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Association between the Concentration and the Elemental Composition of Outdoor $PM_{2.5}$ and Respiratory Diseases in Schoolchildren: A Multicenter Study in the Mediterranean Area

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Abstract: Exposure to outdoor air pollution has been shown to increase asthma symptoms. We assessed the potential role of particulate matter with aerodynamic diameter <2.5 µm ($PM_{2.5}$) on respiratory condition in schoolchildren in the south Mediterranean area. A total of 2400 children aged 11–14 years were recruited, and data on their symptoms were collected through an ISAAC (International Study of Asthma and Allergies in Childhood)-based questionnaire. Outdoor $PM_{2.5}$ was collected for 48 consecutive hours in the schoolyards of their schools and selected residential outdoor areas. The levels of $PM_{2.5}$ were measured, along with its elemental composition. The prevalence of an acute respiratory illness within the first 2 years of life was higher amongst Sicilian children when compared to Maltese children (29.7% vs. 13.5% respectively, $p < 0.0001$). Malta had a significantly higher prevalence of doctor-diagnosed asthma, when compared to Sicily (18.0% Malta vs. 7.5% Sicily, $p < 0.0001$). Similarly, current asthma (7.8% vs. 2.9%, $p < 0.0001$) and use of asthma medication in the last 12 months (12.1% vs. 4.9%, $p < 0.0001$) were more frequent amongst Maltese children. Total median $PM_{2.5}$ was 12.9 µg/m^3 in Sicily and 17.9 µg/m^3 in Malta. $PM_{2.5}$ levels were highest in the Maltese urban town of Hamrun (23.6 µg/m^3), while lowest in the rural Sicilian town of Niscemi (10.9 µg/m^3, $p < 0.0001$). Hamrun also exhibited the highest levels of nickel, vanadium, lead, zinc, antimony, and manganese, whilst the Sicilian city of Gela had the highest levels of cadmium, and the highest level of $PM_{2.5}$ when compared to rural Sicily. Elevated levels of $PM_{2.5}$ were positively associated with the prevalence of doctor diagnosed asthma (odds ratio (OR) 1.05), current asthma (OR 1.06), and use of asthma medication (OR 1.06). All elements in $PM_{2.5}$ showed increased OR for doctor diagnosed asthma, while higher concentrations of Cd and Mn were associated with higher prevalence of rhinitis.

Keywords: asthma; $PM_{2.5}$; outdoor air quality; gravimetric; respiratory diseases; concentration and elemental composition of outdoor $PM_{2.5}$

1. Introduction

Asthma is a worldwide health problem and its prevalence has been increasing in many countries, especially in young children [1]. Asthma prevalence is particularly high in industrialized countries, even though a change in trend was noticed in the most recent years [2]. Multiple genetic factors increase the risk of developing asthma, whilst environmental conditions play a fundamental role in the expression of its symptoms [3]. In fact, the avoidance of air pollution has been suggested as a nonpharmacological intervention for the prevention of asthma exacerbations in the latest Global Initiative for Asthma (GINA) Guidelines [1].

Exposure to outdoor air pollution increases asthma symptoms, and asthmatic children are at increased risk of adverse effects from poor air quality [4,5]. The World Health Organization (WHO) stated that a high level of outdoor pollutant concentration is a determinant of worsening asthma symptoms in both children and adults [6]. In particular, high airborne particulate matter (PM) concentration has been associated with worsening of symptoms, especially in sensitive children [7], and the prevalence of allergic respiratory diseases is higher in urban areas and still on the rise [8].

Children vulnerability to atmospheric pollution was attributed to their high breath rate and to both physiological and anatomical immaturity [9]. A number of studies have demonstrated an association between respiratory symptoms, the diagnosis of asthma, and proximity of residences to industrial settlements such as oil refineries, petrochemical plants [10–12], and power plants [13,14]. Thus, living in urban environments or in proximity to industrial complexes may worsen respiratory health in children.

The aim of the study was to assess the potential role of residing in different areas which had varying levels of pollution on current allergic respiratory diseases in schoolchildren. Thus, by means of a multicenter cross-sectional study, we evaluated children living in areas close to petrochemical and power plants in a southern Mediterranean area, comparing them with those living in rural and urban areas of Sicily and Malta. We used a modified ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire to collect data on individual characteristics and respiratory and allergic symptoms. We also evaluated children exposure to a set of elements measured in outdoor PM with aerodynamic diameter <2.5 µm ($PM_{2.5}$) through a semi-ecological approach.

2. Methods

2.1. Study Design

The study was carried out between March 2012 and March 2013, as part of the *RESPIRA* project, funded by the Cross-Border Program Italy–Malta 2007–2013. A cross-sectional survey was performed by distributing questionnaires to the parents of adolescent children who were attending schools in Sicily and Malta, two islands in the Mediterranean Sea. Sicily is the largest island in the Mediterranean Sea (25,706 km^2) and is located to the south of Italy. It is less densely populated (195 inhabitants/km^2) than Malta (1376 inhabitants/km^2). In Sicily, 1325 schoolchildren were randomly selected from all the lower secondary schools in the four communities of Gela, Niscemi, Mazzarino, and Butera in the Gela Health District, located in the south Mediterranean coast of Sicily. In Malta, 1075 children were recruited from six schools in four coastal and inland communities.

In Sicily, the study involved 12 lower secondary schools of the Gela Health District, with six schools in Gela, an industrial city of 77,000 inhabitants. The rural areas in Sicily were represented by Niscemi, Mazzarino, and Butera. Three schools were selected in Niscemi, which had a population of 26,400 inhabitants, two in Mazzarino, with 11,800 inhabitants, and one in Butera, a small town of

4900 inhabitants. These towns are located about 15, 27, and 16 km from Gela, respectively. In Malta, six schools participated: two in Hamrun (9397 inhabitants), representing the central urbanized harbor area; one in Cospicua (5589 inhabitants) and one in Zejtun (11,521 inhabitants), both together representing the industrial southern part of the island; two in Mosta (20,241 inhabitants), representing the more northern and rural part of the island (Figure 1).

Figure 1. The "RESPIRA" Project involved four communities of the Health District of Gela (red circles in panel **A**) and four communities in Malta (red circles in panel **B**) in the south Mediterranean area (upper panel).

