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Review

Air Pollution and Public Health: A PRISMA-Compliant Systematic Review

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Abstract: (1) Background: Particulate matter increases the risk of respiratory, allergic and oncological diseases in both exposed workers and the general population due to its toxic compounds (e.g., PAHs, gases, heavy metals, microorganisms). The aim of this review is to show the results obtained by our department regarding air pollution's contributions to health damage in both occupationally and non-occupationally exposed people. (2) Methods: This review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, searching articles on PubMed, using eligibility criteria, extracting data independently from reports to reduce bias and considering the accuracy of the statistical analyses. (3) Results: Of fifteen papers, only three respected the abovementioned criteria. A total of 453 cases (174 occupationally exposed and 279 non-occupationally exposed individuals) were included in the review. Qualitative analysis showed that among workers, occupational exposure to air pollution increased the risk of allergic and pulmonary diseases, whereas environmental exposure to PM increased heavy metal intake, the last of which was characterized by well-known carcinogenic effects. 4) Conclusion: The use of personal protective equipment, a meticulous health surveillance program and specific environmental protection policies are needed to protect public health from damages due to air pollution.

Keywords: air pollution; public health; occupational exposure; environmental exposure; allergic diseases; pulmonary diseases; heavy metals

1. Background

The effects on human health due to air pollution exposure have been extensively studied over the last several years. Particulate matter is thought to be able to increase the risk of respiratory [1], cardiovascular and oncological diseases [2] in both adults and children [3]. Moreover, several studies have indicated that occupationally exposed workers may be more susceptible to asthma and Chronic Obstructive Pulmonary Disease (COPD) than is the general population [4].

Particulate matter is divided into PM_{10} (10 micrometers or less in diameter) and $PM_{2.5}$ (2.5 micrometers or less in diameter). The atmospheric concentrations of $PM_{2.5}$ and PM_{10} have been shown to be higher in Bari and Taranto compared to the remaining part of the region, as at first highlighted by Amodio et al. [5]. Pathogenic pathways are likely related to some of the compounds contained in particulate matter, e.g., PAHs (*polycyclic aromatic hydrocarbons*), gases (nitrogen oxides, sulphur oxides, ozone), heavy metals (chromium, arsenic, lead, manganese, mercury), and microorganisms [6]. These pollutants are able to penetrate to the lower airways due to their small sizes, where they can cause damage to the bronchial epithelium, inducing inflammation or neoplastic degeneration, or can be carried into the pulmonary blood to spread throughout the body [7].

1.1. PAHs

Polycyclic aromatic hydrocarbons (PAHs) are common compounds in traffic- and industrial-related air pollution: they are thought to result in an increased risk of allergic and pulmonary diseases (asthma, rhino-conjunctivitis, COPD) in exposed populations, unbalancing Th_2-mediated inflammation, down-regulating FoxP3 gene expression in Th_0 cells [8] and over-expressing PDGF (platelet-derived growth factor) in fibroblasts [9]. Moreover, in in vitro and in vivo studies in B cells, PAHs have been shown to interfere with antigen-presenting processes performed by APC (antigen-presenting cells) [10], inducing an Ig class switch (from G to E) and promoting allergic sensitization [11]. Finally, PAHs promote carcinogenetic mechanisms, unbalancing pro- and anti-apoptotic cell signals through mutations in crucial genes, e.g., K-Ras and TP53 [12].

1.2. Gas

Nitrogen oxides (NO_x), sulphur oxides (SO_2), and ozone (O_3) are emitted by diesel and gasoline engines, wood combustion and power plants. Their air concentrations seem to be related to an increased risk of asthma [13] and, for ozone, an increased risk of death due to asthma [14]. Moreover, ozone and sulphur oxides may increase the short-term risk of death due to stroke and myocardial infarction. However, no trend has been observed with long-term exposure, even to high concentrations of SO_2 [15]. Finally, these oxides were able to damage the bronchial epithelium in in vitro and in vivo studies, promoting oncogene expression, such the epithelial growth factor receptor (EGFR) gene [16].

