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Bioaccumulation of Toxic Metals in Children Exposed to Urban Pollution and to Cement Plant Emissions

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Abstract

Cement plants located in urban areas can increase health risk. Although children are particularly vulnerable, biomonitoring studies are lacking. Toenail concentration of 24 metals was measured in 366 children (6–10 years), who live and attend school in a city hosting a cement plant. Living addresses and schools were geocoded and attributed to exposed or control areas, according to modeled ground concentrations of PM_{10} generated by the cement plant. Air levels of PM_{10} and NO_2 were monitored. PM_{10} levels were higher in the exposed, than in the control area. The highest mean PM_{10} concentration was recorded close to the cement plant. Conversely, the highest NO_2 concentration was in the control area, where vehicular traffic and home heating were the prevalent sources of pollutants. Exposed children had higher concentrations of Nickel (Ni), Cadmium (Cd), Mercury (Hg), and Arsenic (As) than controls. These concentrations correlated each other, indicating a common source. Toenail Barium (Ba) concentration was higher in the control- than in the exposed area. The location of the attended school was a predictor of Cd, Hg, Ni, Ba concentrations, after adjusting for confounders. In conclusion, children living and attending school in an urban area exposed to cement plant emissions show a chronic bioaccumulation of toxic metals, and a significant exposure to PM_{10} pollution. Cement plants located in populous urban areas seem therefore harmful, and primary prevention policies to protect children health are needed.

Keywords Heavy metals · Cement plants · PM_{10} · Nitrogen dioxide · Biomonitoring · Children health

Introduction

Cement plants are frequently located in urban areas at high population density. However, the production of cement generates emission of particulate matter (Leone et al., 2016; Mohebbi and Baroutian 2007), gaseous pollutants (i.e., nitrogen oxides, sulfur oxides, carbon oxides (Lei et al., 2011)), heavy metals (Chen et al., 2010; Chen, 2020; Gupta et al., 2012; Liu et al., 2019; Wu, 2021), and persistent organic pollutants (i.e., polychlorinated dibenzo-p-dioxins and dibenzofurans, polychlorinated biphenyls Richards and Agranovski 2017; Zou et al., 2018)). Thus, the presence of cement plants has been linked with altered air quality in working areas (Noto et al., 2015) and in urban areas (Leone et al., 2016). Furthermore, previous studies indicate an increased risk of adverse health outcomes in exposed adults (Bertoldi et al., 2012; Eom et al., 2017; Raffetti et al., 2019) and children (Bertoldi et al., 2012; Garcia-Perez et al., 2017; Marcon, 2014).

Although fly ashes from industrial combustion in cement kilns are released into atmosphere after appropriate purification, this procedure does not seem to adequately avoid the unintentional contamination of environmental matrices and, as a consequence, human exposure to toxic chemicals.

In particular, previous evidence points to cement production as a relevant contributor for the atmospheric emissions of several heavy metals as mercury (Chen et al., 2020; Wu et al., 2021), copper, arsenic, nickel, cadmium (Chen et al., 2010; Gupta et al., 2012; Liu et al., 2019), and chromium (Hwang et al., 2018; Isikli et al., 2003). Some of these metals have been identified as biomarkers of exposure deriving from cement production (Raffetti et al., 2019).

Heavy metals produced by human industrial activities can generate negative effects to human health and to the environment, because of their persistence, toxicity, biological accumulation, and molecular interactions (Rehman et al., 2018; Wu et al., 2016). In children, in particular,

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health risks include altered growth and development (Shah, 2020), obesity (Fan et al., 2017; Shao et al., 2017), neurologic (Alemany, 2017; Pujol, 2016; Rehmani et al., 2017), cognitive (Lucchini, 2019), respiratory disorders (Madrigal et al., 2018; Zheng et al., 2013), and cancer (Xu 2019; Zhang, 2019a; Zumel-Marne et al., 2019). In adults, long-term exposure t-o heavy metals has been mainly linked with impaired cognitive function and cognitive decline (Bakulski et al., 2020), osteopenia or osteoporosis (Jalili et al., 2020), altered glucose metabolism, insulin resistance and metabolic syndrome (Cortes et al., 2021; Guo et al., 2019; Moon 2014; Wen et al., 2020; Yang et al., 2020), obesity (Wang et al., 2018b), hypertension (Wu, 2018), cardiovascular risk (Domingo-Relloso, 2019; Wang et al., 2019), decrease renal function (Tsai et al., 2017), and cancer (Duan, 2020; IARC 2012).

