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TITLE

Residential exposure to air pollution and adverse respiratory and allergic outcomes in children and adolescents living in a chipboard industrial area of Northern Italy

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HIGHLIGHTS

- Chipboard production emits considerable amounts of wood dust, formaldehyde, and other air pollutants
- We assigned residential air pollution exposures to the pediatric population living in the largest chipboard industrial park in Italy
- Exposures were associated with a higher rate of allergic and respiratory outcomes, including emergency room pneumology admissions
- Estimated associations were stronger at closer distance to the industries
- Industrial chipboard production has a substantial public health impact on the resident population

Graphical abstract

(To be added at the revision stage)

Keywords (MAX 6): air pollution, pediatric, epidemiology, formaldehyde, industrial emissions, particle board.

ABSTRACT (303 of max 300 words)

Background

Chipboard production is a source of wood dust, formaldehyde, and other air pollutants. The Viadana district is the largest chipboard industrial park in Northern Italy. In this cohort study, we assessed whether exposures to NO_2, formaldehyde, PM_{10}, $PM_{2.5}$, and black carbon were associated with adverse respiratory and allergic outcomes among all 7525 resident people aged 0-21 years.

Methods

Data on hospitalizations, emergency room (ER) admissions, and specialist visits in pneumology, allergology, ophthalmology, and otorhinolaryngology were obtained from the Local Health Unit. Residential air pollution concentrations in 2013 (baseline) were derived using local (Viadana II), national (EPISAT), and continental (ELAPSE) exposure models. Associations were estimated using negative binomial regression models for counts of events occurred during 2013-2017, with follow-up time as an offset term and adjustment for sex, age, nationality, and a census-block socio-economic indicator.

Results

Median annual exposures to NO_2, PM_{10}, and $PM_{2.5}$ were below the European Union annual air quality standards but above the World Health Organization 2021 air quality guideline levels. Exposure to NO_2 and $PM_{2.5}$ were significantly associated with higher rates of ER pneumology admissions (13 to 30% higher rates per interquartile range exposure differences). Higher rates of allergology and ophthalmology visits were found for participants exposed to higher pollutants' concentrations. When considering the 4-km buffer around the industries, associations with respiratory hospitalizations became significant, and associations with ER pneumology admissions, allergology and ophthalmology visits became stronger. Formaldehyde was not associated with the outcomes considered.

Conclusion

Using administrative indicators of health effects *a priori* attributable to air pollution, we documented the adverse impact of long-term air pollution exposure in residential areas of the Viadana district close to the largest chipboard industries in Italy. These findings, combined with evidence from previous studies, call for an action to improve air quality through preventive measures especially targeting emissions related to industrial activities.

1. INTRODUCTION

Chipboard production is the industrial sector with the greatest environmental impact in the health district of Viadana, comprising ten municipalities in the Mantova province (Northern Italy) and counting 47,701 inhabitants in 2018 (http://demo.istat.it). The district includes the largest chipboard industrial park in the country. Two big industries in the south of the district are equipped with chemical plants to produce urea-formaldehyde resins (the most used bonding agent), chipboard production and storage facilities, and small incinerators (Marcon et al., 2014). Smaller wood factories, such as sawmills, pallet and plywood production facilities, are spread around the central and southern part of the district.

Typical air pollutants emitted from chipboard production are wood dust, formaldehyde, and combustion by-products such as nitrogen dioxide (NO_2) and particulate matter (PM), which are released from boilers, combustion chambers of dryers, as well as vehicular traffic related to industrial activities (Dahlgren et al., 2003). Like in any urbanized area, PM, NO_2 and formaldehyde are also emitted in Viadana from residential vehicular traffic, biomass burning and domestic heating, particularly in the south of the district, a densely populated area close to the industries (Marcon et al., 2021). Black carbon (BC) is a toxic component of PM deriving from the incomplete combustion of fossil fuels, biofuels, and biomass.

Some epidemiological studies conducted on workers exposed to wood dust and formaldehyde suggested a strong impact on human health, particularly on the onset of respiratory diseases like asthma (Pérez-Ríos et al., 2010), lung cancer (Barcenas et al., 2005), nasopharyngeal cancer, and leukemia (IARC, 2006). However, less is known on the health effects of exposure at lower concentrations that are typical in outdoor air.

Most of the population-based studies investigating the short-term effects of exposure to air pollutants in children found increased occurrence of outpatient visits for respiratory problems, asthma, ocular discomfort and dry eye disease (Dong et al., 2021; Kim et al., 2020; M. Li et al., 2021; Y. Li et al., 2021; Mu et al., 2021; Szyszkowicz et al., 2018). Long-term exposure to air pollutants in childhood has been associated with impaired lung function (Bergstra et al., 2018; Bougas et al., 2018; Gehring et al., 2018; He et al., 2019; Tsui et al., 2018). Two epidemiological studies were carried out in the Viadana district (http://biometria.univr.it/viadanastudy). The Viadana I study in 2006 showed that school-aged children living close to the chipboard industries suffered from an excess of respiratory symptoms, irritation of the eyes and upper airways, they were at increased risk of school absences and hospitalizations for respiratory diseases, compared to the children living in more distant areas (de Marco et al., 2010; Girardi et al., 2012; Marchetti et al., 2014; Rava et al., 2011). In the second survey (Viadana II), carried out in 2010, higher concentrations of air pollutants were found in proximity to the industries, and air pollution exposure was related to higher levels of biomarkers of genotoxic damage in children (Marcon et al., 2014). In the present analysis, a part of the Viadana III study, we investigated the associations between residential exposure to air pollution and adverse respiratory and allergic health outcomes occurred in 2013-2017, with the aim of providing an updated health surveillance of the population living in the district. For this purpose, we considered both the historical cohort recruited for Viadana I (aged 9-21 in 2013) and a new cohort aged 0-8 years. We assigned exposures at home addresses through available exposure models and analyzed outcomes derived from electronic hospital records.