In Sicily, Gela had an active petrochemical plant, operating since 1965 and still active at the time of the survey, located close to the urban coastal area of Gela. The towns of Niscemi, Mazzarino, and Butera were in the inland rural area. On the Maltese side, during the time of the study, two power stations located in the south of the island were still running on heavy fuel oil.

The study was approved by the local Ethical Committees: the Ethics Committee of the Local Health Agency of Caltanissetta on 15 December 2011 for the Sicilian side and the Ethics Committees of Maltese Department of Education on 6 October 2011 for the Maltese side. The parents of all children signed an informed consent form. Respect of individual privacy and clinical data was granted.

2.2. Questionnaires

The parents of the participating children filled out a modified ISAAC [15] questionnaire on their children's respiratory symptoms and individual characteristics; out of a total of 2400 recruited children, 2050 parents participated and completed the questionnaires (85.4%).

A child having "doctor-diagnosed asthma" was defined as a positive answer to the question "*Has your child ever had asthma diagnosed by a doctor?*". "Current asthma" was defined as a positive answer to the previous question together with a positive answer to "*In the past 12 months, has your child had wheezing or whistling in the chest?*". The use of medicines for asthma treatment was established by the question "*In the past 12 months, did your child use any drug (pills, sprays, nebulizers, or any other remedies) for asthma?*". Rhinitis in the last 12 months was defined as a positive answer to the questions "*In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she DID NOT have a cold or the flu?*". Information on the possible confounders or effect modifiers was also collected. The occurrence of acute respiratory diseases in the first 2 years of life was defined by the question "*During the first two years of life, did your child suffer from any infections, such as pneumonia, bronchiolitis, or asthmatic bronchitis?*". Other current potential exposures were explored such as "*Has the child, or any other family member, any pets in the dwelling?*", "*Is there dampness or visible mold growth in your child's bedroom?*", and "*Is your child exposed to tobacco smoke in the dwelling?*" *(Yes if daily or often (1–4 times/week))*.

Parental history for asthma was defined as at least one parent with a history of asthma. Household crowding index (CI), as a proxy for socioeconomic status, was defined as the total number of coresidents per household divided by the total number of rooms, excluding kitchen and bathrooms [16]. The CI was dichotomized as ≤1 or >1.

2.3. $PM_{2.5}$ Sampling

Outdoor fine PM ($PM_{2.5}$) was collected for 48 consecutive hours during working days (Monday to Friday). Measurements were performed using gravimetric samplers (Silent Sampler, FAI Instruments, Rome, Italy) operating at a flow rate of 10 L/min and equipped with inertial impactors having a cut-point diameter of 2.5 μm and housing 47 mm polytetrafluoroethylene (PTFE) filters (2.0 μm pore size, PALL Italia, Buccinasco (Mi), Italy). After sampling, the filters were stored in a dark environment at a temperature of 4 °C, until these underwent chemical analysis.

Using this protocol, the outdoor $PM_{2.5}$ was sampled in each of eight Sicilian and Maltese Communities from schoolyards (SY) of abovementioned schools. Outdoor $PM_{2.5}$ from residences (RE) which homed a selection of students who attended these schools were also sampled to obtain other measurements from the areas surrounding the schools and to be representative of the characteristics (urban, rural, industrial) of Sicilian and Maltese areas.

A total of 136 sites (85 in Sicily and 51 in Malta) had $PM_{2.5}$ sampled: 41 in Gela (6 SY and 35 RE), 22 in Niscemi (3 SY and 19 RE), 13 in Mazzarino (2 SY and 11 RE), 9 in Butera (1 SY and 8 RE), 19 in Hamrun (2 SY and 17 RE), 6 in Cospicua (1 SY and 5 RE), 10 in Zejtun (1 SY and 9 RE), and 16 in Mosta (2 SY and 14 RE). Sampling periods were from May 2012 to March 2013.

2.4. Elemental Analysis

The first step of the analytical procedure was the measurement of the mass concentration of the collected particles. Before and after the sampling phase, PTFE filters were conditioned at 50% relative humidity and 20 °C for 48 h and then weighed using a 1 μg sensitivity automated microbalance (mod. ME5, Sartorius AG, Goettingen, Germany).

The elemental analysis was performed following a procedure which allowed the chemical fractionation of the total elemental content into a water-soluble fraction and a residual fraction. The filters were extracted under ultrasound (20 min) in a solution of acetate buffer (CH_3COOH/CH_3COOK 0.01 M; pH 4.3). The resulting solution was then filtered through cellulose nitrate membranes (0.45 μm pore size). The obtained fraction (extracted fraction) was then analyzed by plasma atomic spectroscopy inductively coupled with plasma mass detection (ICP-MS; 820 MS, Bruker Italia /MI-Italy) for the following elements: cadmium (Cd), manganese (Mn), nickel (Ni), lead (Pb), antimony (Sb), vanadium (V), and zinc (Zn). The samples were then subjected to microwave-assisted acid digestion, using HNO_3:H_2O_2 (2:1), filtered again at 0.45 μm and analyzed by ICP-MS for the residual fraction of the same elements. For each element, the total concentration was obtained by adding the extracted and residual fractions [17]. Limits of detection (LODs) of evaluated elements are reported in Table S1 (Supplementary Materials).

2.5. Statistical Analyses

Within each of the eight municipalities, we calculated the median $PM_{2.5}$ concentration value of all the sampling sites (both SY and RE) in that particular area. Subjects living in each area were then assigned the corresponding median exposure level following a semi-ecological approach [18]. Children selected in Cospicua and Zejtun were analyzed together because the two communities are in close proximity.

Continuous variables were evaluated by means of by one-way ANOVA and Mann–Whitney U-test or Kruskal–Wallis test for normally and not normally distributed variables, respectively. Categorical variables were compared by means of χ^2 test. Multiple logistic regression models were built for investigating the effect of pollutants on respiratory symptoms, taking into account confounders and effect modifying variables, and relevant odds ratio (OR) were computed. Moreover, for cadmium and antimony ORs were considered for increments in concentrations of 0.01 and 0.1 ng/m^3, respectively. Lastly, a Pearson's correlation matrix was built among $PM_{2.5}$ and its elemental components. A p-value < 0.05 was considered significant.