In proximity of cement plants, heavy metals have been detected in environmental air (suspended particulate matter) (Ali-Khodja et al., 2008), in soil (Bermudez et al., 2010; Lv, 2018; Wang et al., 2018a; Yatkin and Bayram 2010) and, in humans (adult age), in biological samples as blood, urine and hair (Afridi, 2011; Dong et al., 2015; Hwang et al., 2018; Isikli et al., 2006).

Although the paediatric age appears particularly vulnerable to emissions generated by cement plants (Bertoldi et al., 2012; Garcia-Perez et al., 2017; Marcon et al., 2014), scarce information exists on body accumulation of several metals in children living close to these industrial facilities.

An increased health risk can also be present when children living in the surrounding of a cement plant are exposed to air concentration of particulate matter not exceeding the exposure limit (Marcon et al., 2014). Particulate matter vehiculates toxic metals, and children exposed to metal pollution early and chronically can accumulate negative health effects (Carrizales, 2006; Claus Henn, 2017,2016; Haynes, 2015; Torres-Agustin, 2013) mainly due to oxidative damage (Pizzino, 2017; Zheng et al., 2013), and to a more significant lung deposition of fine particles, as compared with adults (Sanchez-Soberon et al., 2015).

In this complex scenario, the pathways linking the environmental concentration of pollutants, the bioaccumulation of toxic elements, and the possible development of health effects in the short- and in the long-term, cannot be comprehensively depicted by separate analyses on environmental or biological monitoring. Thus, the combined evaluation of human biomonitoring techniques and environmental monitoring appears as a key tool for an adequate assessment of the body burden of toxic chemicals, and to explore the individual risk linked with an unhealthy environment. This approach adequately evaluates the combined results of different modalities of metals intake (i.e., inhalation, ingestion, dermal absorption) (Joas, 2012; Llobet et al., 2003).

Human nail clips, in particular, represent a valuable sample to assess metal exposure of various origin (Esteban and Castano 2009). The procedure is validated and noninvasive for the assessment of metal concentration, and has been used extensively used in pediatric age (Carneiro et al., 2011a; da Silveira Fleck et al., 2017; Menezes-Filho, 2018; Rodrigues 2018; Slotnick et al., 2005). Thus, the assessment of metal concentration in human nails represents a suitable indicator of long-term exposures (Hunter 1990; Slotnick and Nriagu 2006) to pollutants of anthropogenic origin (Hopps 1977; Hunter et al., 1990; Slotnick and Nriagu 2006; Sukumar 2006; Yaemsiri et al., 2010).

Methods

Study Design

We measured toenail concentration of a wide panel of metals (see below) in children living and attending public elementary schools in the city of Barletta (Apulia region, Southern Italy, 93,275 residents in the year 2020), an urban area hosting a large cement plant with a production capacity of about one-million-ton cement/year, powered with fossil fuels and waste-derived fuel. According to the European Pollutant Release and Transfer Register (E-PRTR, https://prtr.eea.europa.eu/#/home), the main activity of this facility is the production of cement clinker and clinker grinding. An additional activity is the incineration of non-hazardous waste included in the EU directive 2000/76/EC.

A public campaign in five elementary schools (from November 2019 to January 2020) served to explain the aims of the study to teachers, parents and children. At the end of the campaign, a total of 366 children (188 females, age range 6–10 years) were enrolled on a voluntary basis, after both parents signed the informed consent. Children also agreed to participate as volunteers and expressed consent. The enrolled subjects were the 8.5% of children aged 6–10 years living in the city of Barletta in the year 2020 (4,289 children). Inclusion criteria were living at the same address in the last 6 months before enrollment, and the absence of known diseases.