1.3. Heavy Metals

Heavy metals are common in particulate matter, and many sources can introduce them into the atmosphere, e.g., steel factories, oil refining factories, power plants, waste incinerators and diesel and gasoline engines. The most frequent species are lead (Pb^{2+}), mercury (Hg^{2+}), manganese (Mn^{2+}), chromium (Cr^{3+}, Cr^{6+}) and arsenic (As^{3+}, As^{5+}). Heavy metals often pollute soil and water *reservoirs* and can enter the food chain [17,18] Many species have demonstrated pro-carcinogenetic mechanisms: arsenates (AsO_4^{3-}) and arsenites (AsO_3^{3-}) are carcinogenic for bronchial, renal and urinary bladder epithelia [19], while chromium induces cancer in the lung and stomach [20]. DNA repair malfunctions and pro- and anti-apoptotic gene imbalances are the most frequent genic mutations induced by heavy metals [21,22].

1.4. Microorganisms

Microorganisms are widespread in the atmosphere, soil and water, but different sources are well-known: mycetes are more concentrated in outdoor air [23], while bacteria emitted by human airways are more concentrated in indoor air [24]. Recently, urban wastes have been demonstrated to be a huge source of germ spores, and their storage and disposal could be hazardous for workers' health and public safety [25–27]. Indeed, microorganisms release exotoxins (beta-1,3-glucans, Lipopolysaccharde or LPS), which activate neutrophils to trigger IL-6-, IL-8-, and TNF-alpha-mediated inflammation [28] that could lead to rhino-conjunctivitis, bronchitis, Aspergillus-induced allergic bronco-pneumonia [29,30] or, sometimes, pulmonary mismatch diseases (COPD) [31].

The aim of this review is to provide the results from our department regarding air pollution's contributions to health-related damages and to assess the health risks related to exposure to hazardous compounds in both occupationally and non-occupationally exposed individuals.

2. Methods

2.1. Literature Search

According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this review was conducted on our own production papers, dated from 2002 to 2017, indexed and searched on PubMed by National Center of Biotechnology Information or NCBI (last accessed 12-06-2017), using as keywords "Ramazzini Institute", "University of Bari", "air pollution", "heavy metals", "PAHs", "environmental exposure", and "occupational exposure". No ethnic or geographic limits were adopted. The specific PubMed search algorithm is shown in Supplementary File 1. This systemic review is based only on published articles, and no patient or ethical approval is required.

2.2. Screening and Eligibility Criteria

All studies were screened for publication year (before or after 2010) and adopted language (only English accepted), and any data duplication was included. Later, the following eligibility criteria were adopted to include articles in the review process: (1) high sampling number, (2) randomized selection, (3) assessed exposure to air pollution, (4) adjusted analysis for bias, (5) cross-sectional study typology, (6) data collection using dedicated questionnaires and (7) the possibility to compare obtained data with a control group or non-exposed compatible population data taken from the literature. Any cases of overlapping studies were observed among selected publications.

2.3. Data Extraction

At least two people independently extracted data from reports to minimize errors and to reduce potential biases: any inter-researched disagreement was resolved. The principal investigator of each study was contacted via institutional mail to confirm data correctness. Extracted data included the first author's name, the study results, the country in which the study was performed and the publication year. We adopted the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool to assess study quality.

2.4. Statistical Analysis

Risk of bias should be reduced in papers adopting p-values < 0.5. To perform qualitative synthesis, adopted measures should be risk ratio (RR), odds ratio (OR), prevalence risk ratio (PR) or difference in percentiles. The results of each study were combined and discussed, and any additional quantitative analysis was performed.

3. Results

3.1. Literature Search

Fifteen paper [32–46] were collected after the web database research. One of these papers was excluded due to data duplication; later, after screening, a further six were rejected because they had been published before 2010 (the scientific evidence was too old) or because English was not the adopted language (the impact factor and international visibility were too low). Finally, only three [31–33] papers respected the abovementioned eligibility criteria and were included in the qualitative analysis (Supplementary File 2).

3.2. Study Characteristics

The characteristics of the 3 studies are summarized in Supplementary File 3. A total of 453 cases of both occupationally and non-occupationally exposed people were included in these studies. Among them, two cross-sectional studies compared exposed workers with a control group, adopting risk ratios and odds ratios as measures. The other study compared an exposed resident population with data derived from a non-exposed population of the same geographic region, adopting the differences

in 50° and 95° percentiles as measures. All studies were conducted in the same geographic area (Apulia Region, South of Italy) and administered anamnestic questionnaires. An assessment using a QUASAS score indicated high-quality studies, which were positive in at least 12/14 items.