3. Results

A total of 2050 parents' questionnaires were available for analysis (1190 from Sicilian children and 860 from Maltese children). Sicily has one of the highest recorded vehicular densities at 661 cars per 1000 inhabitants [19], slightly higher than the Italian national mean at 616. Malta is a small island state in the middle of the Mediterranean Sea, roughly 90 km south of Sicily, and characterized by high anthropic activities. Most Maltese towns are close to the coast, with areas of agricultural land interspersed between the residential areas. The population density is one of the highest in the world (1376 inhabitants/km^2), and the vehicular density is 615 cars per 1000 inhabitants [20].

Table 1 shows the main characteristics of the secondary school children, separately for the selected Maltese and Sicilian towns. It illustrates the prevalence of symptoms from questionnaires along with confounding/effect modifying variables relevant to home exposures.

When compared to children living in the industrial Sicilian town of Gela and rural Sicily (Niscemi, Mazzarino, and Butera), Maltese children were slightly but significantly older (mean (±SD) age 12.5 ± 0.7 years vs. 11.8 ± 1.1 years, $p < 0.0001$); in Malta, there was a lower male-to-female gender ratio (Malta 378/482, Sicily 594/596, $p = 0.008$), a higher CI (45.9% vs. 31.9%, $p < 0.0001$), a higher prevalence of pet ownership within dwellings (58.8% vs. 20.9%, $p < 0.0001$), and more frequent reported exposure to indoor mold (17.2% vs. 12.1%, $p = 0.001$). No significant difference in environmental tobacco smoke exposure was found.

The prevalence of an acute respiratory illness within the first 2 years of life was higher amongst Sicilian children (29.7%) when compared to Maltese ones (13.5%, $p < 0.0001$). Malta had a significantly higher prevalence of doctor-diagnosed asthma, when compared to Sicily (18.0% Malta vs. 7.5% Sicily, $p < 0.0001$). Similarly, current asthma (7.8% vs. 2.9%, $p < 0.0001$) and use of asthma medication in the last 12 months (12.1% vs. 4.9%, $p < 0.0001$) were more frequent amongst Maltese children. Overall, symptoms of rhinitis in the past 12 months were found to be slightly more frequent among Maltese children than among Sicilian children with a p-value close to statistical significance (27.3% vs. 23.5%, $p = 0.051$). Nevertheless, prevalence of rhinitis in the past 12 months was even lower within rural Sicily (18.3%, $p < 0.0001$). Table 1 shows the different prevalence within each region.

Table 1. Characteristics of the study sample (Total No. = 2,050). The characteristics of each community (urban, rural, industrial) are also indicated.

	Malta (*n* = 860)			**Italy (*n* = 1190)**			
	Hamrun Urban/Industrial (*n* = 341)	**Cospicua/Zejtun Industrial (*n* = 235)**	**Mosta Rural (*n* = 284)**	**Gela Industrial (*n* = 593)**	**Niscemi Rural (*n* = 314)**	**Butera Rural (*n* = 119)**	**Mazzarino Rural (*n* = 164)**
General Characteristics							
Age Years, mean (± SD)	12.9 (±0.7)	12.5 (±0.7)	12.1 (±0.5)	11.8 (±1.1)	11.7 (±1.1)	11.9 (±1.1)	12.0 (±1.1)
Male/Female (*n*)	157/184	101/134	120/164	296/297	154/160	61/58	83/81
Parental atopy, *n* (%)	41 (12.0%)	30 (12.8%)	29 (10.2%)	59 (10.0%)	32 (10.1%)	9 (7.6%)	8 (4.9%)
Crowding index > 1, *n* (%)	147 (43.1%)	88 (37.4%)	108 (66.2%)	179 (30.2%)	78 (24.8%)	37 (31.1%)	55 (33.5%)
Respiratory Health							
Acute respiratory disease in the first 2 years, *n* (%)	43 (12.6%)	33 (14.0%)	40 (14.1%)	168 (28.3%)	102 (32.5%)	24 (20.2%)	59 (36.0%)
Doctor-diagnosed asthma, *n* (%)	63 (18.5%)	48 (20.4%)	44 (15.5%)	57 (9.6%)	22 (7.0%)	3 (2.5%)	7 (4.3%)
Current asthma, *n* (%)	28 (8.2%)	18 (7.7%)	21 (7.4%)	22 (3.7%)	8 (2.5%)	2 (1.7%)	3 (1.8%)
Asthma medication in last 12 months, *n* (%)	40 (11.7%)	36 (15.3%)	28 (9.9%)	40 (6.7%)	15 (4.8%)	1 (0.8%)	2 (1.2%)
Rhinitis in last 12 months, *n* (%)	106 (31.1%)	61 (26.0%)	68 (23.9%)	171 (28.8%)	61 (19.4%)	18 (15.1%)	30 (18.3%)
Home Exposures							
Dampness exposure, *n* (%)	81 (23.8%)	20 (8.5%)	47 (16.5%)	73 (12.3%)	34 (10.8%)	14 (11.7%)	20 (12.2%)
Domestic exposure to tobacco smoke, *n* (%)	77 (22.6%)	37 (15.7%)	52 (18.3%)	101 (17.0%)	88 (28.0%)	25 (21.0%)	27 (16.4%)
Pets, *n* (%)	204 (59.8%)	145 (61.7%)	157 (55.3%)	145 (25.0%)	47 (15.0%)	14 (11.8%)	37 (22.6%)
Traffic, *n* (%)	97 (28.8%)	44 (18.7%)	59 (20.8%)	178 (30.0%)	56 (17.8%)	13 (10.9%)	33 (20.1%)

Median (interquartile range) $PM_{2.5}$ concentration was 12.9 (10.3–17.3) μg/m^3 in Italy and 17.9 (10.6–26.5) μg/m^3 in Malta ($p = 0.006$). In Table 2, the recorded $PM_{2.5}$ and total elemental concentration (extracted + residual fraction) are reported for each Italian and Maltese community. The distribution of $PM_{2.5}$ and of all the evaluated $PM_{2.5}$ elemental components varied significantly between Maltese and Italian towns. In Table S2 (Supplementary Materials), the same information is provided for the Maltese area, the industrial area of Gela, and the remaining Sicilian rural areas. The overall comparisons of medians always showed significant differences. Similarly, the Sicilian rural area was consistently lower in the comparisons with both Malta and Gela (with only the exception of Zn between Gela and rural area). The Maltese town of Hamrun had the highest median level of $PM_{2.5}$ (Figure 2) and for all the evaluated elements with the exception of cadmium (highest in Gela) when compared to the rest of the Maltese and Sicilian towns (all *p*-values < 0.0001; see Figures 3–5 for Ni, V, and Pb, respectively).

