# AIR POLLUTION AND SYMPTOM SEVERITY IN HOSPITALIZED SUBJECTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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## SUMMARY

*Air pollution has been demonstrated to represent a major threat to mental health, leading to higher risk of development or exacerbation of serious psychiatric disorders. The current study was aimed at investigating the associations between air pollutant concentrations (particulate matter 2.5 and 10, ozone, carbon monoxide, nitrogen dioxide) and symptom severity in a sample of inpatients suffering from schizophrenia spectrum disorders. We collected sociodemographic, clinical, and psychopathological characteristics of subjects (n=118) with schizophrenia spectrum disorders who were hospitalized in the Psychiatric Inpatient Unit of the University Hospital of Perugia in the period 1st January 2015-31st December 2016. Psychopathological characteristics were assessed using the Positive And Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global impressions (CGI) scale. Hierarchical multiple regressions were run to assess the association between air pollutants concentrations and the PANSS, BPRS, and CGI total subscale scores, controlling the analyses for sex/age and meteorological data. We found a significant positive association between the average concentration of ozone before admission and the anxiety-depression factor score domain at the PANSS. No significant associations between the other pollutants and the different scores at the scales used for the psychopathological assessment were found. Short-term exposure to ozone may influence the clinical presentation of schizophrenia spectrum disorders and should be thus considered among the potentially modifiable risk factors in the urban environment. Air pollution should be considered among the main threats to human mental health and policymakers should address the built of sustainable urban environments.*

*Key words: urbanization - air pollution – ozone - schizophrenia*

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## INRODUCTION

The impact of air pollution and climate change on mental health is increasingly evident, as elucidated by research conducted during the last years (for review, see Radua et al. 2024). Air pollutants were demonstrated to be associated with the development (Braithwaite et al. 2019, Khan et al. 2019) and exacerbation of serious psychiatric disorders (Ji et al. 2021, Tota et al. 2024). In psychiatric emergency settings, higher air pollutants concentrations were associated with a greater number of daily accesses (Bernardini et al. 2019, Lee et al. 2019) and hospitalizations (Duan et al. 2018). The association between urbanization, air pollution, and serious psychiatric disorders deserves attention due to the impairment of overall quality of life and functioning exerted by these conditions, which are also linked to a significant economic and social burden. In particular, growing evidence suggests that air pollution exposure may increase the risk for developing psychotic disorders such as schizophrenia (Antonsen et al. 2020, Attademo et al. 2017). To note, it has been suggested that the association between urban residency and adolescent psychotic experiences may be partly explained by higher levels of outdoor air pollution in urban settings (Newbury et al. 2019). Despite robust evidence concerning the relationship between pollutants exposure and schizophrenia spectrum disorders, few data is available on the possible effect of air pollutants on symptom severity in these conditions. Anyway, preliminary findings lead to the hypothesis that not only does air pollution exposure increase the risk of developing schizophrenia spectrum disorders, but it may also affect the clinical presentation in terms of severity. Indeed, an increase in mental health service use, which can be considered an indirect marker of illness severity and relapse, was highlighted in case of higher residential exposure to air pollutants (Newbury et al. 2021). Moreover, respirable particulate matter (PM), and particularly $PM_{2.5}$, was associated with symptom severity in people suffering from schizophrenia, with higher effects in elderly patients (Eguchi et al. 2018). Due to the progressive increase in urbanization, a deeper understanding of how factors related to this phenomenon influence mental

health represents a crucial need in order to implement prevention strategies. Subsequently, the influence of factors like air pollution on the clinical presentation and severity of psychiatric disorders should be better elucidated. Given these premises, the present study aims to assess the relationship between air pollutants concentrations and symptom severity in hospitalized patients with schizophrenia spectrum disorders.