2. MATERIAL AND METHODS

2.1 Study design

This is a prospective study of two pediatric cohorts living in the Viadana district followed up from 1/1/2013 to 31/12/2017. The first cohort included 3854 boys and girls aged 9-21 years at baseline (birth years 1992-2003) who were attending district's schools in 2006, when their parents were surveyed (93% of the eligible population) (de Marco et al., 2010). The second is a new cohort of 4233 children aged 0-8 years (birth years 2004-2012) which was identified from the list of the resident population receiving healthcare services by ATS Val Padana (local Health unit of Mantova). This article reports results for the two cohorts combined. Preliminary results on the separate cohorts were published in the form of a report in Italian language (Ricci et al., 2020). Overall, 166 of 3854 participants in the first cohort and 12 of 4233 participants in the second cohort were excluded because they could not be traced or they were living out of the district area at baseline (2013). Residential addresses of the remaining 7909 children were geocoded to obtain geographic coordinates as previously described (Marcon et al., 2021). The addresses that were successfully geocoded were 7525 (95.1%): 3482 (94%) and 4043 (96%) for the older and younger cohorts, respectively. The study was approved by the local Ethical board (Comitato Etico Val Padana, prot. n. 4813, 12/09/2019).

2.2 Electronic health records

We obtained electronic health records on hospital admissions, emergency room (ER) admissions, and specialist visits from ATS Val Padana during 2013-2017. These records include healthcare services provided to cohort participants from ATS Val Padana and any other health unit in the country. Hospital discharge diagnoses were coded according to the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) or equivalent 10th revision (ICD-10). In the present analysis, we considered hospital admissions for respiratory diseases (ICD-9: 460-519 or ICD-10: J00-J99) identified using the primary diagnoses reported in the records, which refer to the main condition treated or investigated during hospitalization. We also identified ER admissions in pneumology wards and specialist visits in pneumology (excluding lung function tests for competitive sports medical certificates), allergology (excluding dermatological examinations for non-allergological conditions e.g., skin moles), ophthalmology, and otorhinolaryngology (ORL) wards (supplementary Table S1). Specialist visits include outpatient examinations provided within the national healthcare system either for free or upon payment of a fixed amount (typically less than 40€), as well as outpatient examinations provided on payment inside healthcare system premises.

2.3 Exposure indicators

We obtained estimates of residential exposure to outdoor air pollution at the 7525 geocoded addresses by applying exposure models available from three projects for baseline (or closest year), as described elsewhere (Marcon et al., 2021). In brief, the "Viadana II" study provided NO_2 and formaldehyde concentrations for 2010 by applying ordinary kriging models to passive sampling data (Marcon et al., 2014). The ELAPSE (Effects of Low-level Air Pollution: a study in Europe) study provided NO_2, $PM_{2.5}$, and black carbon (BC) concentrations for 2010 estimated by land use regression models using data from routine air quality stations in Western Europe combined with a range of predictor variables (de Hoogh et al., 2018). The EPISAT study ("Dati satellitari ed uso del territorio per la stima delle esposizioni a livello nazionale") provided PM_{10} concentrations for 2012 and $PM_{2.5}$ concentrations for 2013, estimated by spatiotemporal land use regression models using data from routine air quality stations in Italy in combination with spatial and temporal predictor variables (Badaloni et al., 2018; Stafoggia et al., 2017).

We also calculated distance between children's homes and industrial emission sources in the district and defined two further exposure indicators based on proximity: the minimum distance to chipboard industries in km, and a categorical indicator: 1) no wood factories (reference group); 2) ≥1 small wood factory (but no chipboard industries); 3) one chipboard industrial facility in the 2 km buffer around participants' homes.

2.4 Socio-economic status

We linked residential addresses to census blocks (number inhabitants: mean=208, SD=245), and for each census block we obtained the deprivation index, a measure of the socio-economic disadvantage at a "micro-ecological" level. The index was calculated as the sum of 5 standardized indicators of poverty derived from the 2001 Italian population census data: percentage of the population with a low education level, percentage of unemployed, percentage of houses not owned, percentage of single-parent families with children, and number of people per 100 m^2 (Caranci et al., 2010). The index was recalibrated for the Lombardia region and categorized according to its population quintiles, from highest (index=1) to lowest socio-economic status (index=5).

2.5 Statistical analysis

Qualitative and quantitative data were described with percentage and median with 1st to 3rd quartile (Q1-Q3), respectively. To assess the association between exposure indicators and annual rates of outcome events, Rate Ratios (RR) were estimated using negative binomial regression models. These analyses were adjusted for sex, age at baseline categorized into 6 groups to account for non-linear associations (3 groups for the younger cohort: 0-3, 3.1-5, 5.1-9 years, and 3 groups for the oldest cohort: 9.1-12, 12.1-16, 16.1-21 years), nationality, and census-block deprivation index (a proxy of individual socio-economic status). An "offset" term was included for follow-up time (the 5-years follow-up time or time until change of address). RRs were calculated for interquartile range (IQR) differences of air pollutant concentrations (Viadana II model: NO_2, 3.3µg/m^3, formaldehyde, 0.3µg/m^3; ELAPSE model: NO_2, 4.2µg/m^3, $PM_{2.5}$, 2.8µg/m^3, BC, 0.2 10^{-5} m^{-1}; EPISAT model: $PM_{2.5}$, 2.0µg/m^3, PM_{10} , 4.4µg/m^3), and for a 1-km increase in the minimum distance to the chipboard industries. Non-linear associations with the minimum distance were tested using natural spline functions. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to choose between linear and nonlinear models, and to select the optimal number of knots for nonlinear models.

To assess whether exposure misclassification due to changes in residential addresses was a source of bias, the analyses were repeated after restricting the cohorts to the participants who did not move during the study period. Finally, to better appreciate the potential impact of emissions related to industrial activities, the study area was restricted to the 4-km circular buffers around the two chipboard industries (as previously done, Marcon et al., 2014).

The statistical analyses were performed by using STATA 16.0 (StataCorp, College Station, Texas) and R software (version 3.5.2).

3. RESULTS

Overall, 7525 subjects were included in the study (4043 in the 0-8 years cohort and 3482 in the 9-21 years cohort). Of these, 48.6% were females, 24.2% had foreign parents and more than half had a deprivation index ≤2 (Table 1). The children admitted to hospital for respiratory diseases or ER in the pneumology ward were 324 and 2278, respectively (Table 2); 145, 594, 1838, and 848 children were visited by specialists in pneumology, allergology, ophthalmology, and ORL, respectively. Except for specialist allergology visits, mean annual counts of events per child were higher in the younger cohort (Table 2).