In the explored area, ground concentrations of particulate matter with a diameter of ≤ 10 µm (PM_{10}) emitted by the cement plant had been previously modeled by a 3-D Lagrangian Particle Model (SPRAY) (Rotatori and Pirrone 2012). This model is particularly fit to assess the environmental impact of industrial facilities located in complex geographical areas, where land/sea breeze and topography generate complex circulation patterns. The model allows an accurate assessment of the atmospheric dispersion of pollutants in non-homogenous and non-stationary conditions, also considering a reliable reconstruction of complex wind and turbulence fields (Gariazzo et al., 2004). The pollutant concentration used as input was the maximal PM_{10} stack emission limit allowed for the cement plant (20 mg/Nm^3) (Rotatori and Pirrone 2012). Results, expressed by a colorimetric map, represent the average yearly ground concentration of PM_{10} following atmospheric transport. According to the pollutant dispersion model, the urban area with the minimal estimated ground concentrations of PM_{10} (i.e., below 0.5 μg/m^3) was considered as the control area. Conversely, the exposed urban area was that with the estimated ground concentration of PM_{10} in the range 0.5–40 μg/m^3 (Fig. 1). The address of the five explored schools and the home address of each enrolled children were geocoded and attributed to exposed or control area. According to the E-PRTR, the only industrial facility releasing air pollutants in the exposed area is the cement plant. Other relevant sources of air pollutants in both the exposed and the control area are vehicular traffic and home heating.

According to geocoding, 174 children attended two schools in the exposed area, and 192 attended the remaining three schools in the control area (Fig. 1). Not all children lived in the same area of the attended school. Thus, in order to evaluate the role of the individual exposure during the whole day, children were also divided according to home address, and the following three subgroups were considered: children living and attending schools in the control area (group A, $n = 189$, the less exposed subgroup); children living or attending schools in the exposed area (group B, $n = 110$, children only exposed at school or at home); children living and attending schools in the exposed area (group C, $n = 67$, the most exposed subgroup).

The study was approved by the local ethics committee (inter-provincial ethics committee, ASL FG/ASL BAT authorization n. 108/CE/2019).

Nail Collection, Sample Preparation, and Analysis

Toenail sample collection was conducted in all schools in a unique day (February 26, 2020). Parents were asked not to cut children's nails in the month before sample collection (from January 25 to February 26, 2020). Toenails were selected for sampling as preferential to fingernails due to the minor risk of external contamination (Barbosa et al., 2005). The procedure for toenail collection, sample preparation, and analysis is a well standardized technique (Sanches and Saiki 2011), and used extensively (Butler, 2018; Carneiro et al., 2011b; Chanpiwat et al., 2015; Coelho, 2014; da Silveira Fleck et al., 2017; Di Ciaula et al., 2020; Gault, 2008; Grashow et al., 2014; Oyoo-Okoth et al., 2010; Slotnick et al., 2005; Wickre et al., 2004; Wilhelm et al., 1994).

