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Short-term air pollution exposure is associated with lower severity and mixed features of manic episodes in hospitalized bipolar patients: A cross-sectional study in Milan, Italy

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A R T I C L E I N F O

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A B S T R A C T

Bipolar Disorder (BD) alternates depressive, manic or hypomanic phases. A manic episode (ME) is the main psychopathological condition of BD and it often requires hospitalization. Air pollution is thought to play a role in onset and exacerbation of several psychiatric disorders. We aimed to verify the association between exposure to particulate matter ≤10 μm (PM10) and ME severity, assessed through the Young Mania Rating Scale (YMRS).

We evaluated clinical records regarding 414 hospital admissions of 186 patients residing in Milan (Italy), hospitalized for ME in the Psychiatry Unit of the Policlinico Hospital from 2007 to 2019. Patients were assigned mean daily PM10 and apparent temperature levels of the Milan municipality. As exposure windows, we considered single days preceding hospitalization (lag0 to 7) and their average estimates (lag0-1 to 0-7). We applied mixed effect models, adjusted for relevant confounders.

Short-term PM10 exposure was associated with a reduction in YMRS, both when considering daily lags [β: −0.43 (95% Confidence Interval: −0.83; −0.03) at lag0] and their average [−0.47 (−0.90; −0.04) at lag0-1]. YMRS was higher in psychotic patients (24.8) and lower in ME with mixed components (15.5) if compared to episodes characterized by neither mixed nor psychotic features (17.4, $p < 0.001$). While PM10 did not influence the risk of psychotic symptoms at admission, it was associated with a higher risk of ME with mixed features, with Odds Ratios ranging from 2.43 (1.02; 5.76) at lag0 to 3.60 (1.22; 10.7) at lag0-2.

Our findings show that increasing levels of PM10 move the ME towards the depressive pole of the BD spectrum and augment the probability of hospitalization for ME with mixed components. These results have important clinical implications, as mixed features worsen the course of ME and make the management of bipolar patients challenging.

1. Introduction

Bipolar Disorder (BD) is a chronic condition affecting around 2.4% of the world population (Merikangas et al., 2011), associated with social dysfunction and poor quality of life (Bonnin et al., 2019). Manic/hypomanic episodes (with or without mixed features), alternating with period of euthymia or major depression, characterize the illness (Takeshima, 2017). Some authors indicate that manic episodes (despite generally shorter than the depressive ones) can worsen the global functioning of bipolar subjects more than the depressive phases, as shown by their association with greater cognitive impairment and greater likelihood of lifetime psychotic symptoms (Altamura et al., 2019; Buoli et al., 2014). The presence of mixed features during manic episodes can also complicate the course of the disorder, because of reduced response to treatment and greater probability of future recurrences (Fagiolini et al., 2015). Different factors were identified as fostering the occurrence of manic episodes in BD, including recent cannabis misuse, sleep loss, and treatment with antidepressants (Gibbs

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et al., 2015; Lewis et al., 2017; Patel et al., 2015).

Environmental factors also seem to contribute to the onset of manic episodes, as shown in particular for childhood adversity (Lindgren et al., 2017). Air pollution is currently considered one of the main environmental contributors of poor human health, being responsible for a relevant burden of mortality and morbidity worldwide (Cohen et al., 2017; Lelieveld et al., 2015). Recent data also suggest that air pollution may impact on human mental health (Xue et al., 2019). Several studies reported that both short- and long-term exposure to particulate matter (PM) might be responsible for onset or worsening of depressive symptoms (Buoli et al., 2018a). A recent meta-analysis summarized the data regarding the association between PM and different psychiatric disorders, reporting that short-term exposure to PM with aerodynamic diameter ≤10 μm (PM10) would increase the risk of completed suicide, while no clear association was found between both short- and long-term exposure to PM10 and BD, depression, anxiety, or psychotic disorders (Braithwaite et al., 2019). On the other hand, the analysis of two large independent datasets revealed that poor air quality is associated with apparently higher rates of BD and major depression both in the US and in Denmark (Khan et al., 2019). These latter evidences seem to support the role of air pollution in the onset and/or worsening of psychiatric conditions (Rowland and Majid, 2020), partly overcoming a more traditional view that attributes the poorer mental health of urban vs. rural contexts mainly to psychosocial factors (Peen et al., 2010).