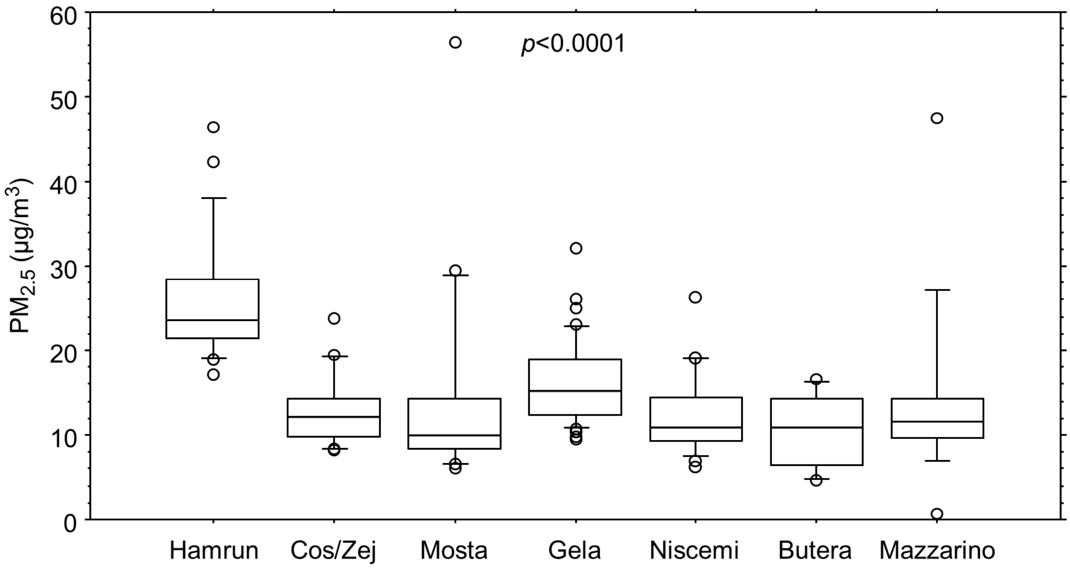

Figure 2. Distribution of outdoor total particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) measures in each community. Boxplot bars indicate (from the bottom to the top) 10th, 25th, 50th (median), 75th, and 90th percentiles. Values below 10th and above 90th percentiles are plotted as circles. The *p*-value was computed using the Kruskal–Wallis test.

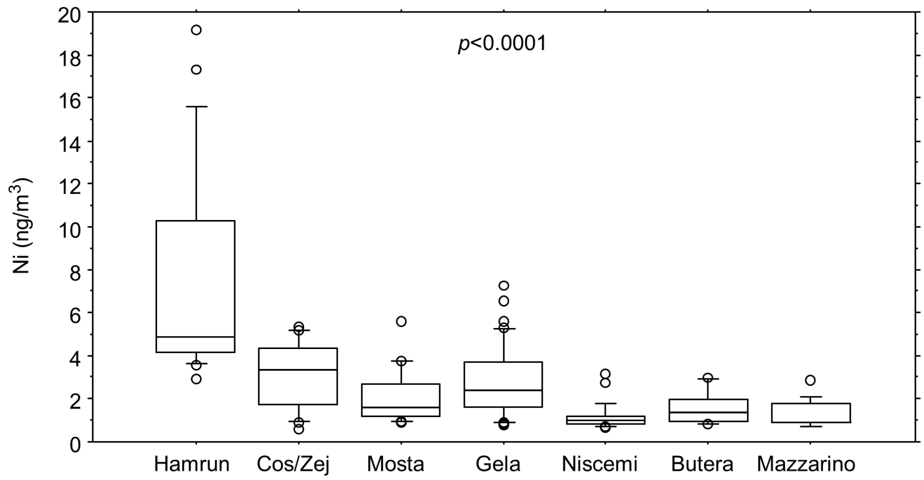

Figure 3. Distribution of nickel concentration in outdoor $PM_{2.5}$ in each community. Boxplot bars indicate (from the bottom to the top) 10th, 25th, 50th (median), 75th, and 90th percentiles. Values below 10th and above 90th percentiles are plotted as circles. The overall *p*-value was computed using the Kruskal-Wallis test.

Table 2. Median (interquartile range) of $PM_{2.5}$, vanadium (V), nickel (Ni), cadmium (Cd), lead (Pb), manganese (Mn), antimony (Sb), and zinc (Zn) outdoor values for each Maltese and Italian investigated site. Total outdoor measurements = 138.

	Malta (*n* = 51)			Italy (*n* = 85)				*p*-Value *
	Hamrun (*n* = 19)	Cospicua/Zejtun (*n* = 16)	Mosta (*n* = 16)	Gela (*n* = 41)	Niscemi (*n* = 22)	Butera (*n* = 9)	Mazzarino (*n* = 13)	
$PM_{2.5}$ (μg/m^3)	23.6 (21.5–28.5)	12.2 (9.8–14.3)	10.0 (8.4–14.2)	15.2 (12.3–18.9)	10.9 (9.2–14.4)	10.8 (6.4–14.3)	11.6 (9.6–14.4)	<0.0001
V (ng/m^3)	8.8 (6.5–19.3)	3.2 (2.2–6.1)	1.3 (0.6–3.0)	3.2 (2.0–5.8)	0.9 (0.7–1.8)	1.8 (1.3–3.2)	1.3 (0.8–1.6)	<0.0001
Ni (ng/m^3)	4.9 (4.2–10.3)	3.3 (1.7–4.3)	1.6 (1.2–2.7)	2.4 (1.6–3.7)	1.0 (0.8–1.2)	1.3 (1.0–2.0)	0.9 (0.9–1.8)	<0.0001
Cd (ng/m^3)	0.11 (0.07–0.15)	0.07 (0.04–0.07)	0.06 (0.06–0.07)	0.12 (0.07–0.32)	0.06 (0.05–0.07)	0.06 (0.06–0.11)	0.06 (0.05–0.07)	0.0004
Pb (ng/m^3)	5.3 (3.2–10.0)	3.1 (1.5–4.7)	1.8 (1.2–2.9)	4.4 (2.9–6.3)	1.7 (1.2–2.8)	1.8 (1.0–2.3)	1.8 (0.9–2.5)	<0.0001
Mn (ng/m^3)	3.8 (2.8–4.3)	1.7 (0.9–2.3)	1.5 (1.2–2.2)	3.1 (1.8–4.3)	1.2 (0.6–1.6)	1.7 (0.5–3.1)	0.8 (0.5–1.7)	<0.0001
Sb (ng/m^3)	0.90 (0.44–1.41)	0.33 (0.21–0.70)	0.18 (0.11–0.33)	0.80 (0.61–1.74)	0.27 (0.19–0.63)	0.30 (0.22–0.59)	0.24 (0.21–0.30)	<0.0001
Zn (ng/m^3)	19.5 (10.6–25.7)	17.3 (12.5–27.3)	11.4 (6.6–13.6)	7.0 (6.7–7.4)	6.9 (6.8–7.2)	7.1 (6.8–7.3)	6.9 (6.8–7.2)	<0.0001

