text that expands the public health implication to a global scale, showing that mood and anxiety disorders are a global problem. We have therefore updated our text as follows (track marked and highlighted here in red): “The World Health Organization conducted a community-based study in 14 countries on the prevalence and severity of mood disorders and found that the 1-year prevalence of mood and anxiety disorders in developed nations ranged from 3.1%-5.3% in Japan to 9.6%-18.2% in the US [48] ... Globally, the burden of mood disorders such as depression is on the rise, with only 30% of cases worldwide receiving appropriate care for depression (ref added). Hence, mood and anxiety disorders present a global crisis which heavily burden society with serious implications for daily quality of living, economic costs, and the need for individually-tailored treatment.”