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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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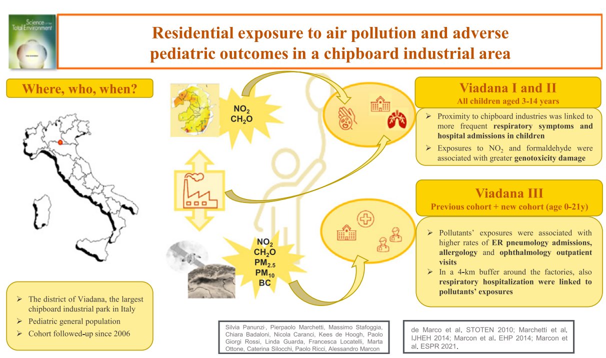
HIGHLIGHTS

- Chipboard production emits considerable amounts of wood dust, formaldehyde, and other air pollutants
- We assigned air pollution exposures to the pediatric population living in the largest chipboard industrial park in Italy
- Exposures were related to higher rates of emergency room pneumology admissions and other allergic/respiratory outcomes
- 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



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ABSTRACT

Background: Chipboard production is a source of wood dust, formaldehyde, and combustion-related pollutants such as nitrogen dioxide (NO_2) and particulate matter (PM). 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 people aged 0–21 years residing in the Viadana district, an area in Northern Italy including the largest chipboard industrial park in the country.

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-

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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 (40, 40, and 25 μg/m^3) but above the World Health Organization 2021 air quality guideline levels (10, 15, and 5 μg/m^3). Exposures 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, all $p < 0.01$). 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 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 the 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 are located in the south, the most densely populated area in the district. These facilities 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. A map of the district area can be found elsewhere (Fig. 1 of Marcon et al., 2014).

Typical air pollutants emitted during chipboard production, mainly from boilers and combustion chambers of dryers, are wood dust, formaldehyde, and combustion by-products such as nitrogen dioxide (NO_2), particulate matter (PM) (Dahlgren et al., 2003). Black carbon (BC), a toxic component of PM, can also be emitted through incomplete combustion of fossil fuels, biofuels and biomass (Janssen et al., 2011). All the previously mentioned air pollutants are also released from anthropogenic sources such as vehicular traffic, biomass burning, and domestic heating (Morawska and Zhang, 2002).

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 health 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. The initial study (Viadana I) in 2006 showed that children aged 3–14 years living at a distance <2 km to the chipboard industries suffered from excesses of respiratory symptoms (33 %), irritation of the eyes (24 %) and upper airways (47 %), school absences (24 %) (de Marco et al., 2010; Girardi et al., 2012), and they were also at increased risk of hospitalizations for respiratory diseases (80 %), compared to the children living in areas at ≥2 km from any wood factory in the district (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).

As part of the Viadana III study, we investigated the associations between residential exposure to air pollution and adverse respiratory and allergic health outcomes occurring from 2013 to 2017. The objective was to provide an updated health surveillance of the young population living in the district taking into account distance from the manufacturing sites and controlling for sex, age, and indicators of socio-economic status. 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 follow-up study of two pediatric cohorts living in the Viadana district 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). The two cohorts were combined for the present study. 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 <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. Root mean square errors (RMSE) from leave-one-out cross-validation were 11.997 and 0.089 μg/m^3, respectively (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 (de Hoogh et al., 2018). In ELAPSE, land use regression models were estimated for Western Europe using annual mean concentrations calculated from routine air quality measurements for $PM_{2.5}$ and NO_2; annual mean concentrations of BC were obtained as $PM_{2.5}$ absorbance based on reflectance measurement of the filters collected in the European Study of Cohorts for Air Pollution Effects (Eeftens et al., 2012). RMSE from five hold-out validations (each holding 80 % sites for model training and 20 % for validation) were 9.51 μg/m^3 ($PM_{2.5}$), 2.97 μg/m^3 (NO_2), and 0.58 10^{-5} m^{-1} (BC) (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, 2019). Co-authors MS and CB optimised exposure models for the study area aimed to capture PM variation due to very local sources i.e., stage 4 modelling in Stafoggia et al. (2017, 2019). RMSE computed on held-out monitoring stations were 8.0 μg/m^3 for PM_{10} (year 2012) and 6.6 μg/m^3 for $PM_{2.5}$ (year 2013).