The distribution of estimated annual exposures to air pollution are reported in sypplementary Table S2. As regards regulated pollutants, the median concentrations of NO_2, PM_{10}, and $PM_{2.5}$ were below the European Union annual air quality standards (40, 40, and 25 µg/m^3, respectively). However, they were higher than the World Health Organization 2021 guideline levels (10, 15, and 5 µg/m^3, respectively), the most recent evidence-based recommendation for health protection. There was an increasing gradient of exposures to NO_2, $PM_{2.5}$, and BC estimated using the Viadana II and ELAPSE models from reference areas (no factories <2 km) to the areas with the chipboard industries (supplementary Table S2); differences between median concentrations were quite small for formaldehyde. Median concentrations of PM_{10} and $PM_{2.5}$ estimated using the EPISAT models were similar across groups, or slightly lower in the group of children living closer to smaller wood factories. Correlations between estimated exposures to air pollutants were low, apart from moderate correlations for air pollutants estimated by the same exposure model (ELAPSE: spearman's ρ 0.72 to 0.77; EPISAT: spearman's ρ 0.63) (Table 3).

3.1 Associations between air pollution exposures and health outcomes

There were no associations between exposures to air pollutants and the rates of respiratory hospitalizations or specialist visits in pneumology (Figure 1, A and C). Associations with ER admissions in pneumology were positive and significant for four of seven pollutants (Figure 1, B): for these, the estimated excess of annual ER admissions for an IQR difference in exposure ranged from 13% for NO_2 (Viadana II model, RR 1.13, 95% CI: 1.06-1.22) to 30% for $PM_{2.5}$ (ELAPSE model, RR 1.30, 95% CI: 1.20-1.41). For the remaining three pollutants (formaldehyde, and $PM_{2.5}$ and PM_{10} from EPISAT model), estimated associations were close to the null. Increasing exposures were associated with higher rates of specialist allergology visits for all pollutants; the increase in annual rates ranged from 10% for an IQR difference in NO_2 exposure (Viadana II model, RR 1.10, 95% CI: 0.93-1.31) to 32% for an IQR difference in PM_{10} exposure (EPISAT model, RR 1.32, 95%CI 1.14-1.52) (Figure 2, A). The increase in ophthalmology visits per an IQR higher concentration of pollutants ranged from 2% for formaldehyde (RR 1.02, 95% CI: 0.94-1.10) to 12% for NO_2 (Viadana model, RR 1.12, 95% CI: 1.03-1.22) (Figure 2, B). The rate of ORL visits was not consistently associated with air pollutants concentrations (Figure 2, C).

The sensitivity analysis on the participants who did not move their residential address during the follow-up period provided similar association estimates (supplementary Figure S1). The sensitivity analysis on the participants living within 4 km from the chipboard industries confirmed the lack of association also observed in the main analysis for pneumology and ORL specialist visits, but for the other outcomes estimated associations were shifted away from the null towards higher RRs (supplementary Figure S2). In particular, exposures resulted associated with the rates of hospitalization for respiratory diseases: the excess in hospitalizations ranged from 4% per IQR difference in exposure to $PM_{2.5}$, EPISAT model (RR 1.04, 95%CI: 0.79-1.38) to 140% per IQR difference in exposure to $PM_{2.5}$, ELAPSE model (RR 2.40, 95%CI: 1.09-5.67). Five of seven pollutants showed a significant association with ER admissions in pneumology, with an estimated increase in rates ranging from 9% for PM_{10} (EPISAT model, RR 1.09, 95%CI: 1.00-1.18) to 76% for $PM_{2.5}$ (ELAPSE model, RR 1.76, 95%CI: 1.36-2.30). Allergology and ophthalmology visits also shifted towards stronger associations.

3.2 Associations between indicators of proximity and study outcomes

Compared with the reference exposure group of children living at >2km from any wood factory in the district, the children living close to the chipboard industries (<2 km) had a 51% higher rate of ER admissions in pneumology (RR 1.51, 95%CI: 1.35-1.69) and an 87% higher rate of specialist pneumology visits (RR 1.87, 95%CI: 1.11-3.14) (Table 4). The children living close to the small wood factories (<2 km) showed a 17% higher rate of ER admissions in pneumology (RR 1.17, 95%CI: 1.05-1.31), compared to the reference group.

When looking at exposures in terms of minimum distance of homes to chipboard industries, a linear downward relationship was found for pneumology visits (supplementary Table S3), with a 5% decrease in rates per km (RR 0.95, 95%CI: 0.92, 0.98). Nonlinear exposure-outcome associations were found for ER admissions and specialist allergology visits (supplementary Figure S3). ER admission rates were highest for the children living closest to the chipboard industries (15 per 100 children/year) but were increased also for the children living 8-10 km away from the industries (12 per 100 children/year), and were lowest at a distance greater than 20 km (5 per 100 children/year) (panel left). A J-shaped relationship was found for allergology visits, with higher rates estimated both for the children living closer to the chipboard industries (4 per 100 children/year) and for those living 20 km away (4-6 per 100 children/year), compared to the children living at 8-10 km (3 per 100 children/year) (panel right).

4. DISCUSSION

This prospective cohort study provides evidence on the health effects of air pollution in the paediatric population living in the health district of Viadana, an industrial area of the Po Valley in Northern Italy. The air quality in the Po Valley is among the worst in Europe, due to the intensity of urban and industrial emissions and meteorological conditions favouring air stagnation (Zhu et al., 2012). We followed up two cohorts covering overall the ages from birth up to 21 years. For the older cohort (9-21 years), a greater health risk in relation to air pollution exposure and proximity to industrial premises was previously reported (de Marco et al., 2010; Marchetti et al., 2014; Marcon et al., 2014; Rava et al., 2011). The younger cohort (0-8 years) was included because infants and children are expected to be particularly susceptible to the air pollution effects. In fact, they typically spend more time outdoors, have higher ventilation rates, and their immune systems are not fully developed, which causes their lungs and airways to adsorb higher internal doses and predisposes this age group to greater air pollution effects (Schultz et al., 2017). Exposure to high air pollution levels in early life may result in increased acute lower respiratory illnesses, respiratory symptoms, bronchitis, and asthma; moreover, children exposed to higher levels of ambient air pollution have impaired lung growth and are at risk of accelerated lung function decline in adulthood (Garcia et al., 2021; Sly & Flack, 2008).