Different mechanisms were proposed to explain the link between air pollution and mental health. One model hypothesizes that air pollution increases inflammation in vulnerable subjects, resulting in abnormalities in the brain levels of neurotransmitters (Altamura et al., 2014; Liu et al., 2018). Alternatively, the smallest pollutants (e.g. PM with aerodynamic diameter ≤2.5 μm or PM2.5) could pass the blood brain barrier and trigger direct inflammation in the Central Nervous System by activation of microglial cells (Boda et al., 2019).

Despite the hypothesized impact of PM on mental health, no sound data have been published until now regarding manic episodes of BD. A previous analysis did show an association between air pollution and an increased risk of BD diagnosis, but did not focus on PM or on subjects hospitalized for manic episodes (Khan et al., 2019). Furthermore, a very recent manuscript failed to find an association between air pollutants different from PM (carbon monoxide and nitrogen dioxide) and BD (Thilakaratne et al., 2020). The available evidences are thus not fully consistent. In this context, the purpose of the present study is to assess the effect of air pollution, especially PM with aerodynamic diameter ≤10 μm (PM10), on the severity of manic episodes of bipolar patients.

2. Materials and methods

2.1. Study population and outcome definition

We collected clinical records of patients that underwent hospitalization for a manic episode in the Psychiatry Inpatient Clinic of the Policlinico Hospital in Milan, Italy, from 2007 to 2019. Only patients resident in the capital city of Milan were selected.

The diagnosis of manic episode was formulated by expert psychiatrists using the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-I) (Gan et al., 2012). Patients' clinical and demographic information were retrieved from the clinical records, in particular: sex, age at hospitalization, length of hospitalization, smoking habit, number of cigarettes per day, age at disorder onset, duration of illness, duration of untreated illness. We also collected information on whether the manic episode was characterized by mixed components (according to DSM IV-TR or DSM-5 criteria in relation to the year of hospitalization) or psychotic features (i.e. the presence of delusions or hallucinations or both).

The severity of the episode was quantified at hospital admission by the Young Mania Rating Scale (YMRS). The YMRS score ranges from 0 to 60 (with higher scores indicating more severe mania) and has also been categorized as follows: ≤12 = remission, 13-19 = minimal symptoms, 20-25 = mild mania, 26-37 = moderate mania, 38-60 = severe mania (Young et al., 1978).

Written informed consent was collected from patients before hospitalization. All the study procedures satisfied the principles outlined in the Declaration of Helsinki (World Medical Association, 2013). The study was approved by the Policlinico Hospital institutional review board (approval number 802_2020).

2.2. Exposure assessment

Air pollution concentration estimates were derived from a chemical transport model provided by the environmental protection agency of the Lombardy region (ARPA Lombardia), available as daily means at a 4 × 4 km resolution or at municipality level for the entire regional territory (Silibello et al., 2008). Each subject was assigned the daily mean concentration of PM10 of the city of Milan, available from January 1st' 2014 to December 31st' 2019. When the information was available only at 4 × 4 km resolution (2007–2013), mean municipality levels were obtained by calculating a weighted city average, where the weights were represented by the percentage of overlap of each grid cell over the territory of the city of Milan. To analyze short-term effects of air pollution, different time windows were investigated: i) *daily lags*, obtained considering PM10 daily means from the day of hospitalization (lag 0) up to 7 days before (lag 7); ii) *averaged daily lags*, obtained by averaging PM10 levels of the day of admission with the levels of the day before (lag 0-1) and of each preceding day up to 7 days before (lag 0-7).

Data on temperature and humidity were obtained from the ARPA network of meteorological monitoring stations for the same time windows as for air pollution data. Apparent temperature was then calculated as summary meteorological variable (Analitis et al., 2008).

2.3. Statistical analysis

We used standard descriptive statistics [means, standard deviations (SDs), and proportions] to summarize data. Differences in the distribution of the YMRS score across different categories of features characterizing the manic episode were assessed using the analysis of variance (ANOVA).