* Kruskal–Wallis test.

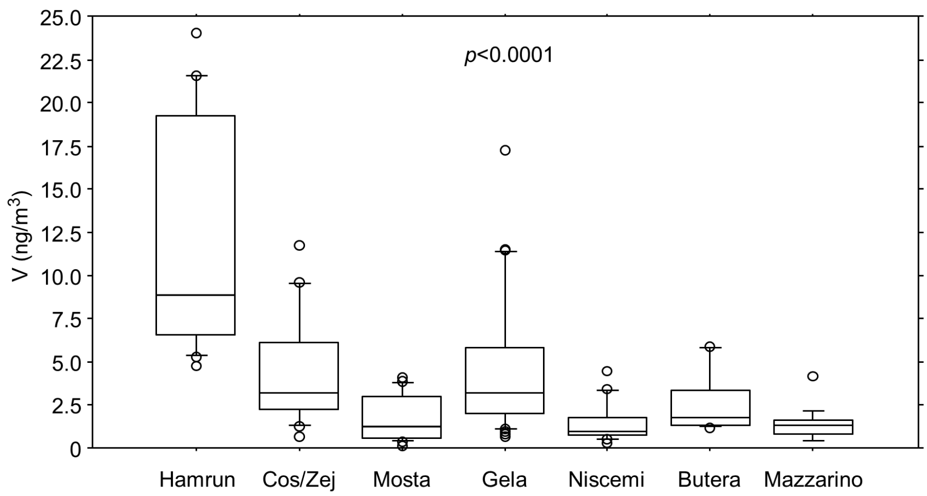

Figure 4. Distribution of vanadium concentration in outdoor $PM_{2.5}$ in each community. Boxplot bars indicate (from the bottom to the top) 10th, 25th, 50th (median), 75th, and 90th percentiles. Values below 10th and above 90th percentiles are plotted as circles. The overall *p*-value was computed using the Kruskal-Wallis test.

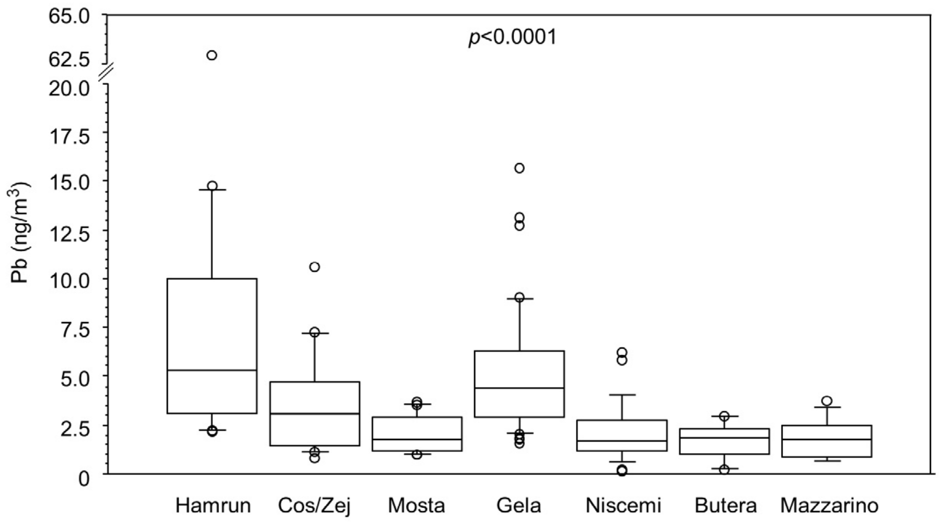

Figure 5. Distribution of lead concentration in outdoor $PM_{2.5}$ in each community. Boxplot bars indicate (from the bottom to the top) 10th, 25th, 50th (median), 75th, and 90th percentiles. Values below 10th and above 90th percentiles are plotted as circles. The overall *p*-value was computed using the Kruskal-Wallis test.

In a logistic regression analysis model performed to assess the relationships between prevalent respiratory symptoms/diseases and identified $PM_{2.5}$ elements, also adjusting for confounders/effect modifiers, we found that significant ORs for doctor-diagnosed asthma were observed for $PM_{2.5}$ and V, Ni, Pb, Mn, Sb, and Zn. Significant ORs for current asthma and medicines for asthma in the last 12 months were observed for $PM_{2.5}$ and V, Ni, and Zn (Table 3). Lastly, significant ORs for rhinitis in the last 12 months were observed for Cd and Mn. For example, Figure 6 shows a schematic representation of the relationship between the prevalence of doctor diagnosed asthma, current asthma, use of medicines for asthma in the last 12 months, rhinitis in the last 12 months, and median outdoor vanadium concentration in each evaluated community. The same figures are presented in Figures S1 and S2 (Supplementary Materials) for $PM_{2.5}$ and nickel concentrations.