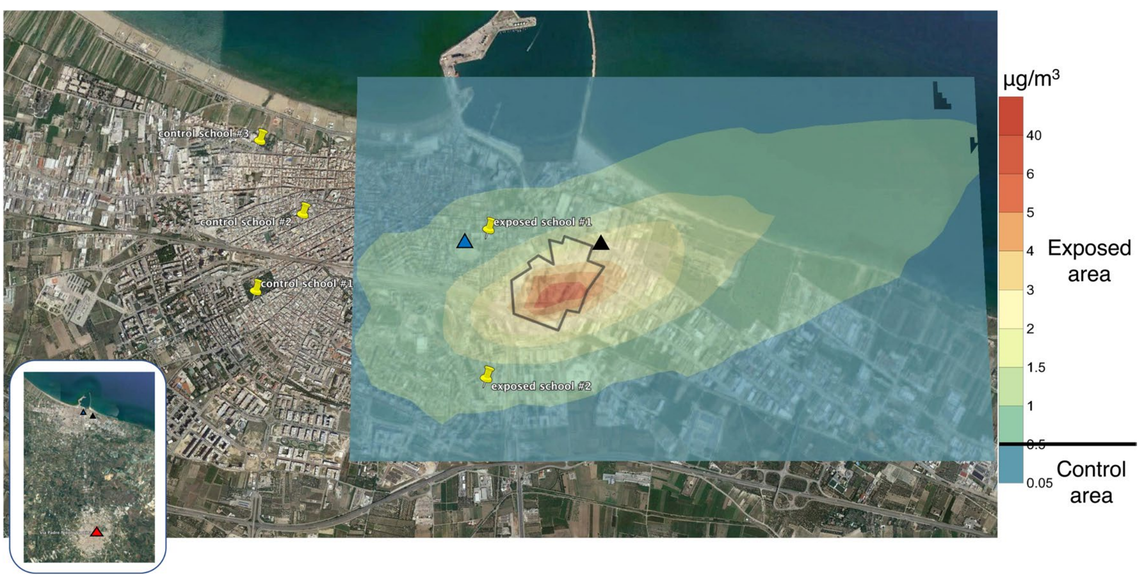

Fig. 1 Map of the explored city (Barletta, southern Italy, Apulia region), with a colorimetric modeling of the average yearly ground concentrations of PM_{10} emitted by the cement plant, following atmospheric transport. The site of the cement plant is delimited by a black line. The ground concentrations of PM_{10} generated by the cement plant have been estimated by a 3-D Lagrangian model (Rotatori and Pirrone 2012). According to the dispersion model, the urban area with the minimal estimated ground concentrations of PM_{10} (i.e., below 0.5 μg/m^3) has been considered as the control area. The exposed urban area was that with estimated ground concentration of PM_{10} in the range between 0.5 and 40 μg/m^3. The five yellow marks indicate the location of the explored schools (i.e., two exposed, three control schools). The black triangle indicates the location of the air monitoring station positioned in the high exposure area. The blue triangle indicates the location of the air monitoring station positioned in the intermediate exposure area. In the inlet, the red triangle indicates the monitoring station used for control exposure (see methods section). Map elaborated from Google Earth Pro and pollutant dispersion model (Rotatori and Pirrone 2012)

Toenails were clipped using ceramic blade to avoid possible contamination. Samples were stored in a 10 mL polypropylene tube for subsequent analysis, and scissors were cleaned with a light-acid solution.

Before assessing metal concentrations, samples were immersed in a 70% ethanol solution without stirring or sonication for a period of 10 min, to reduce the risk of microbiological contamination. Exogenous impurities were removed by a multistep washing procedure with acetone and Milli-Q purified water, and the cleaned samples were kept at room temperature for a period from 24 to 48 h for drying. The dry samples were weighed, and the concentration of 24 elements was subsequently calculated, using inductively coupled plasma mass spectrometry (ICP-MS): Antimony (Sb), Arsenic (As), Barium (Ba), Beryllium (Be), Boron (B), Cadmium (Cd), Chromium (Cr), Cobalt (Co), Manganese (Mn), Mercury (Hg), Molybdenum (Mo), Nickel (Ni), Lead (Pb), Copper (Cu), Selenium (Se), Silver (Ag), Thallium (Tl), Tellurium (Te), Thorium (Th), Titanium (Ti), Tungsten (W), Uranium (U), Vanadium (V) and Zinc (Zn). Given the mass variation of the nail samples, specific methodological Limits of Detection (LOD) were adopted for each sample. The analytical procedure was performed using a standardized technique, according to the EPA 6020A 2007 method. https://19january2017snapshot.epa.gov/sites/production/files/2015-07/documents/epa-6020a.pdf

Assessment of Air Pollutants

The average daily air concentrations of PM_{10} and nitrogen dioxide (NO_2) were assessed during the four months preceding toenail sampling (from November 1, 2019 to February 26, 2020), and during the whole year 2019 by three air monitoring stations positioned and regularly managed by the Regional Environmental Agency (ARPA Puglia). Periodic quality control and validation of recorded data are performed by ARPA Puglia according to technical criteria depicted by national and international directives (D. Lgs. 155/2010, EU Directive 2008/50/CE). The concentrations of PM_{10} and NO_2 are available, for each monitoring station, as average daily values expressed in μg/m^3. The full database of recorded data is publicly available (http://old.arpa.puglia.it/web/guest/meta-aria).