Association between air pollution levels and selected variables of interest was evaluated by applying mixed models with a random intercept on subject identification code (to properly account for multiple hospitalizations per subject). When considering YMRS as dependent variable, we applied multivariable linear models and expressed results as regression coefficients (β) and 95% Confidence Intervals (95%CI); when considering dichotomous variables (i.e. mixed/psychotic features only vs. neither mixed nor psychotic features) as outcomes of interest, we applied multivariable logistic models and expressed results as Odds Ratios (OR) and corresponding 95%CI. All results were reported per 10 $\mu g/m^3$ increase in PM10 concentration. All models were adjusted for age at hospitalization, sex, smoking habit (yes vs. no), number of cigarettes per day, year of hospitalization (to properly account for time trends), season (four categories), and apparent temperature. Adjustment variables were chosen *a priori* and based on previous expertise on air pollution studies. As a sensitivity analysis, all models were re-run after removing variables on individual characteristics. Analyses were performed using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

3. Results

3.1. Study population

We collected data on 414 hospital admissions experienced by 186 patients. Seventy-eight were males (41.9%) and 88 were current smokers (47.3%); information on smoking habit was missing for 36 subjects (19.4%). About 53% of the study population had only one hospitalization, 22.6% of them were hospitalized twice, and 24.2% thrice or more. When considering all hospital admissions (Table 1), 272 (65.7%) were experienced by females and 240 (58%) by subjects currently smoking almost one pack of cigarettes per day. Mean age at hospitalization was 45.5 years, with an average length of hospitalization of 14 days. When looking at the characteristics of the disorder, the average age at onset was 27.3 years, with a mean duration of illness of about 18 years, and an average duration of untreated illness of 3.6 years. Out of a total of 414 hospitalizations for manic episodes, 20% presented neither mixed nor psychotic features, 25% were characterized by mixed components only, 46% by psychotic features only, and the remaining 9% presented both features. Thirty-eight percent of the hospitalizations regarded manic episodes classified as non- or minimally severe, about 40% as mildly severe, and 22% as moderate or severe according to YMRS scores calculated at hospital admission.

3.2. Young Mania Rating Scale (YMRS)

When comparing the YMRS score across different categories of features characterizing the manic episode (Table 2), we found higher YMRS values in manic episodes characterized by psychotic features only (24.8) and lower YMRS values when considering episodes with mixed components only (15.5), if compared to episodes characterized by neither mixed nor psychotic features (17.4). Manic episodes with both components had a mean YMRS score comparable to those occurring in psychotic patients (24.3).

3.3. Air pollution across years

PM10 average annual levels ranged from a minimum of 23 μg/m^3 in 2019 to a maximum of 51 μg/m^3 in 2010 (Supplemental Table 1). Daily concentration values of the pollutant were higher than the 50 μg/m^3 limit value set by the European Union (not to be exceeded for more than 35 days/year, https://ec.europa.eu/environment/air/quality/standards.htm) in 1,040 out of the total 4,748 days considered in the study period (≈22%, Fig. 1).

Table 1
Main characteristics of hospital admissions for manic episodes at the Policlinico Hospital in Milan, Italy, 2007-2019.

Characteristics	No./Mean (*%*/*SD*)
Sex	
Males	142 (*34.3*)
Females	272 (*65.7*)
Smoking habit	
No	104 (*25.1*)
Yes	240 (*58.0*)
Unknown	70 (*16.9*)
Cigarettes/day (in smokers)	18.9 (*9.3*)
Age at hospitalization (years)	45.5 (*13.6*)
Length of hospitalization (days)	14.0 (*9.0*)
Age at disorder onset (years)	27.3 (*10.8*)
Duration of illness (years)	18.2 (*11.8*)
Duration of untreated illness (years)	3.6 (*5.6*)
Characteristic of the manic episode	
Neither mixed nor psychotic features	84 (*20.3*)
Mixed features only	104 (*25.1*)
Psychotic features only	189 (*45.7*)
Both mixed and psychotic features	37 (*8.9*)
YMRS[a] (score)	21.0 (*6.8*)
No (0–12)	49 (*11.9*)
Minimal (13–19)	109 (*26.4*)
Mild (20–25)	164 (*39.7*)
Moderate (26–37)	86 (*20.8*)
Severe (38–60)	5 (*1.2*)
Total	414 (*100*)

[a] Young Mania Rating Scale.

Table 2
Young Mania Rating Scale (YMRS) values across different features characterizing the manic episode entailing hospitalization.