Table 3. Logistic regression models for doctor-diagnosed asthma, current asthma, use of asthma medicines in the first 2 years of life, and rhinitis in the last 12 months. In each logistic regression model, odds ratio (ORs) and 95% confidence intervals (95% CI) were adjusted for sex, age, acute respiratory diseases in the first 2 years of life, crowding index, parental atopy, home exposure to dampness, environmental tobacco smoke, and presence of pets in the dwelling. Significant OR values are presented in bold.

		Doctor Diagnosed Asthma	Current Asthma	Medicines for Asthma in the Last 12 Months	Rhinitis in the Last 12 Months
$PM_{2.5}$ (µg/m^3)	**OR**	**1.05**	**1.06**	**1.06**	1.02
	95% CI	1.02–1.08	1.01–1.10	1.00–1.08	0.99–1.04
V (ng/m^3)	OR	**1.08**	**1.08**	**1.06**	1.02
	95% CI	1.03–1.12	1.02–1.14	1.01–1.11	0.99–1.05
Ni (ng/m^3)	OR	**1.15**	**1.15**	**1.12**	1.04
	95% CI	1.07–1.23	1.04–1.27	1.04–1.22	0.98–1.09
Cd (ng/m^3) *	OR	**1.05**	**1.05**	**1.05**	**1.03**
	95% CI	1.02–1.09	1.00–1.11	1.01–1.09	1.00–1.05
Pb (ng/m^3)	OR	**1.10**	**1.10**	**1.09**	1.04
	95% CI	1.04–1.15	1.01–1.19	1.01–1.16	0.99–1.09
Mn (ng/m^3)	OR	**1.20**	**1.07**	**1.21**	**1.16**
	95% CI	1.03–1.40	1.02–1.12	1.01–1.46	1.04–1.29
Sb (ng/m^3) **	OR	**1.07**	**1.15**	**1.07**	1.02
	95% CI	1.04–1.11	1.00–1.32	1.03–1.11	0.99–1.04
Zn (ng/m^3)	OR	**1.06**	**1.05**	**1.05**	1.01
	95% CI	1.04–1.08	1.02–1.08	1.03–1.07	0.99–1.02

* Adjusted ORs for cadmium were computed for increments of 0.01 ng/m^3. ** Adjusted ORs for antimony were computed for increments of 0.1 ng/m^3.

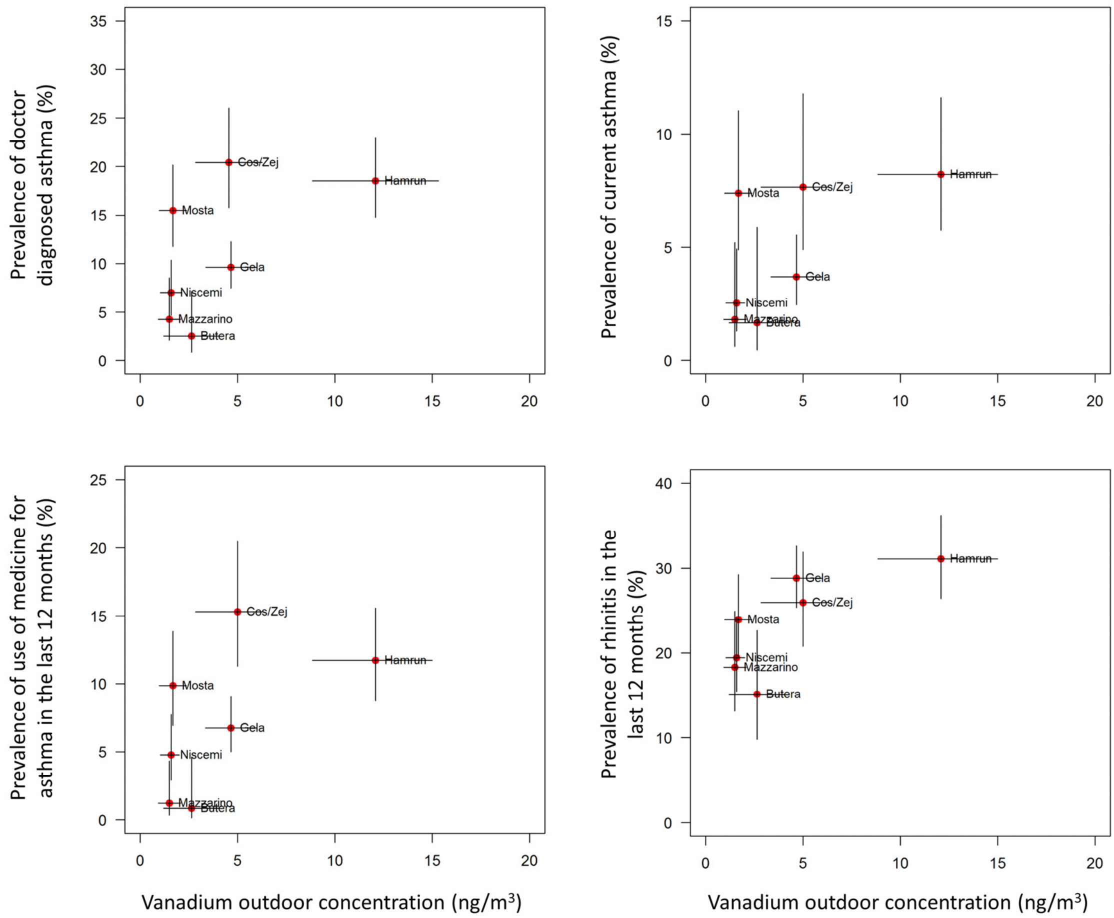

Figure 6. Schematic representation of the relationships between > prevalence (and 95% confidence interval) of doctor diagnosis of asthma, current asthma, use of medicine for asthma in the last 12 months, and rhinitis in the last 12 months, and outdoor Vanadium concentration (mean and 95% confidence interval) per each community (Cos/Zej: Cospicua/Zejtun).

4. Discussion

We found significant differences in the concentration of $PM_{2.5}$ and its elemental composition (V, Ni, Cd, Pb, Mn, Sb, and Zn) among Mediterranean communities with different site characteristics. Such differences were associated with the prevalence of allergic respiratory diseases in adolescents.