As shown in Fig. 1, the first monitoring station is positioned at about 0.5 km from the cement plant, in an area with an average yearly ground concentration of PM_{10} above 2 μg/m^3, as estimated by the dispersion model (Rotatori and Pirrone 2012). This was defined as high exposure area. The second monitoring station is positioned at about 0.7 km from the cement plant, in an area (defined as intermediate exposure) with an average yearly ground concentration of PM_{10} in the range 0.5–1 μg/m^3, as estimated by the dispersion model (Rotatori and Pirrone 2012). The third monitoring station (control exposure) is located at 9 km from the cement plant, in a nearby urban area (city of Andria, 98,414 residents in the year 2020), with characteristics similar to the city of Barletta but with urban pollution primarily generated by vehicular traffic and home heating. In this control area there are no industrial plants with stack emissions recorded in the E-PRTR.

Assessment of Potential Confounders

Further environmental conditions or personal behaviors possibly influencing the concentration of metals in toenails were explored by a specific questionnaire administered at enrollment. Considered as confounders were domestic heating using biomass, orthodontic treatments, regular outdoor sports, regular exposure to passive smoke, consumption of locally grown vegetables. The questionnaire was administered to parents for self-compilation.

Statistical Analysis

Frequencies of categorical variables, means, standard errors, medians and range of continuous variables were calculated. The χ^2 test (proportions), the Mann–Whitney U test (unpaired data) or the Kruskal–Wallis Multiple-Comparison Z Value test (inter-group differences) were employed to evaluate differences. Correlations were tested using the Spearman's rank correlation coefficient. Tobit regression models were employed to examine the associations between the toenail concentration of metals, the location of the attended schools, and the role of potential confounders. Tobit regression was used to accommodate the left-censored nature of values, due to the presence of samples with metal concentration below the limit of detection (Lubin, 2004). Metal concentrations were log-transformed to meet the normal assumption (Tobin 1958). P values < 0.05 were considered statistically significant. Analyses were performed using R software version 3.5.1 (R Project for Statistical Computing, available from https://www.r-project.org/).

Results

As shown in Table 1, in the four months preceding toenail sampling, the average daily (24 h) air concentration of PM_{10} was significantly higher in the two exposed areas, than in the control area. As expected, the highest PM_{10} air concentration was recorded in the high exposure area (i.e., closest to cement plant). The annual mean PM_{10} concentration was above 20 μg/m^3, the limit set by the World Health Organization (World Health Organization 2006), in the control and in the two exposed areas, and the highest value was recorded in the high exposure area.

Table 1 Average concentration of air pollutants in the exposed and in the control area

	Control area	Intermediate exposure area	**High exposure area**
PM_{10} (μg/m^3)			
Mean of daily (24 h) concentrations in the 4 months before toenail sampling	20.8 ± 0.9	23.3 ± 0.9*	27.8 ± 1.0*°
Annual mean (year 2019)	21.8 ± 0.6	22.0 ± 0.6	25.5 ± 0.6*°
NO_2(μg/m^3)			
Mean of daily (24 h) concentrations in the 4 months before toenail sampling	77.2 ± 2.7	59.0 ± 2.2*	50.8 ± 1.9*°
Annual mean (year 2019)	62.0 ± 1.6	43.0 ± 1.5*	59.5 ± 1.6*°

PM$_{10}$ particulate matter with a diameter of ≤ 10 μm; *NO*$_2$ nitrogen dioxide. Data are expressed as mean ± SEM of daily (24 h) concentrations of air pollutants measured during the 4 months before toenail sampling (November 1st to February 27, 2020), and during the whole year 2019 (annual mean). Differences were tested by Kruskal–Wallis Multiple-Comparison *Z* Value Test

*$P = 0.000001$vs control area; $P = 0.000001$ vs intermediate exposure area

The two exposed schools were located in the intermediate exposure area (Fig. 1). In this site, the average daily PM_{10} concentration measured in the four months before toenail sampling was lower than in the high exposure area, but was still significantly higher than in the control area.