Air pollution is a complex mixture of highly correlated chemical components. Such high correlations are due to the fact that air pollutants share combustion-related emission sources (e.g., vehicular traffic, power generation, and heating) but it is also linked to their common mechanisms of transport, dispersion, and ground deposition, mainly related to meteorological conditions. Some pollutants, such as PM_{10}, $PM_{2.5}$, and NO_2 are typically considered in epidemiological studies both for their specific health effects and as proxy indicators of exposure to the complex air pollution mixture. Long-term exposure to NO_2, $PM_{2.5}$ and its subcomponent BC were found to be associated with the development of childhood asthma, asthma exacerbations, wheeze, and rhinitis (Burte et al., 2018; Khreis et al., 2017; Lau et al., 2020; Norbäck et al., 2019; Tétreault et al., 2016). These pollutants can induce airway inflammation, oxidative stress, and enhance respiratory sensitization to aeroallergens, which could also contribute to the development and exacerbation of asthma (Guarnieri & Balmes, 2014). Like for the previous studies conducted in the Viadana district, formaldehyde was included as a marker of activities related to chipboard production. Nonetheless, formaldehyde is also produced as a secondary pollutant through photooxidation of pollutants emitted by vehicular traffic and other combustion-related processes.

Strengths of the present study compared to the previous ones in the district are the large sample size, the variety of health outcomes investigated, and the availability of residential exposure estimates derived from diverse models developed at the international (ELAPSE), national (EPISAT), and local (Viadana II) scales. In our study, estimates of exposure to $PM_{2.5}$ (ELAPSE and EPISAT) and NO_2 (Viadana II and ELAPSE) were available from two models, while formaldehyde (Viadana II), BC (ELAPSE), and PM_{10} (EPISAT) were derived from a single exposure model. It is relevant to consider that the three available exposure models employed a variety of data sources (routine air quality measurements vs *ad hoc* sampling), methodologies (kriging vs LUR), and input data periods (2010–2013 vs 2017–2018). As also discussed elsewhere (Marcon et al., 2021), none of these models could be considered a "gold standard" for exposure assessment, also because we could not identify a priori the exposure metrics that would better fit the postulated mechanism of action of air pollutants emitted from chipboard production. Moreover, we were interested in assessing the impact of exposure to a mixture of air pollutants, rather than disentangling the effects of specific pollutants. These considerations imply that the key factor for a causal interpretation of the estimated air pollution effects must be consistency across associations obtained from analyses considering different air pollution metrics. Extending this concept, understanding whether air pollution emissions related to the chipboard industrial areas are an important contributor to the observed health effects requires to take indicators of proximity to the industrial premises into account.

Findings from the present study support a relationship between exposure to air pollution and adverse health outcomes in children and adolescents residing in the district. The outcomes hereby considered were selected among those more likely attributable to exposure of the mucosae of the upper and lower airways and eyes. The most consistent finding was the association of air pollution exposures with ER pneumology admissions. Significant detrimental associations were seen for NO_2, estimated by the Viadana II and ELAPSE models, and for $PM_{2.5}$ and BC estimated by the ELAPSE model. The facts that proximity to the chipboard industries was also associated with an excess of ER admissions, and that associations estimated within the 4 km buffer around the industries were stronger, suggest that emissions related to industrial activities play a key role. In fact, the 4-km buffers around the industrial facilities represent a smaller district area where bias due to exposure misclassification and unmeasured confounding are expected to be smaller. Null associations in the main analysis for $PM_{2.5}$ and PM_{10} estimated using the EPISAT model shifted towards RRs greater than one in the analysis of the 4-km buffers. Likewise, exposures to NO_2, $PM_{2.5}$, and PM_{10} were not associated with hospitalisations for respiratory diseases in the main analysis, but they were associated with hospitalisations in the analysis restricted to the 4-km buffer. Outpatient visit in pneumology were associated with proximity indicators, but not with air pollution exposures, which could be in part related to the lower number of events for this outcome (n=283 visits from 145 participants) compared to the others. The lack of association between formaldehyde exposure and the outcomes investigated in the present study suggests that these health effects are not on the same pathogenetic pathway of the known formaldehyde cancerogenic effects; in fact, in the Viadana II study, genotoxicity in mouth mucosa cells was found to be increased with formaldehyde exposure levels similar to those observed in the present study (Marcon et al., 2014). Taken together, associations of health outcomes with a variety (but not all) exposure indicators support that, rather than specific airborne chemicals, the mixture of pollutants emitted both from industrial (including power generation and heavy traffic induced by production) and non-industrial (urban) sources has an adverse public health impact.

Our findings fall in line with other studies on air pollution effect in children. A study carried out in the United States showed that, among children aged 5 to 20 years, hospitalizations and ER admissions for asthma increased by 7.2% and 4.2%, respectively, for a 1 µg/m^3 increase in $PM_{2.5}$ exposure (Keet et al., 2018). NO_2 has also been associated with increased respiratory symptoms and ER admissions among people with asthma (Madaniyazi & Xerxes, 2021).

Long-term exposure to PM and NO_2 has been associated with symptoms of the upper airways (runny nose, sore throat, cough, and ear pain) also by increasing susceptibility to viral infections as well as lower airways symptoms (persistent cough, shortness of breath-dyspnoea, wheezing, and chest pain) (Liu et al., 2018). Exposure to air pollutants can have a negative impact on the eyes by promoting inflammation, conjunctivitis, oxidative stress of the conjunctiva and cornea (Dadvand et al., 2017; Łatka et al., 2018). It is also known that short-term air pollution exposure can trigger allergic reactions. Powders can adsorb and transport pollen and other aeroallergens (D'Amato et al., 2007; Grundström et al., 2017).