The incidence and burden of asthma and allergies among schoolchildren remain substantial and, in many countries, have continued to increase over the years [21–23]. In the ISAAC studies, the small island state of Malta was shown to have one of the highest rates of asthma in Europe [22]. The results of our study questionnaires were consistent with previous ISAAC studies, showing similarly high allergic and asthma symptom prevalence in Malta. More remarkably, the prevalence of asthma amongst Maltese children was more than twice as high as the prevalence observed amongst Sicilian children (asthma as diagnosed by a doctor was 18.0% in Malta vs. 7.5% in Sicily).

Geographically and culturally, Malta and Sicily are similar: two southern Mediterranean islands located within 100 km of each other, with parallel historical and cultural backgrounds. Large towns are located close to the coast and, traditionally, the sea has a lot of influence on the way of life with the presence of industrial and maritime activities near populated areas. The two islands share a similar climate with hot and humid summers with plenty of sunshine and mild winters. However, despite similarities, in our study, we found large differences in the prevalence of allergic respiratory diseases, as well in the concentration and composition of outdoor $PM_{2.5}$.

The two islands had different geographical catchment systems to allocate children to the respective schools. In Sicily, where the cities tended to have larger populations when compared to the small island of Malta, the children would attend smaller schools within the cities. On the other hand, Malta had larger schools, which would include school children not only from the locality, but also from towns located within an area around it.

When compared to the general monitoring of PM concentrations, carried out in most air quality networks, particle collection on filters with subsequent chemical analysis offers a suitable method for the detailed characterization of PM chemical components, while also providing information on the potential PM emission sources [24]. In our study, we measured the concentration of outdoor $PM_{2.5}$ and of elements in schoolyards and in additional outdoor sites (for a total of 85 in Sicily and 51 in Malta). We used an analytical procedure for element determination fully validated in previous air quality studies [24–27].

Total median $PM_{2.5}$ was 12.9 μg/m^3 in Sicily and 17.9 μg/m^3 in Malta; these values are consistent with other urban and suburban European sites [28]. As expected, the rural towns of Sicily exhibited lower levels of $PM_{2.5}$ (median of 11.3 μg/m^3), when compared with the industrial city of Gela and the highly urbanized island of Malta (15.2 μg/m^3 and 17.9 μg/m^3, respectively). Within Malta, the central area of Hamrun, however, demonstrated significantly higher $PM_{2.5}$ levels (23.6 μg/m^3) than the rest of the island, Gela, and rural Sicily (Table 2 and Figure 2). The central area of Hamrun also exhibited the highest levels of nickel (Figure 3), vanadium (Figure 4), lead (Figure 5), zinc, antimony, and manganese, whilst Gela had the highest levels of cadmium and the highest level of $PM_{2.5}$ when compared to rural Sicily. This is not surprising, with V and Ni being interpreted as residual of fuel oil combustion from industrial processes, such as power plants and/or oil refineries, and maritime traffic [29]. Similarly to Gela in Sicily, where a large petrochemical plant is located very close to the urban area, the central area of Hamrun in Malta is industrial and is very close to a coastal electric power station which, at the time, was running on heavy fuel oil. Hamrun is also largely urbanized, characterized by heavy vehicular congestion (with a higher number of vehicles per surface area with respect to Sicily) and located very close to the main harbor area with heavy maritime industry and commercial and passenger maritime traffic. The elements vanadium, nickel, lead, manganese, antimony, and zinc are known markers of vehicular and diesel emissions, more commonly found in fine PM. Cadmium, zinc, lead, and manganese are also commonly associated with industrial emissions, which could explain the high levels of cadmium found in Gela, as well as in Hamrun [30–36]. In general, the correlation among elements and between elements and $PM_{2.5}$ is modest, as the chemical composition of PM in different geographical areas and during different time periods may vary quite a lot. For this reason, the covariance between tracers of the same source may become less solid. The considered sites were characterized by relevant heavy oil emission from ship traffic and, in the case of Malta, by the activity of a heavy fuel oil fired power station. Our data (Figure 7) showed that the main tracers of these emissions, Ni and V, were very well correlated (R^2 = 0.92). A good correlation of Ni and V with Pb and Zn was also observed (range 0.5–0.7). Pb and Zn are nonspecific tracers of many anthropogenic and industrial sources, among which heavy oil combustion is a known source [29].

It is well known that exposure to ambient air pollution and particulate matter can exacerbate asthma and other respiratory diseases, particularly in vulnerable groups such as children [5]. The developing lung also remains at risk of future cardiovascular and respiratory lung disease with increased exposure to poor outdoor and indoor air quality [37–41]. In fact, particulate matter is a mixture of solid and liquid particles that remain suspended in the air after being emitted into the atmosphere. Particles have complex and various compositions, and their classification relies on different diameter sizes: fine particulate matter ($PM_{2.5}$), including particles with aerodynamic diameter <2.5 μm, is able to reach the distal airways and the alveoli. Thus, its health effects are not limited to upper airway symptoms, but to more specific small airway diseases including asthma. In fact, substantial evidence exists of an association between ambient PM and respiratory symptoms and/or drugs against asthma use in asthmatic children [42–44]. Moreover, $PM_{2.5}$ is associated with anthropogenic combustion sources, which include vehicular emissions from cars, trucks, and ships, as well as from industry and power plants.