## SUBJECTS AND METHODS

### Clinical characteristics of acute inpatients

In this retrospective study, clinical data was collected at the Psychiatric Inpatient Unit of the General Hospital of Perugia, the main hospital in the Local Health Unit 1 catchment area. The high-specialty services are provided to about 493,960 residents with a population density of 114 inhabitants per $km^2$ (USL Umbria 1) on an area of 4298.38 $km^2$. Patients suffering from schizophrenia spectrum disorders according to DSM-5 criteria (APA 2013), who were admitted to the clinic due to an acute episode of psychopathology in the period of time 1st January 2015-31st December 2016, were considered for this analysis. We collected socio-demographic data and administered scales for the evaluation of symptom severity, particularly the Italian versions of the Clinical Global Impressions (CGI) (Guy 1976), the Positive and Negative Syndrome Scale (PANSS) (Pancheri & Brugnoli 1991), and the Brief Psychiatric Rating Scale (BPRS) (Morosini et al. 1995). We used previous factor analyses of the PANSS (Shafer & Dazzi 2019) and BPRS (Dazzi et al. 2016) scales in order to better disentangle psychopathological dimensions in our population. All the scales were administered at admission by a group of three psychiatrists who received specific training. Informed consent for participation in retrospective studies was obtained by all the subjects included in the study.

### Air pollution data

We collected information about air pollution and meteorological data for each day of admission based on the datasets provided by the regional agency for environmental protection of Umbria (Agenzia Regionale per la Protezione Ambientale dell'Umbria – ARPA Umbria) (ARPA 2017). We used air monitoring data concerning different types of air pollutants that were averaged across up to 16 monitor stations located in various parts of the region, with a maximum distance of 91 km among the stations. In particular, we collected data about average levels of $PM_{10}$, $PM_{2.5}$, carbon monoxide (CO), nitrogen dioxide ($NO_2$), and ozone ($O_3$) during the 7 days prior to admission. Information about average meteorological conditions during the 7 days prior to admission was also entered in the dataset, with particular interest in daily average temperature, daily

average pressure, and daily average humidity. Meteorological data was obtained from the meteorological station of Perugia-Monteluce, which is located nearby the urban center (monteluce.lineameteo, 2017).

### Statistical analysis

We performed descriptive analyses to evaluate the distribution of the variables of interest in the overall sample. To assess the association between average daily levels of pollutants and the severity of psychopathology we ran a set of hierarchical multiple regression analyses using the scores and subscores of the considered scales (CGI severity score; PANSS total score and positive, negative, anxiety-depression, excitement, and disorganization factor scores; BPRS total score and affect, positive, negative, and activation factor scores) as dependent variables. After controlling for socio-demographic (sex and age) and meteorological (daily average temperature, pressure, and humidity) data, we inserted the average daily concentrations of air pollutants as independent variables. $PM_{10}$ was excluded from the model due to the violation of the multicollinearity assumption (tolerance values $>0.1$ and variance inflation factors $<10$). A p value of $<0.05$ was considered as significant. We analyzed R squared values for evaluating the percentage of variance explained by the dependent variables. Beta values were reported to assess the strength of the significant associations.

### RESULTS

We included an overall sample of 118 patients (53.4% male, mean age 40.5±13.1 years) suffering from schizophrenia spectrum disorders. The most prevalent diagnosis was represented by schizoaffective disorder (33.1%), followed by schizophrenia (31.4%). The mean symptom severity measured by the CGI severity score was 5.2±0.8, coinciding with marked illness severity. The PANSS and BPRS mean total scores were respectively 85.4±19.5 and 60.1±13.2.

As for regression analyses, only one of the models, including the PANSS anxiety-depression factor as dependent variable, turned out to be significant. Socio-demographic and meteorological variables were entered at step 1 and step 2 of the hierarchical regression, explaining respectively 3.5% and 10.7% of the variance in PANSS anxiety-depression score. After entry of the concentrations of air pollutants, the total variance explained by the model as a whole was 18.2%, F=2.399, p=0.017. The variables explained an additional 7.5% of the variance, with R squared change=0.075, F change $(4, 97)$=2.217, p=0.075. As for the association between air pollutants and PANSS anxiety-depression factor score, in the final model, a significant association was detected for ozone concentrations (p=0.010), with a beta value of 0.594 (see Table 1).