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

The statistical analyses were performed using STATA 16.0 (StataCorp, College Station, Texas) and R software (version 3.5.2). 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, which provided a significantly better fit to the data than Poisson regression models due to the presence of overdispersion. Dependent variables were counts of events per participant (rates). An "offset" term was included for follow-up time (the 5-year period or time until change of address). The 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 (Italian vs other), and census-block deprivation index. RRs were calculated for interquartile range (IQR) differences of air pollutant concentrations (Viadana II model: NO_2, 3.3 μg/m^3, formaldehyde, 0.3 μg/m^3; ELAPSE model: NO_2, 4.2 μg/m^3, $PM_{2.5}$, 2.8 μg/m^3, BC, 0.2 10^{-5} m^{-1}; EPISAT model: $PM_{2.5}$, 2.0 μg/m^3, PM_{10}, 4.4 μg/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.

2.6. Secondary analyses

1) To assess whether exposure misclassification due to changes in residential addresses was a source of bias, the analyses were repeated after excluding the participants who moved during the follow-up period (Supplementary Fig. S1). 2) 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) (Supplementary Fig. S2). 3) We tested effect modification by sex and deprivation index (binary variable coding the two most deprived groups vs the others) by including interaction terms in the models.

3. Results

Overall, 7525 subjects were included in the study. Of these, 48.6 % were females, 24.2 % had foreign parents, and more than one out of four had a disadvantaged socio-economic status (deprivation index ≥4) (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 is reported in Supplementary 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 (WHO, 2021). There was an increasing gradient of exposures to NO_2, $PM_{2.5}$, and BC estimated using the Viadana II and ELAPSE models from the reference area (no factories <2 km) to the areas with the chipboard industries (Supplementary Table S2); differences

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

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 those 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 (Fig. 1, A and C). Associations with ER admissions in pneumology were positive and significant for four of seven pollutants (Fig. 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, $PM_{2.5}$ 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 (reaching statistical significance for three of them); 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) (Fig. 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) (with three of seven pollutants reaching statistical significance) (Fig. 2, B). The rate of ORL visits was not consistently associated with air pollutants concentrations (Fig. 2, C).

Table 3
Spearman's rank coefficients for the correlations among annual estimated exposures to 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

The sensitivity analysis on the participants who did not move during the follow-up period provided similar association estimates (Supplementary Fig. S1). The sensitivity analysis on the participants living within 4 km from the chipboard industries confirmed the lack of association 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 Fig. S2). This was particularly the case for respiratory hospitalizations, an outcome that was not significantly associated with any exposures in the main analysis. In fact, excesses ranged from 4 % per IQR difference for $PM_{2.5}$, EPISAT model (RR 1.04, 95%CI: 0.79–1.38) to 140 % per IQR difference for $PM_{2.5}$, ELAPSE model (RR 2.40, 95%CI: 1.09–5.67); three of seven associations were statistically

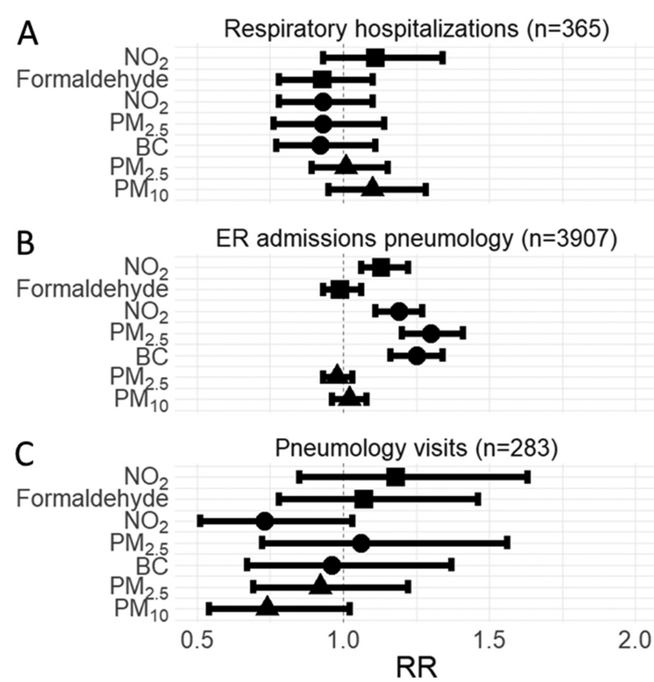

Fig. 1. Estimated associations of exposure to air pollutants with annual counts of hospitalizations (A), ER admissions (B), and specialist visits (C) for respiratory diseases during 2013–2017 (age 0–21, n = 7525)*.
* Rate Ratios (RR) with 95 % CI for a 1-IQR increase in air pollutant concentrations, obtained using negative binomial regression models adjusted for sex, age at baseline (0–3, 3.1–5, 5.1–9, 9.1–12, 12.1–16, 16.1–21 years), nationality (Italian/other), and census-block deprivation index; symbols indicate exposure models: squares = Viadana II; circles = ELAPSE; triangles = EPISAT.