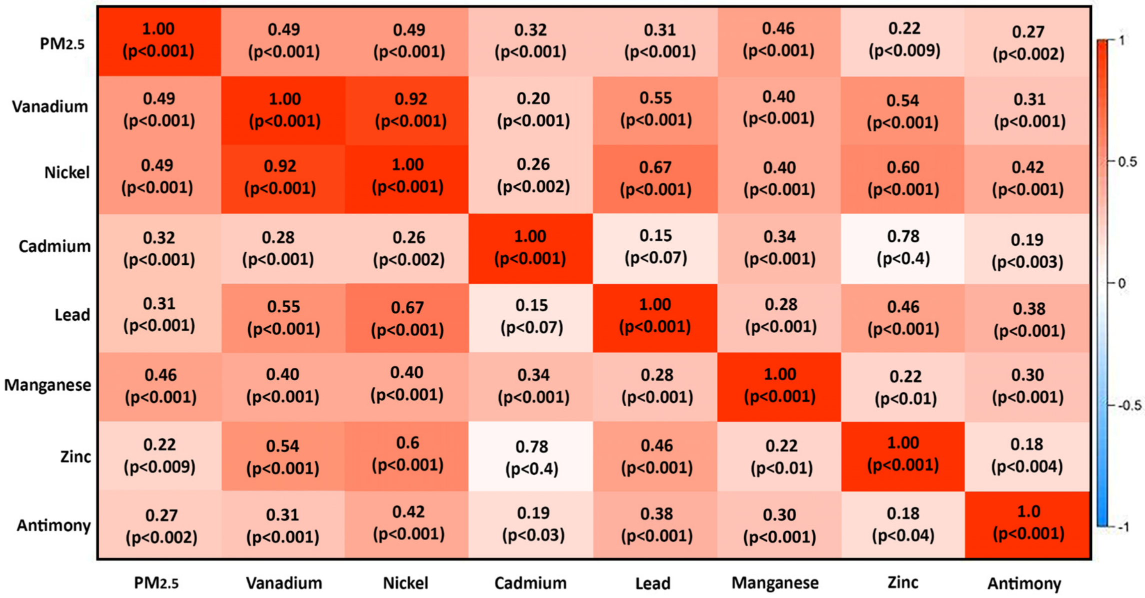

Figure 7. Pearson's correlation matrix among $PM_{2.5}$ and its evaluated elemental components. For each intersection, the R^2 and relevant p-values are indicated.

As shown in Table 1, when compared to rural Sicily, Gela had the higher rates of asthma, rhinitis, current asthma, and use of asthma medication in the past 12 months. However, all the above respiratory symptoms were significantly higher within all of the Maltese localities with respect to Sicilian towns. In Malta, the central area of Hamrun had the highest rate of current asthma and rhinitis. The southern area of Malta, represented by Cospicua/Zejtun, had the highest prevalence of doctor-diagnosed asthma and increased use of asthma medication in the past 12 months. Within the south of Malta lies a second electric power station, which also ran on heavy fuel oil at the time of study.

When adjusted for confounding factors, elevated levels of $PM_{2.5}$ were positively associated with the prevalence of doctor-diagnosed asthma, current asthma, and use of medicines for asthma in the last 12 months, while the OR for rhinitis was lower but not significant (Table 3). In addition, elevated levels of cadmium, manganese, and antimony within the fine particulate matter were also associated with increased rhinitis amongst our cohort of secondary schoolchildren. Interestingly, the highest prevalence of rhinitis was found in Hamrun and Gela, which also had the highest Cd, Mn, and Sb levels detected in $PM_{2.5}$. These elements, representing markers of vehicular and industrial emission sources, are known to be directly hazardous to human health [45,46]. In particular, higher concentrations of heavy metals in suspended PM have been related to asthma and respiratory symptoms in pediatric age [47]. Behrendt et al. found higher blood levels of cadmium in subjects who had allergic rhinitis compared to those with nonallergic rhinitis and to the control group [48]. These data could explain conflicting results found in the study of the association between $PM_{2.5}$ and rhinitis in absence of elemental characterization of particulate [49]. Although numerous studies explored the association of air pollution and particulate matter with respiratory symptoms and asthma, most focused on the evaluation of air quality through the measurement of $PM_{2.5}$ concentration. The method used in this study for collecting $PM_{2.5}$ allowed its elemental analysis and, thus, the linking of specific $PM_{2.5}$ composition with prevalent respiratory symptoms. All PM measurements were taken at the same period of time in which the RESPIRA questionnaires were being completed.

Limitations of our study included the fact that each evaluated subject was assigned the same average exposure level computed for the community of residence. However, our results remain consistent with previously conducted studies [50]. The individual elements measured and associated with asthma and respiratory disease may not be directly involved with the elicitation of symptoms, but may instead reflect other covarying pollutants or the interplay of several factors.

Moreover, outdoor $PM_{2.5}$ was collected for 48 h at each residential site. This limitation in collection methodology means that every household only had a "snapshot" of outdoor $PM_{2.5}$. However, several sites were measured individually in each community and, cumulatively, these made for an adequate representation of the air quality in each area in terms of $PM_{2.5}$ concentration and chemical composition.

Lastly, despite positive correlations between elevated $PM_{2.5}$ and its elemental composition and increasing asthma symptoms, the statistically significant differences in asthma prevalence between Malta and Sicily are unlikely to be fully explained by the differences in measured outdoor $P_{2.5}$ alone. Schoolchildren are more often exposed to indoor air. Indoor air quality—which is generally related to outdoor air quality but is also affected by the contribution of indoor sources—would play a significant role. We only analyzed the elemental composition of $PM_{2.5}$, and our methodology did not allow for measurements of elemental carbon and organic components, which would have added more information regarding the contribution of wood and fossil-fuel combustion.

In conclusion, the evaluation of the elemental composition of outdoor $PM_{2.5}$ allows a better comprehension of the relationships between outdoor pollution and respiratory symptoms; in fact, all the evaluated elements—with the exception of Cd—showed increased OR for doctor-diagnosed asthma with respect to total $PM_{2.5}$, while higher concentrations of Cd and Mn were associated with higher prevalence of rhinitis.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4433/11/12/1290/s1: Figure S1: Schematic representation of the relationships between prevalence (and 95% confidence interval) of doctor diagnosis of asthma, current asthma, use of medicine for asthma in the last 12 months, and rhinitis in the last 12 months, and outdoor $PM_{2.5}$ concentration (mean and 95% confidence interval) per each community (Cos/Zej: Cospicua/Zejtun); Figure S2: Schematic representation of the relationships between prevalence (and 95% confidence interval) of doctor diagnosis of asthma, current asthma, use of medicine for asthma in the last 12 months, and rhinitis in the last 12 months, and outdoor nickel concentration (mean and 95% confidence interval) per each community (Cos/Zej: Cospicua/Zejtun); Table S1: Limits of detection (LODs) of elements, calculated as the mean value plus three standard deviations of the blank (six replicates). Air concentrations refer to a sampling volume of 30 m^3; Table S2: Median (interquartile range) of $PM_{2.5}$, vanadium (V), nickel (Ni), cadmium (Cd), lead (Pb), manganese (Mn), antimony (Sb), and zinc (Zn) outdoor values for Malta, Italy, and separately for Italian Gela and Rural areas. Total outdoor measurements = 138. The *p*-values were computed by means of the Kruskal-Wallis test, and pairwise comparisons were evaluated.

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