These results are consistent with the Viadana I questionnaire survey carried out in the district that found an excess risk of nose, mouth, throat, and eye irritation symptoms in children who lived near the chipboard industries (de Marco et al., 2010). It is plausible that irritation symptoms of the airways and eye conjunctiva may have increased the prescription of allergological and eye specialist visits. Short-term exposure to NO_2 and $PM_{2.5}$ has also been associated with the occurrence of nonspecific conjunctivitis (Bourcier et al., 2003; Chang et al., 2012); in particular children with conjunctivitis under 4 years of age were reported to seek medical attention more frequently (Szyszkowicz et al., 2016). Interestingly, preliminary cohort-specific analyses highlighted that excesses of eye visits in relation to exposure were mainly seen in the older cohort, an age group where refractory disorders are typically more frequent than at younger ages (Ricci et al., 2020). In a cross-sectional study carried out in Spain, traffic related air pollutants were associated with the use of spectacles in children, a surrogate indicator for myopia (Dadvand et al., 2017). Similarly, a study conducted in Taiwan showed that $PM_{2.5}$ and NO_2 concentrations were associated with the incidence of myopia in children, and provided experimental data on animals suggesting that exposure to ambient air pollutants may be a risk factor for the pathogenesis of this condition (Wei et al., 2019).

Eye examinations were more frequent among the children living closer to the industries than further away. On the other hand, we observed a J-shape relationship between distance to the industries and the rate of allergology visits, with an increase of events close to the industries but also at the maximum distance. One possible explanation is that the children living in the rural area far away from the industries might be more exposed to green spaces, which have been linked to increased allergic and respiratory diseases in children, possibly due to a higher exposure to pollen (Parmes et al., 2020).

Limitations

One study limitation is that we did not have data on some potential confounders. Second-hand smoking exposure, but also active smoking for young adolescents (Marcon et al., 2018), could be an uncontrolled source of confounding in our study. Although we adjusted for a micro-ecologic indicator of deprivation, we lacked individual-level data that could have captured different aspects of the association between socio-economic position and exposure to air pollution (Temam et al., 2017). For the cohort aged 9-21 years, some additional information on these factors were available from the Viadana I parental questionnaire administered in 2006, but only common covariates were considered in the present combined analysis of the two cohorts. Nonetheless, results from the analysis of the older cohort were quite similar to the results of the combined analysis when further adjusting for parental smoking habits and parental education (Ricci et al., 2020). In our study, outcomes were derived from administrative data, and we had no information on clinical validity. This is particularly relevant for outpatient visits, which have been scarcely used in Italy for defining outcomes related to pollution. Data on visits by private providers outside the hospital premises were not available. Another drawback is that, given the proximity between the chipboard industries and the most urbanised areas in Viadana, it was not possible to disentangle between industrial emissions and other anthropic sources of contaminants.

5. CONCLUSIONS

Our follow-up study documented associations of air pollution exposure and proximity to chipboard industries with the risk of adverse respiratory and allergic outcomes among 7525 children and adolescents living in a chipboard industrial area in Northern Italy. These findings, combined with evidence from previous studies analyzing different subjective (parent-reported symptoms) and objective outcomes (markers of genotoxicity), call for an action to improve air quality in the study area through preventive measures targeting all known air pollution sources and, in particular, emissions directly and indirectly related to the industrial activities.

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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.

Ethical approval The Viadana III study has been approved by the Ethical Committee Val Padana (Prot. n. 4813, 12/02/2019).

Consent to participate The parents or guardians of each child participating in the questionnaire survey in 2006 signed an informed consent. The need for a consent to participate was waived for children identified through electronic health records since data were anonymized.

Appendix A. Supplementary material

TABLES

Table 1. Baseline socio-demographic characteristics of participants.

Characteristics	**Cohort 0-8 years** (N=4043)	**Cohort 9-21 years** (N=3482)	**Overall** (N=7525)
Age, median [Q1, Q3] (years)	4.6 [2.4, 6.8]	14.6 [11.8, 17.4]	8.4 [4.3, 14.2]
Female sex, n (%)	2038 (50.4)	1622 (46.6)	3660 (48.6)
Foreign nationality, n (%)	1322 (32.7)	502 (14.4)	1824 (24.2)
Deprivation index, n (%)			
1 (least deprived)	982 (24.3)	856 (24.6)	1838 (25.0)
2	1064 (26.3)	976 (28.0)	2040 (27.7)
3	749 (18.5)	677 (19.4)	1426 (19.4)
4	749 (18.5)	575 (16.5)	1324 (18.0)
5 (most deprived)	387 (9.6)	339 (9.7)	726 (9.9)

Table 2. Summary statistics on the events occurred during the follow-up period (2013-2017).

Events	**Cohort 0-8 years** (N=4043)	**Cohort 9-21 years** (N=3482)	**Overall** (N=7525)
Moving outside the district, n (%)	793 (19.6)	499 (14.3)	1292 (17.2)
Hospitalizations for respiratory diseases			
N. children admitted	264	60	324
Mean count per child admitted	1.15	1.03	1.13
ER admissions in pneumology			
N. children admitted	1405	873	2278
Mean count per child admitted	1.87	1.47	1.72
Specialist visits in pneumology			
N. children visited	67	78	145
Mean count per child visited	2.25	1.69	1.95
Specialist visits in allergology			
N. children visited	266	328	594
Mean count per child visited	2.12	2.38	2.26
Specialist visits in ophthalmology			
N. children visited	1001	837	1838
Mean count per child visited	1.92	1.83	1.88
Specialist visits in ORL			
N. children visited	533	315	848
Mean count per child visited	1.55	1.41	1.50

Table 3. Spearman's rank coefficients for the correlations among air pollutants, calculated using data from all the children (n= 7525). For each pollutant, the source study is reported.