**Table 1.** Hierarchical linear regression model procedure of variables associated with affective symptoms severity (PANSS anxiety-depression factor)

| Socio-demographic variables | Beta | t | p |
|---|---|---|---|
| Age | -0.045 | -0.468 | 0.641 |
| Sex | 0.148 | 1.561 | 0.122 |
| Meteorological variables | | | |
| AVG day 0-7 *temperature* | -0.740 | -3.501 | 0.001 |
| AVG day 0-7 *pressure* | 0.250 | 1.849 | 0.067 |
| AVG day 0-7 *humidity* | 0.067 | 0.325 | 0.746 |
| Air pollutants | | | |
| AVG day 0-7 *particular matter (* $PM_{2.5}$) | 0.207 | 0.881 | 0.381 |
| AVG day 0-7 *carbon monoxide (CO)* | -0.132 | -0.597 | 0.552 |
| AVG day 0-7 *ozone (O$_3$)* | *0.594* | 2.625 | *0.010** |
| AVG day 0-7 *nitrogen dioxide (NO$_2$)* | -0.155 | -0.875 | 0.384 |

*$p<0.05$; Overall model (step 3) considered (F=2.399; p=0.017)

## DISCUSSION

To the best of our knowledge, this is one of the first studies worldwide investigating the association between daily levels of air pollutants concentrations and psychopathological symptom severity in a sample of schizophrenia spectrum patients hospitalized in an acute inpatient unit. Our results showed a statistically significant association of daily ozone levels and affective symptoms in schizophrenia, measured by the PANSS anxiety-depression factor score. Ozone represents one of the most important and powerful air pollutants, mainly due to its oxidant effect (Lauer 2010). Exposure to ozone has largely been demonstrated to be a risk factor for medical diseases, such as respiratory conditions, and its detrimental effects have also been observed at central nervous system (CNS) levels, e.g., decreasing cognitive response and motor activity, as well as causing headaches and sleep-wake disruptions (Martinez-Lazcano et al. 2013). Animal studies showed that ozone inhalation may reduce dopaminergic neurons and increase lipid peroxidation (Pereyra-Munoz et al. 2006) and the production of pro-inflammatory cytokines, e.g., vascular endothelial growth factor, interleukin-6, and tumour necrosis factor α (Araneda et al. 2008). Moreover, ozone seemed to be involved in the hippocampus, striatal and substantia nigra neurodegeneration, possibly leading to behavioural changes (Block et al. 2012). The increase in inflammation and oxidative stress is thus considered the main mediator of harmful effects of ozone in the CNS (Block et al. 2012). This is particularly important in consideration of the role that neuro-inflammatory mechanisms were demonstrated to play in the development of depressive symptoms, also leading to the hypothesis of an "inflammatory depression" subtype with increased blood concentrations of cytokines (Köhler et al. 2017).

Although previous reports concerning the association between environmental ozone exposure and mental health outcomes were considered to be inconclusive (Zhao et al. 2018), our results are in line with previous studies showing that ozone air concentrations may be associated with increased psychiatric emergency services admissions (Bernardini et al. 2020), as well as increased risk of depression and anxiety in the general population (Zhao et al. 2020), including depression-related hospitalizations (Gao et al. 2023). Subsequently, our results add to previous literature on existing evidence for air pollution to have a role in mental disorders and psychiatric symptom severity (Bakolis et al. 2021, Braithwaite et al. 2019, Attademo et al. 2017). Moreover, the relationship between air pollution and affective features in schizophrenia is even more relevant if we consider that this often-neglected symptom domain can be particularly impactful for patients suffering from this conditions, since they increasing the risk of suicide and significantly reduce quality of life (Morrissette & Stahl 2011). Counterintuitively, we did not find associations between most of the air pollutants considered in our study and symptoms severity in our sample as measured with CGI, PANSS, and BPRS. This could be explained by the methodological limitations of our study, which are several. First, the sample size is smaller than previous studies in the field, which may significantly limit the generalizability of findings. Second, the single-center design that consider a relatively low-polluted area of Italy, while previous research on the topic is mainly coming from highly-polluted countries, with high population density, and often rely on a multi-center design. Finally, we should consider that the individual exposure to air pollutants may be subjected to interpersonal variations that would deserve real-time monitoring, while we used measurements from fixed-site monitoring stations. Future studies on larger sample sizes are expected to

delve into the possible effects of air pollutants exposure on the clinical phenomenology of serious psychiatric disorders, possibly using reliable data on individual exposure.

## CONCLUSIONS

The present study suggests the possible contribution of short-term air pollution exposure to the development of a more severe clinical picture in schizophrenia spectrum disorders. Urbanicity-related risk factors should be taken into account when implementing risk mitigation strategies in mental health, and policymakers should consider the importance of building more sustainable and safer urban environments where the overall well-being of citizens should be largely prioritized.

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