Characteristic of the manic episode	YMRS[a]	*p*[b]
Neither mixed nor psychotic features	17.4 (5.0)	*< 0.001*
Mixed features only	15.5 (5.8)	
Psychotic features only	24.8 (5.4)	
Both mixed and psychotic features	24.3 (5.1)	

[a] Mean (SD).
[b] ANOVA.

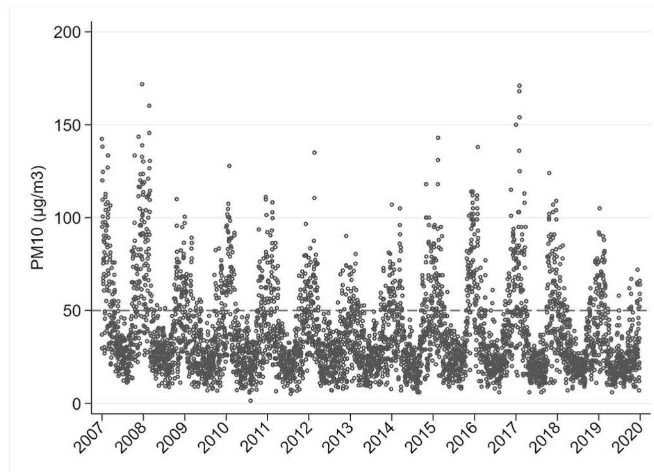

Fig. 1. PM10 daily concentration levels (μg/m^3) across years in Milan, Italy, 2007-2019. Ticks in the x-axis correspond to January 1st of each indicated year. The dashed horizontal line represents the average daily limit value set by the European Union not to be exceed for more than 35 days/year.

3.4. PM10 and YMRS

When examining the association between PM and disorder severity (YMRS), we observed a reduction in YMRS score associated with a 10 μg/m^3 increase in PM10 concentration at daily lags 0, 1, 2, and 3 (Fig. 2A) and a similar pattern when considering averaged daily lags from lag0-1 to lag0-4 (Fig. 2B), with an apparent trend toward the null value when moving away from the day of hospitalization: regression coefficients ranged from −0.57 (95%CI: −1.07; −0.08) at lag0-3 to −0.28 (95%CI: −0.68; 0.13) at lag3 (Supplemental Table 2).

3.5. PM10 and characteristics of the manic episode

Since the YMRS score differed across subgroups defined on the basis of the clinical characteristics of the manic episodes, we also looked at possible associations between PM exposure and the risk of being hospitalized for a manic episode characterized by psychotic symptoms or mixed features. In both cases, the reference category was represented by manic episodes characterized neither by psychotic symptoms nor by mixed components. No association was observed between PM10 levels and the risk of being hospitalized for a manic episode with psychotic features (data not shown). On the other hand, we found a 10 μg/m^3 increase in PM10 exposure levels to be associated with an augmented risk of having a manic episode with mixed features, with OR of 2.43 (95%CI: 1.02; 5.76) and 2.50 (95%CI: 1.03; 6.08) at lags 0 and 1, respectively. An even higher effect was observed when considering averaged daily lags 0-1 to 0-3, with OR ranging from 3.07 (95%CI: 1.18; 8.00) at lag 0-1 to 3.60 (95%CI: 1.22; 10.7) at lag 0-2 (Fig. 3 and Supplemental Table 3).

All results were substantially confirmed with similar trends in sensitivity analyses where variables on individual characteristics (i.e.