Study		Viadana		Elapse			Episat	
	Pollutant	**NO_2**	**Form.**	**NO_2**	**$PM_{2.5}$**	**BC**	**$PM_{2.5}$**	**PM_{10}**
Viadana	**NO_2**	1						
	Form.	0.37	1					
Elapse	**NO_2**	0.39	0.36	1				
	$PM_{2.5}$	0.50	0.41	0.75	1			
	BC	0.39	0.29	0.77	0.72	1		
Episat	**$PM_{2.5}$**	0.18	0.26	0.37	0.29	0.31	1	
	PM_{10}	0.15	0.32	0.35	0.23	0.30	0.63	1

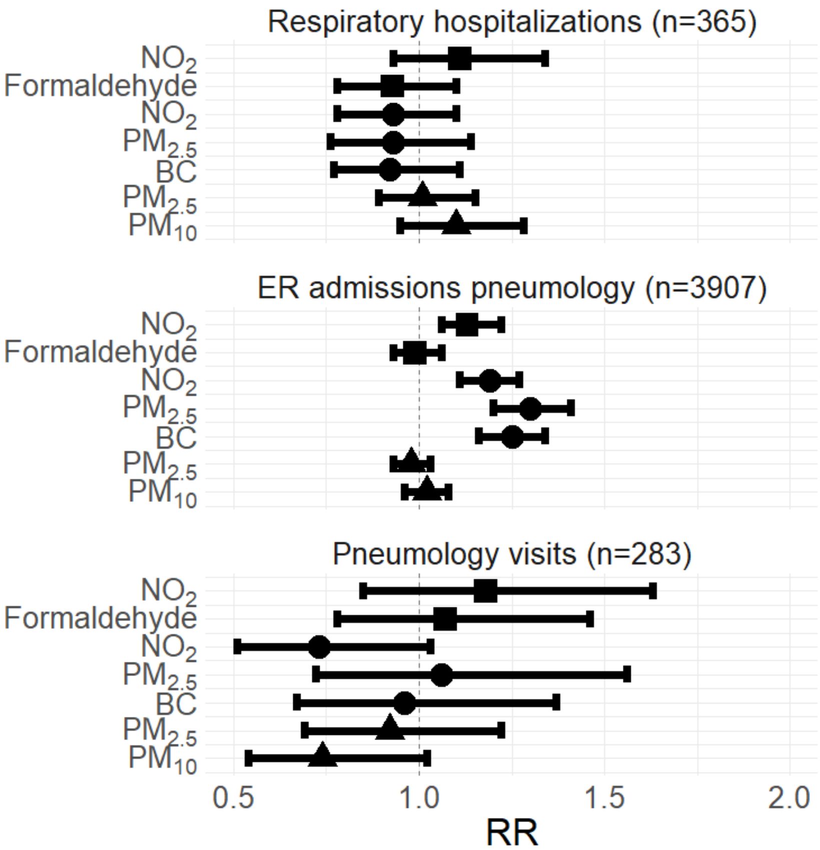
*Table 4. Estimated associations (95% CI) of distance to chipboard industries and small wood factories with the count of outcome events during 2013-2017 in the pediatric population (age 0-21, n=7525).**

Outcome	**Categorical Exposure (buffer's level)**	**IRR (95%CI)**
Hospitalizations for respiratory diseases	< 2 km small factories	0.86 (0.64, 1.14)
	< 2 km chipboard industries	0.95 (0.72, 1.26)
ED admissions in pneumology	< 2 km small factories	1.17 (1.05, 1.31)
	< 2 km chipboard industries	1.51 (1.35, 1.69)
Specialist visits in pneumology	< 2 km small factories	1.32 (0.78, 2.23)
	< 2 km chipboard industries	1.87 (1.11, 3.14)
Specialist visits in allergology	< 2 km small factories	0.80 (0.61, 1.05)
	< 2 km chipboard industries	1.00 (0.76, 1.31)
Specialist visits in ophthalmology	< 2 km small factories	0.95 (0.84, 1.09)
	< 2 km chipboard industries	1.12 (0.99, 1.28)
Specialist visits in ORL	< 2 km small factories	1.04 (0.86, 1.25)
	< 2 km chipboard industries	0.89 (0.73, 1.08)

* obtained using negative binomial regression models adjusted for sex, age (sextiles), and nationality (Italian/not Italian).

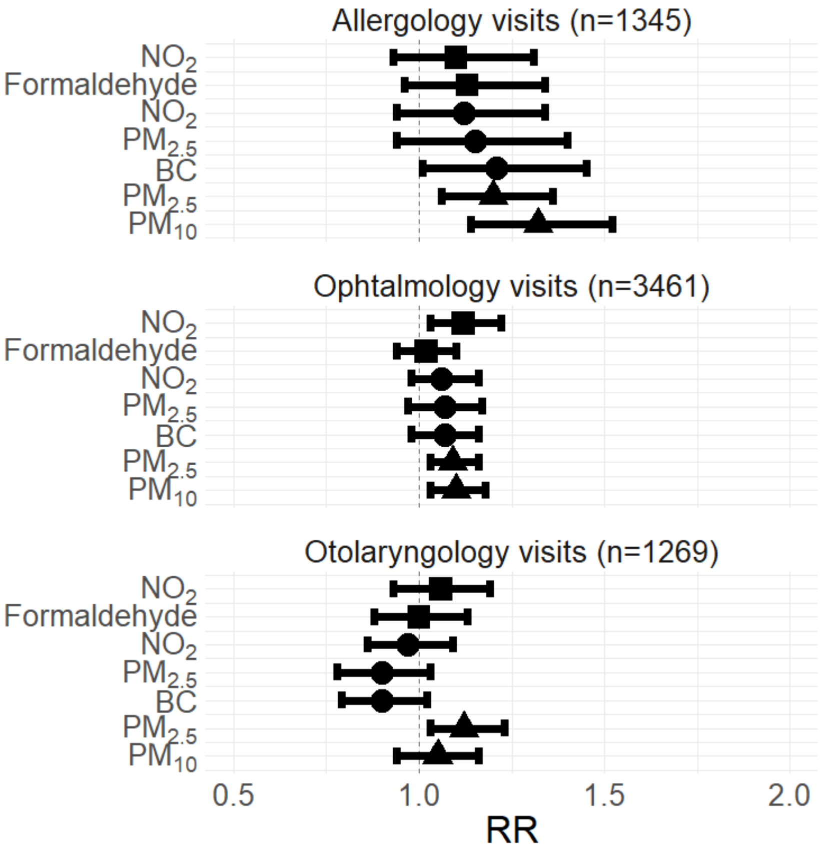
FIGURES

*Figure 1. Estimated associations of exposure to air pollutants with counts of hospitalizations (A), ER admissions (B), and specialist visits (C) for respiratory diseases during 2013-2017 (age 0-21, n=7525)**



* Rate Ratios (RR) with 95% CI for a 1-IQR increase in air pollutant concentrations, obtained using negative binomial regression models adjusted for sex, age at baseline, nationality, and census-block deprivation index; symbols indicate exposure models: squares = Viadana II; circles = ELAPSE; triangles = EPISAT

*Figure 2. Estimated associations of exposure to air pollutants with counts of specialist visits in allergology (A), ophthalmology (B), and otolaryngology (C) during 2013-2017 (age 0-21, n=7525)**



* Rate Ratios (RR) with 95% CI for a 1-IQR increase in air pollutant concentrations, obtained using negative binomial regression models adjusted for sex, age at baseline, nationality, and census-block deprivation index; symbols indicate exposure models: squares = Viadana II; circles = ELAPSE; triangles = EPISAT

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Supplementary materials

Manuscript title: Residential exposure to air pollution and adverse respiratory and allergic outcomes in children and adolescents living in a chipboard industrial area of Northern Italy

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Table S1. Count of outcome events by cohort.