3.3. Qualitative Analysis of Environmental Exposure to Air Pollution

A total of 279 subjects were included in this part of the systematic review, and data concerning urinary concentrations of five heavy metals (As species, Cr species, Hg^{2+}, Mn^{2+}, and Pb^{2+}) were extracted and analyzed. All participants lived in a polluted urban area near the industrial pole of Taranto Gulf (Apulia Region, South of Italy), characterized by the presence of steel plants, cement plants and oil refinery plants. Urinary concentrations were compared with reference values found in a non-exposed population (taken from the SIVR database, "Società Italiana Valori di Riferimento").

Regarding chromium, the median value of urinary excretion was in the SIVR range (0.05–0.35 μg/L), while the p95 value was higher, at 1.3 μg/L in the whole population. However, in two towns (Statte and Taranto-Paolo VI), the median values were above the reference limits, at 0.5 μg/L and 0.4 μg/L, respectively (Table 1).

Table 1. Urinary concentrations (in μg/L) attesting environmental exposure in the Apulia Region. Bold values are higher than the Società Italiana Valori di Riferimento (SIVR) range.

Compound	Measure	Whole Population	Laterza	Statte	Taranto	Taranto New Town	Taranto Tamburi	Taranto Paolo VI	SIVR
Cr species	p50	0.3	0.3	**0.5**	0.3	0.3	0.3	**0.4**	0.05–0.35
	p95	**1.3**	**1.2**	**2.5**	**1.0**	**0.9**	**1.2**	**0.8**	
Pb^{2+}	p50	**7.3**	**4.1**	**12.1**	**7.3**	**7.5**	**7.3**	**7.0**	0.01–2.00
	p95	**24.3**	**12.5**	**24.7**	**25.9**	**24.9**	**28.7**	**13.6**	
As species	p50	3.8	2.7	8.8	3.8	3.8	4.6	2.7	2.0–15.0
	p95	**16.8**	**8.5**	**27.1**	**11.1**	9.7	14.3	9.1	
Hg^{2+}	p50	0.8	0.8	1.8	0.7	0.6	0.9	0.8	0.1–5.0
	p95	4.5	2.4	**7.6**	**3.9**	2.8	4.5	1.4	
Mn^{2+}	p50	1.3	2.2	0.5	1.6	1.6	0.9	2.2	0.2–4.0
	p95	**8.7**	**22.5**	1.9	7.9	**4.9**	4.5	**8.7**	
Total (N)		279	45	55	179	90	50	39	

For lead, both the median and the p95 values were higher (7.3 μg/L and 24.3 μg/L, respectively) than the SIVR values (0.1–2.0 μg/L) in the whole population. A higher concentration was found in Statte (12 times above the cut-off), with a lower concentration in Taranto city. Individuals who had eaten fish and shellfish 48–72 h before urine collection showed higher lead concentrations (Table 1).

The median urinary concentration of inorganic As, monomethylarsonic acid and dimehylarsinic acid (respectively *iAs*, *MMA* and *DMA*) was within the SIVR range (2.0–15.0), while the p95 value was higher in the whole population and in most of Statte (16.8 μg/L and 27.1 μg/L, respectively). Moreover, higher levels of As were found in smokers, tap water drinkers and fish consumers.

Regarding Hg^{2+}, the p50 and p95 values were not above the SIVR range (0.1–5.0 μg/L) in the whole population. However, higher levels were found in Statte and Taranto (7.6 μg/L and 3.9 μg/L, respectively) (Table 1). Smokers, women and fish consumers had higher levels than did the other groups.

Finally, the p95 but not the p50 values were higher for Mn^{2+} urinary concentrations (8.7 μg/L and 1.3 μg/L, respectively) in the whole population. Higher levels were detected in Taranto (especially in the Paolo VI district, 8.7 μg/L) and Statte (22.5 μg/L) (Table 1) and in smokers, women and tap water drinkers.