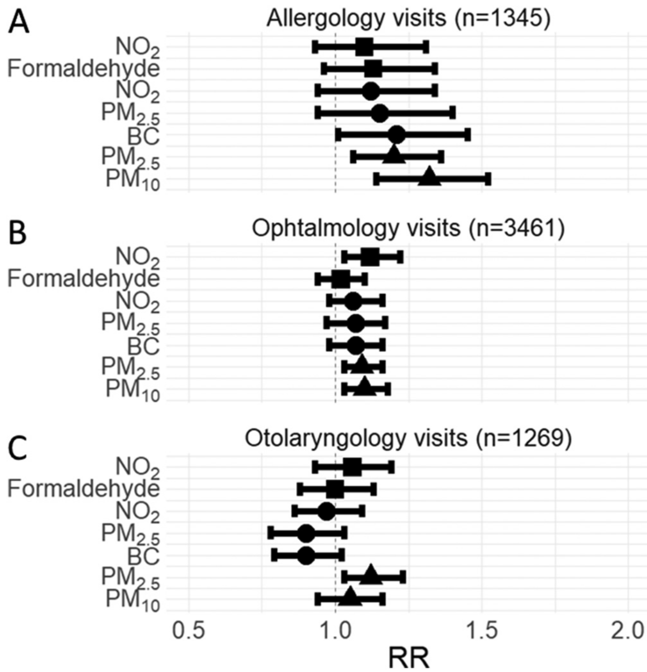

Fig. 2. Estimated associations of exposure to air pollutants with annual counts of specialist visits in allergology (A), ophthalmology (B), and otolaryngology (C) during 2013–2017 (age 0–21, n = 7525)*.
* Rate Ratios (RR) with 95 % CI for a 1-IQR increase in air pollutant concentrations, obtained using negative binomial regression models adjusted for sex, age at baseline (0–3, 3.1–5, 5.1–9, 9.1–12, 12.1–16, 16.1–21 years), nationality (Italian/other), and census-block deprivation index; symbols indicate exposure models: squares = Viadana II; circles = ELAPSE; triangles = EPISAT.

significant. 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.

There were no interactions between pollutant exposures and sex. As regards the deprivation index, only few interactions were statistically significant, but no consistent pattern emerged. Results are reported in Supplementary Table S3.

3.2. Associations between proximity to chipboard industries and health outcomes

Compared with the reference exposure group of children living at >2 km 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 S4), 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 Fig. S3). ER admission rates were highest for the children living at <2 km to the chipboard industries (12–15 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 >20 km (5 per 100 children/year) (left panel). 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) (right panel).

4. Discussion

This prospective cohort study provides evidence on the health effects of air pollution in the pediatric 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 the 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 and Flack, 2008).

Air pollution is a complex mixture of highly correlated chemical components (WHO, 2021). 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 (Lyons and Scott, 1990). Some pollutants, such

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).[a]

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)

[a] Obtained using negative binomial regression models adjusted for sex, age at baseline (0–3, 3.1–5, 5.1–9, 9.1–12, 12.1–16, 16.1–21 years), nationality (Italian/other), and census-block deprivation index.

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 (WHO, 2021). 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 and 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 (Kheirbek et al., 2012).

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. These 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). Weak correlations between exposure metrics reflect uncertainty in exposure assessment that is common to most epidemiological studies, which consequently leads to uncertainty in estimating associations. Since exposure misclassification is generally nondifferential (i.e., random), the direction of bias is typically towards underestimating associations. 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. As also discussed elsewhere (Marcon et al., 2021), none of the exposure models can be considered a “gold standard” for exposure assessment, because we did not have an external validation set for comparison of models, and 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 metrics; for this reason, little focus was given on single statistically significant associations in line with a less dichotomic interpretation of *p*-values (Nuzzo, 2014). 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 health effects 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 visits 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 effects in children. A study carried out in the United States showed that, among participants aged 5 to 20 years, hospitalizations and ER admissions for asthma increased by 7.2 % and 4.2 %, respectively, for a 1 $\mu g/m^3$ 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 and 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). 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).

4.1. 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 and nationality (a strong determinant of the socio-economic position in Italy), we lacked further 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, the present results were quite similar to the results from the analysis of the older cohort, which was further adjusted 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 specialist 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. Finally, we only assigned exposures for the baseline year, and we acknowledge that considering changes in exposure over time would have reduced exposure misclassification. Nonetheless, several studies suggested that exposure contrasts are stable over time (Eeftens et al., 2011; Marcon et al., 2015, 2021).

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 an 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.

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.

Data availability

The data that has been used is confidential.

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. AM is member of the scientific committee of ATS Val Padana, an advisory board for environmental studies commissioned or conducted by ATS Val Padana.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.161070.

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