Outcome	Cohort 0-8 years	Cohort 9-21 years	Overall count
Hospitalizations for respiratory diseases	303	62	365
ER admissions in pneumology	2627	1280	3907
Specialist visits in allergology	563	782	1345
Specialist visits in pneumology	151	132	283
Specialist visits in ORL	824	445	1269
Specialist visits in ophthalmology	1926	1535	3461

Tab S2. Distribution of air pollutant concentrations at baseline according to distance to the chipboard industries and the other wood factories. *

			Distance to the factories		
		Overall	≥ 2 km from any factory	< 2 km from small wood factories	< 2km from a chipboard industrial facility
Exposure model	n	7525	2861	2228	2436
VIADANA	NO_2, µg/m^3	16.4 (14.8, 18.1)	15.4 (13.9, 16.2)	16.6 (14.3, 17.8)	18.3 (16.7, 19.3)
	Formaldehyde, µg/m^3	2.6 (2.4, 2.7)	2.4 (2.2, 2.6)	2.5 (2.4, 2.6)	2.7 (2.6, 2.7)
ELAPSE	NO_2, µg/m^3	27.3 (24.9, 29.1)	26.0 (24.1, 28.0)	26.7 (24.8, 28.7)	28.9 (27.4, 29.9)
	$PM_{2.5}$, µg/m^3	26.0 (23.9, 26.7)	23.9 (23.1, 25.5)	25.7 (24.1, 26.4)	26.8 (26.4, 26.9)
	BC, 10^{-5} m^{-1}	1.9 (1.8, 2.0)	1.9 (1.8, 2.0)	1.9 (1.8, 2.0)	2.0 (2.0, 2.0)
EPISAT	$PM_{2.5}$, µg/m^3	25.3 (24.3, 26.3)	25.2 (23.8, 26.3)	25.1 (24.2, 26.4)	25.4 (24.8, 26.1)
	PM_{10}, µg/m^3	36.4 (34.2, 38.5)	36.7 (34.5, 38.8)	35.1 (32.6, 37.5)	37.0 (35.5, 39.2)

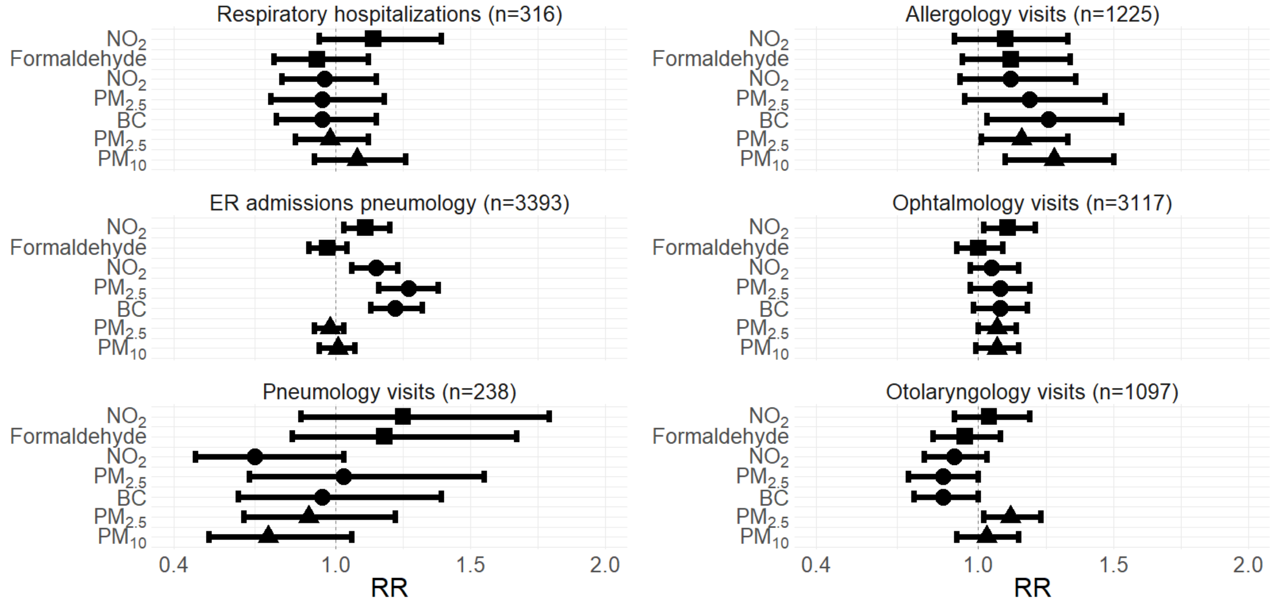
* median (Q_1-Q_3) reported; p<0.001 for all the comparisons across strata (Kruskal Wallis tests)

*Table S3. Estimated associations of the minimum distance to the chipboard industries with count of outcome events during 2013-2017 (age 0-21, n=7525).**

Outcome	IRR (95%CI)
Hospitalizations for respiratory diseases	1.00 (0.98, 1.02)
Specialist visits in pneumology	0.95 (0.92, 0.98)
Specialist visits in ORL	1.00 (0.99, 1.01)
Specialist visits in ophthalmology	0.99 (0.99, 1.00)