3.4. Qualitative Analysis of Occupational Exposure to Air Pollution

In this part of the systematic review, 336 subjects, of which 174 were occupationally exposed to particulate matter and 162 were non-exposed workers, were included. Data concerning symptoms of allergic and pulmonary diseases, along with results from allergic tests (skin prick tests, specific IgE detection, nasal cytology, rhino-manometry) and spirometric tests, were collected. Previous history of respiratory or allergic diseases was an excluding criterion in either study. All participants lived in a polluted urban area around Bari (Apulia Region chief town, South of Italy), characterized by the presence of a thick industrial area producing several assets (e.g., iron products, tires). Occupationally exposed people worked in the town center (or around it) at least six hours a day, five days a week, as traffic warders or waste collectors.

Within the first worker category, the prevalence of allergies, diagnosed in people with typical symptoms and at least one positive allergic test, was higher than in office-employed colleagues (31.5% vs. 15.8%, RR = 2.01). Moreover, traffic warders equipped with automobiles were afflicted by allergies less frequently than those who travelled via motorcycle or any other vehicle (47.4% vs. 61.6%, p-value < 0.05). The prevalence of allergy symptoms (referenced as rhino-conjunctivitis) was higher in traffic warders with respect to controls (45.9% vs. 15.8%, RR = 2.79). Finally, spirometric anomalies exhibited the same prevalence among exposed and non-exposed individuals.

Waste collectors had FEV_1 values and, in particular, Tiffenau indices that were statistically lower than those of colleagues who worked in an office (75.08% vs. 79.93%, p-value = 0.001). Altogether, spirometric pathological alterations were more frequent in waste collectors with respect to the controls (OR = 7.9, 95% CI = 1.7–37.0, p-value = 0.008). Unlike the traffic warders, dustmen frequently exposed to air pollution were less afflicted by rhino-conjunctivitis (Table 2).

Table 2. Data concerning exposed workers' characteristics, results of allergic and spirometric tests and results of dedicated questionnaires.

Office Employees	Traffic Warders	Investigations	Ecological Operators	Office Employees
94.1	93.5	**FVC% (mean)**	115.06	114.2
92.4	91.5	**FEV_1% (mean)**	105.89	111.03
Data not found	Data not found	**Tiffenau index (mean)**	76.09	80.12
45%	56.8%	**Positive allergic tests**	Not performed	Not performed
15.8%	45.9%	**Positive allergic Anamnesis**	17.4%	31.1%
15.8%	31.5%	**Allergy diagnosis**	Not performed	Not performed
101	111	**N**	63	61

4. Discussion

Air pollution can induce adverse effects on human health. In fact, particulate compounds (PAHs, heavy metals, gases, and microorganisms) particularly promote respiratory and oncological disease onset in the general population [47]. To date, the IARC has assessed that As^{3+}/As^{5+}, Cr^{3+}/Cr^{6+}, Cd^{2+} and Ni^{2+} are carcinogens (I group) [48], while other heavy metals (Pb^{2+}, Mn^{2+}, Hg^{2+}) damage target organs after long-term intake [49,50]. Arsenic mono- and dimethylated compounds (respectively MMA and DMA) and other arsenic organic compounds do not seem to be as dangerous [51]. Our investigations indicated that populations living around industrial area have higher intakes and higher urinary excretion levels of these heavy metals with respect to the non-exposed general population.

The median value for chromium (0.3 µg/L) was the upper limit value of the relative SIVR range, while the 95th percentile was actually higher than the proposed SIVR upper limit. There were no significant differences in urinary excretion by age, sex or drinking water source, unlike in other reports in the literature, in which an association was found between residing in an industrial area and the type of water consumed [52–54]. Indeed, drinking water is a well-known source of exposure to chromium; thus, a drinking water concentration limit (50 µg/L) has been applied in Italy and USA to guard the health of the resident population [55,56]. However, multivariate analysis found a statistical association

between chromium urinary excretion and residence: it is possible that the inhalation of chromium-rich dusts, pumped into the atmosphere by steel, cement and oil refinery plants, could constitute significant sources of exposure for the resident population [57–59]. Further studies are needed in the future to investigate the possible increased incidence rates of certain cancer histological types, such as lung cancer, related to Cr^{6+} exposure [60].