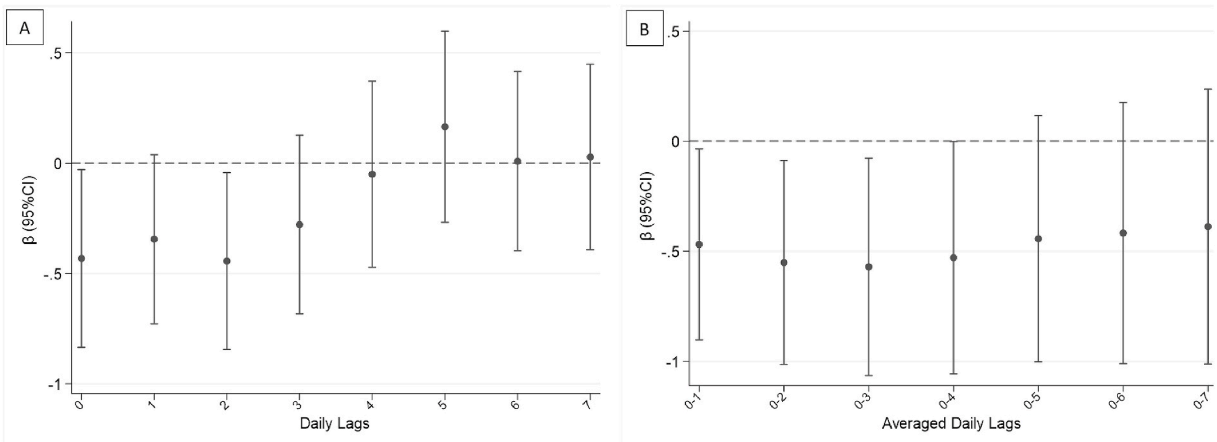

Fig. 2. Association between PM10 and young mania rating scale (YMRS), Milan, Italy, 2007-2019. Results expressed as regression coefficients (β) and corresponding 95% confidence intervals (95%CI) per 10 μg/m^3 increase in: (2A) PM10 concentration occurring daily from the day of admission (lag 0) up to 7 days before (lag 7); (2B) PM10 concentration values obtained by averaging PM10 levels of the day of admission with the levels of the day before (lag 0-1) and of each preceding day up to 7 days before (lag 0-7).

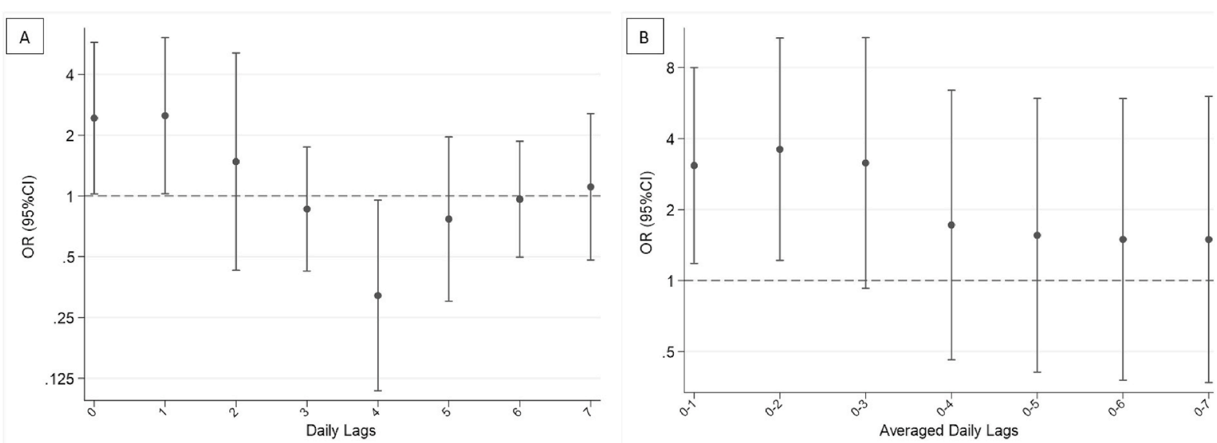

Fig. 3. Association between PM10 and risk of manic episodes with mixed features, Milan, Italy, 2007-2019. Results expressed as Odds Ratios (OR) and corresponding 95% confidence intervals (95%CI) per 10 μg/m^3 increase in: (3A) PM10 concentration occurring daily from the day of admission (lag 0) up to 7 days before (lag 7); (3B) PM10 concentration values obtained by averaging PM10 levels of the day of admission with the levels of the day before (lag 0-1) and of each preceding day up to 7 days before (lag 0-7).

age at hospitalization, sex, smoking habit, and number of cigarettes per day) were removed from the models (data not shown).

4. Discussion

In a study on hospitalized bipolar patients covering over a decade, we observed two main findings: recent exposure to increasing PM10 levels is associated with (1) less severe manic symptoms at hospital admission and (2) a greater risk of mixed vs. pure manic episodes. Of note, manic patients with mixed episodes present a lower mean YMRS score than subjects with classical mania. Taken as a whole, these results point out that PM10 might have a short-term depressogenic effect that accounts for the observed higher risk of manic episodes with mixed components associated with increasing levels of air pollution exposure in the days close to hospitalization.