The opposite trend was evident for NO_2. In fact, in the four months preceding toenail sampling, the highest air concentration of NO_2 was recorded in the control area, and the lowest in the high exposure area. This trend was also confirmed when the annual mean concentration of NO_2 was considered (Table 1). Although NO_2 is also emitted from cement industries, and not only from vehicular traffic and domestic heating, these findings might indicate a different prevalent origin of these two pollutants.

The analysis of toenail metal concentration found that Be, Te, Tl and Th levels were lower than LOD in all samples (Table 2; Fig. 2). The rate of samples with toenail metal concentrations above the LOD was comparable in children attending schools in the exposed or in the control area in all cases, except for Ni (37% exposed vs 55% control schools), Cd (19% exposed *vs* 11% control schools), Ba (94% exposed vs 99% control schools), and Hg (59% exposed *vs* 48% control schools) (Fig. **2**).

Table 2 shows the average concentration of each metal, as measured in children attending schools in the exposed or in the control area. Children attending schools in the exposed area had significantly higher concentrations of Ni, Cd, Hg, as compared with the control area. The opposite was evident in the case of Ba, since the toenail concentration of this metal was higher in children from the control, than in those from the exposed area.

Children with the highest individual toenail concentration of Ni (109.2 μg/g), Cd (4.2 μg/g) and Hg (1.56 μg/g) attended school in the exposed area. Conversely, the

Table 2 Absolute toenail metals concentration in children attending school in the exposed or control area

Metal	Exposed schools (*n* = 174)	Control school (*n* = 192)	*P*
Be	0	0	–
B	0.11 ± 0.11	0.1 ± 0.1	NS
Ti	0.15 ± 0.6	0.7 ± 0.3	NS
V	0.008 ± 0.004	0.047 ± 0.01	NS
Cr	0.28 ± 0.09	0.7 ± 0.2	NS
Mn	0.57 ± 0.13	1.5 ± 0.7	NS
Co	0.18 ± 0.1	0.19 ± 0.2	NS
Ni	0.97 ± 0.7	0.7 ± 0.1	0.0003
Cu	4.3 ± 0.5	4.5 ± 0.8	NS
Zn	76.5 ± 1.8	78.6 ± 3.8	NS
As	0.12 ± 0.07	0.05 ± 0.01	NS
Se	0	0.007 ± 0.003	NS
Mo	0.01 ± 0.01	0.04 ± 0.03	NS
Ag	0.02 ± 0.005	0.02 ± 0.009	NS
Cd	0.08 ± 0.03	0.01 ± 0.004	0.01
Sb	0.12 ± 0.03	0.16 ± 0.02	NS
Te	0	0	–
Ba	4.1 ± 0.5	7.8 ± 1.7	0.004
W	0.006 ± 0.006	0.027 ± 0.03	NS
Hg	0.15 ± 0.02	0.09 ± 0.02	0.001
Tl	0	0	–
Pb	0.36 ± 0.7	0.67 ± 0.2	NS
Th	0	0	–
U	0.008 ± 0.005	0.005 ± 0.001	NS

Data are expressed in μg/g. Values are reported as mean ± SEM. Differences were tested by Mann–Whitney *U* test

NS not significant

Fig. 2 Absolute number of toenail samples with metal concentration above the limit of detection (LOD) for each of the explored metals. Samples were from children attending school in the exposed or in the control area. Asterisks indicate $P<0.01$ ($\chi 2$ test)