Regarding arsenic species, multivariate analysis revealed associations with the city of residence and the consumption of crustaceans 48–72 h before urine collection [61]. There were significant differences between people who drank tap water and those who habitually drank bottled mineral water. Indeed, the contamination of the main water supply remains a major source of exposure to inorganic As in many parts of the world. However, Apulia aqueduct water has total As values lower than 1 μg/L, while recently, five water brands were determined to have total As values higher than 10 μg/L [62,63]. Interestingly, a statistical association was found between arsenic urinary excretion and residence, but no association was detected with pesticides. According to this finding, particulate matter could be an important route of exposure to arsenic and its metabolites. Indeed, steel plant furnaces melt iron scraps, releasing arsenic-rich dusts into the atmosphere: these dusts can also pollute proximal lands for many years after plant closure [64].

Regarding lead and mercury, the median value and the 95th percentile were significantly higher than the upper limits of the references. As with arsenic, people who had eaten seafood 48–72 h before collection had higher excretion levels of both metals. Indeed, principal mercury intake is due to fish and crustaceans. No association was found between lead excretion and the use of paint. Both mercury and lead, along with manganese, had positive associations with residence in a multivariate analysis. These findings could be related to the presence of the industrial area of Taranto, which, in 2009, emitted 38 tons of lead and 510 kg of mercury into the atmosphere [65]. Further studies are needed to confirm these data and to precisely determine the route of exposure.

Health damages also have been demonstrated in occupationally exposed workers: Santos et al. recently determined that occupational exposure to air pollution can cause significant statistical reductions of FEV_1 and FVC in traffic wardens, rangers and taxi drivers [66]. However, for the first time, our own study demonstrated that air pollution is a significant occupational risk factor for allergic disease onset. In fact, the prevalence of diagnosed allergy in traffic warders (almost 50%) was statistically higher than in non-exposed office employers. Before us, Proietti et al. found no statistically significant association between occupational exposure and diagnosis of allergic diseases [67], while Gao et al. highlighted only a greater risk of allergic-related respiratory symptoms [68]. Regarding the latter, our analysis found no difference in pulmonary function between the exposed and control groups. However, other studies did not confirm these data, and further investigations are required [69]. Pathogenic mechanisms are still poorly understood: The most likely hypothesis is that *Polycyclic Aromatic Hydrocarbons from Diesel Exhaust Particles (PAHs-DEP)*, plentiful in urban air pollution, are able to switch from Th_1- to Th_2-mediated inflammation and to interfere in the B cell to plasma cell differentiation process, inducing higher IgE production [70,71].

Moreover, our data indicate that waste collection and, consequently, germ-related toxin inhalation, promote pulmonary functional decline in dustmen exposed to this unhealthy particulate matter. Indeed, waste collectors had FEV_1 values and Tiffenau indices that were statistically lower than those in non-exposed colleagues, as demonstrated by Athanasiu in Greece and Heladk in Norway [72,73]. Similar to traffic warders, waste collectors were more afflicted by rhino-conjunctivitis than was the control group, but the data were inadequate to diagnose allergic diseases in this exposed group. Few studies in the literature have investigated pathogenic pathways of respiratory impairment: beta-(1-3)-glucans and similar volatile compounds (NO_2, SO_2, CO, etc.) [74] are thought to be able to release several types of cytokines from neutrophils and monocytes, such as IL-6, IL-8 and TNF-alpha, and to promote epithelial inflammation in upper and lower airways, ultimately resulting in obstructive diseases [75,76]. However, other studies did not confirm these data, and further investigations are required [77].

5. Conclusions

Air pollution is an emergent topic in human health wards. Particulate matter is able to increase the risk of allergic and respiratory diseases in occupationally exposed workers; therefore, the use of personal protective equipment and a meticulous health surveillance program including spirometry and in vivo or in vitro allergic tests, are required to protect at-risk individuals. Moreover, environmental protection policies are needed to regulate industrial emissions in the most polluted areas and to defend resident populations from excessive intake of compounds due to air pollution, particularly heavy metals, characterized by their well-known carcinogenic effects.

Supplementary Materials: The following are available on-line at www.mdpi.com/2073-4433/8/10/183/s1, Supplementary File 1: Specific search algorithms used for PubMed, Supplementary File 2: Study selection flowchart (according to PRISMA guidelines), Supplementary File 3: Characteristics of studies included in this systematic review.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

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