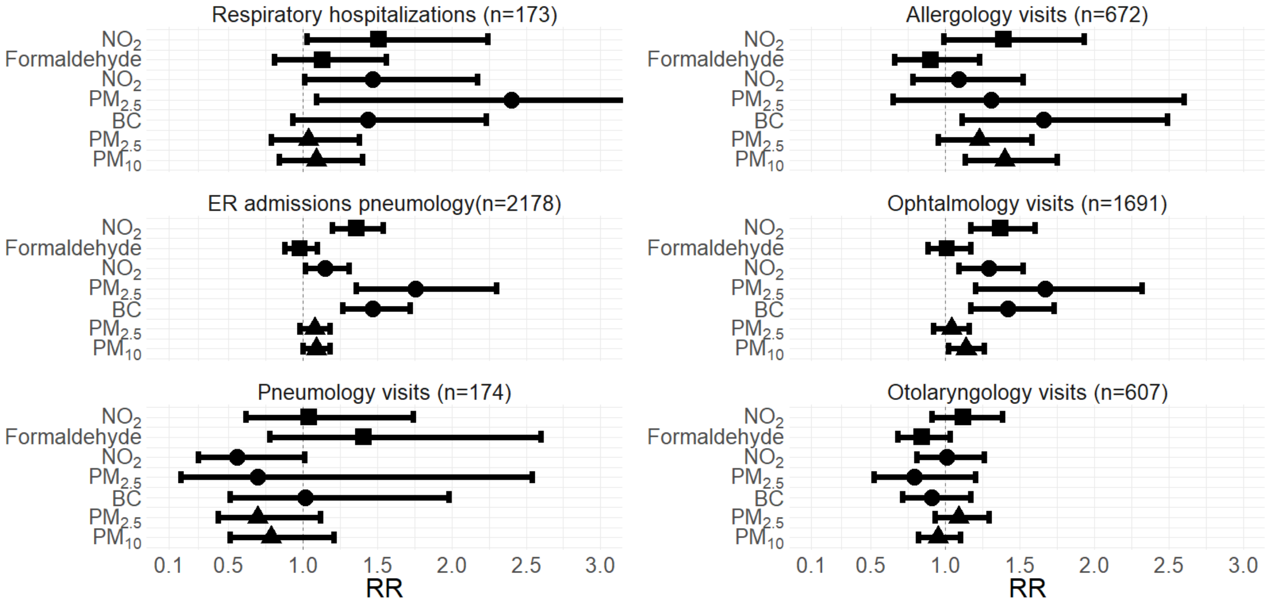
* Rate Ratios (RR) with 95% CI for a 1-km increase in the minimum distance, obtained using negative binomial regression models adjusted for sex, age at baseline, nationality, and census-block deprivation index

*Fig S1. Estimated associations of exposure to air pollutants with counts of respiratory hospitalizations, ER admissions in pneumology, and specialist visits in pneumology, allergology, ophthalmology, and ORL during 2013-2017: sensitivity analysis among participants who did not move during the follow-up (n=6,233)**



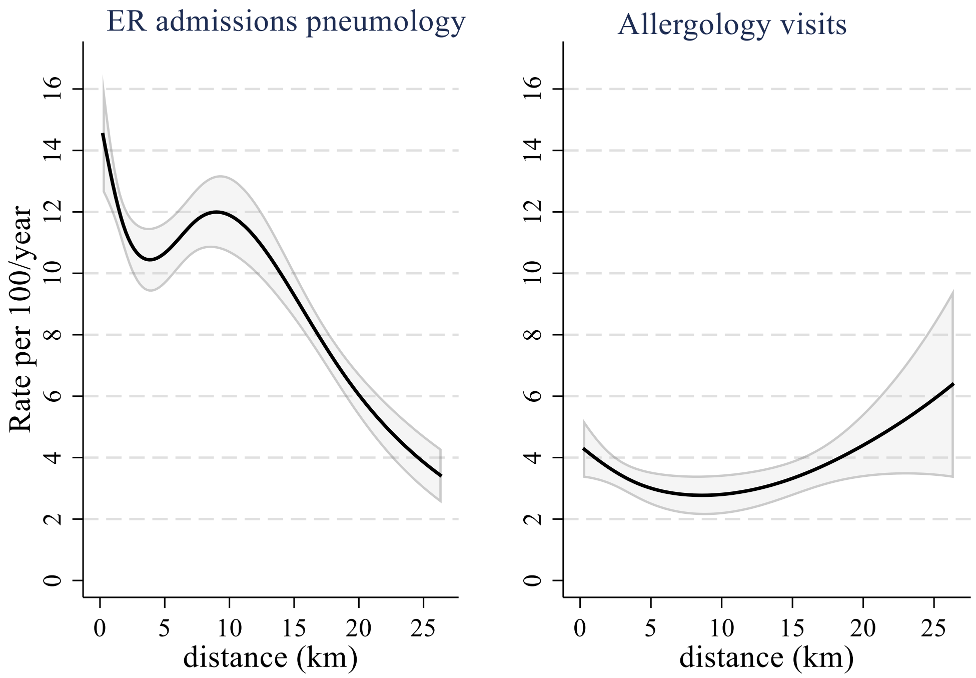
* Rate Ratios (RR) with 95% CI for a 1-IQR increase in air pollutant concentrations, obtained using negative binomial regression models adjusted for sex, age at baseline, nationality, and census-block deprivation index; symbols indicate exposure models: squares = Viadana II; circles = ELAPSE; triangles = EPISAT

*Fig S2. Estimated associations of exposure to air pollutants with counts of respiratory hospitalizations, ER admissions in pneumology, and specialist visits in pneumology, allergology, ophthalmology, and ORL during 2013-2017: sensitivity analysis among participants living in the 4 km buffers around the chipboard industries (n=3,591) **



* Rate Ratios (RR) with 95% CI for a 1-IQR increase in air pollutant concentrations, obtained using negative binomial regression models adjusted for sex, age at baseline, nationality, and census-block deprivation index; symbols indicate exposure models: squares = Viadana II; circles = ELAPSE; triangles = EPISAT. Panel A, $PM_{2.5}$ ELAPSE: 95%CI confidence interval cut for graphical reasons: RR 2.40, 95% CI: 1.09-5.67

Fig S3. Predicted count of ER admissions in pneumology and specialist visits in allergology by minimum distance to the chipboard industries.



* calculated using negative binomial regression models adjusted for sex, age at baseline, nationality, and census-block deprivation index; distance was modelled using natural spline functions with 4 (A) and 3 knots (B), respectively.