A recent article reported that long-term exposure to higher average levels of PM10 is associated with a slightly increased risk of depression in the general population (Zhao et al., 2020). This association was also reported for PM10 exposure in the day preceding hospitalization for depression (Gu, 2020), in agreement with our data. This finding should arise concern in clinicians, as data from different research groups remarked that short-term PM10 exposure may also increase the risk of suicide (Braithwaite et al., 2019). On the other hand, few data were published on bipolar patients, and previous studies, reporting contrasting results, either assessed other air pollutants (Thilakaratne et al., 2020) or focused on the association with BD without considering the phase of the disorder (manic or depressive episodes) (Khan et al., 2019; Thilakaratne et al., 2020). Partly coherent with our results are the findings of a study investigating the effect of carbon monoxide exposure (i.e., smoking) during pregnancy on the future risk of BD in the offspring, which found an association with non-psychotic forms of bipolar disorder (Talati et al., 2013).

A plausible biological mechanism underlying our findings might be related to the model hypothesizing that acute exposure to PM10 may boost innate inflammation in vulnerable subjects (Buoli et al., 2018b; Huls et al., 2017), thus inducing neurotransmitter imbalance and epigenetic alterations (Buoli et al., 2018b, 2019). In addition, over-inflammation may vary the expression of clock genes with a change in circadian rhythms and an exacerbation of depressive symptoms (Buoli et al., 2019). In this framework, we hypothesize that increased inflammation due to PM10 exposure may favor the development of mixed features in subjects about to develop a manic episode. The potential role of epigenetic mechanisms in the negative effects of air pollution is also supported by the fact that maternal smoking during pregnancy is associated with higher risk of BD in the offspring as a result of an early exposure to carbon monoxide with potential modification of gene expression (Maj, 2013; Talati et al., 2013). A very recent work reported that maternal exposure to PM10 during pregnancy could increase the umbilical concentration of asprosin, a marker of insulin resistance (Hosseini et al., 2020). The severity of insulin resistance accounts in turn for mood instability, as it happens in bipolar patients with mixed episodes (Calkin et al., 2015). Taken as a whole, these data indicate that we might be starting to better comprehend the complex interplay between PM, biological alterations, and clinical characteristics of BD.

The results of the present investigation have important clinical implications, as mixed features worsen the course of manic episodes and make the management of these patients challenging (Fagiolini et al., 2015). This is even truer if we consider that both mixed features and PM10 increase the risk of suicidal behavior. Reduction in PM10 levels could therefore improve mental health of bipolar patients, and prevention strategies in this direction could be implemented.

Limits of the present study should be mentioned: (1) some information was obtained by clinical records, that can sometimes result inaccurate; (2) factors such as education or time spent outside, that might influence both the probability of exposure and be associated with the clinical outcomes at study, were not available and have not been considered; (3) some clinical factors such as substance misuse may have contributed to the onset or severity of manic episodes: however, this characteristic is unlikely to influence the probability of exposure and should not thus have confounded the reported associations; (4) finally, the limited sample size of our study population prevents definite conclusions.

5. Conclusions

This is one of the first investigations about the effect of air pollution on manic episodes. Future research will have to confirm the present findings, also studying different clinical aspects of BD (e.g. the risk of hypomania, suicidal ideation or rapid cycling) in relation to air pollution. Notwithstanding the relatively low prevalence of BD, manic episodes can aggravate the global functioning of bipolar subjects more than the depressive phases, thus contributing to worsening social dysfunction and poor quality of life; in addition, exposure to air pollution is a risk factor affecting the entire general population. These factors, taken together, highlight the public health relevance of air pollution control policies in reducing the associated burden of disease.

Authors' contribution

Michele Carugno: conceptualization, methodology, formal analysis, writing – original draft; Dario Palpella: investigation, data curation, writing – original draft; Alessandro Ceresa: investigation, data curation, writing – review & editing; Angela Cecilia Pesatori: conceptualization, methodology, writing – review & editing; Massimiliano Buoli: conceptualization, supervision, writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.110943.

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