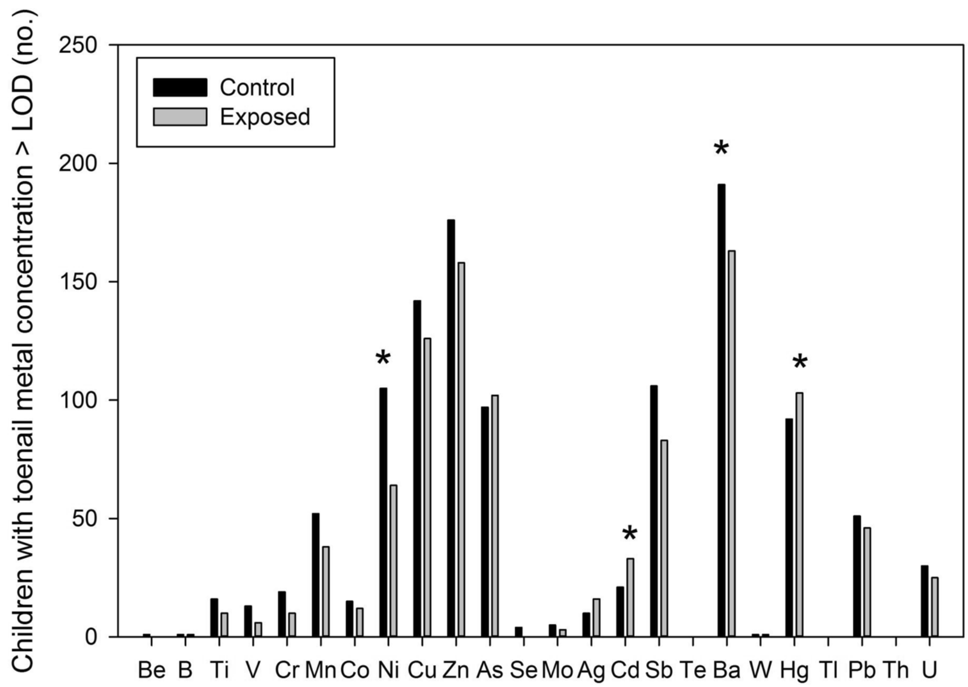

Table 3 Absolute toenail metals concentration in children selected according to the location of both attended school and home address

	Group A	Group B	Group C
n	189	110	67
Ni	0.7 ± 0.18 0.28 (0–22.9)	0.3 ± 0.07* 0 (0–4.5)	2.0 ± 1.7* 0 (0–109.2)
Cd	0.015 ± 0.004 0 (0–0.58)	0.06 ± 0.02* 0 (0–1.2)	0.1 ± 0.07 0 (0–4.2)
Ba	7.9 ± 1.7 3.2 (0–198.6)	4.6 ± 0.7 2.99 (0.58–61.7)	3.3 ± 0.3* 2.5 (0.26–14.8)
Hg	0.09 ± 0.01 0 (0–1.03)	0.14 ± 0.02* 0.07 (0–1.56)	0.16 ± 0.03* 0.08 (0–1.28)
As	0.04 ± 0.005 0.009 (0–0.55)	0.06 ± 0.02 0.036 (0–2.01)	0.25 ± 0.18* 0.05 (0–12.0)

Group A: children living and attending school in the control area; Group B: children living or attending school in the exposed area; Group C children living and attending school in the exposed area. Data are expressed in µg/g, and as means ± SEM, median (range)

*$0.002<P<0.03$ vs Group A (Kruskal–Wallis Multiple-Comparison *Z* Value test)

highest toenail concentration of Ba (198.6 µg/g) was recorded in a child attending school in the control area.

When both home and school address of enrolled children were considered, toenail concentration of metals in the group A, B and C were comparable in all cases (data not shown), except for Ni, Cd, Ba, Hg and As (Table 3). Children who either lived and attended schools in the exposed area had significantly higher toenail concentrations of Ni, Hg and As, than those living and attending schools in the control area. A similar trend was evident for Cd, and the opposite was shown in the case of Ba (Table 3).

According to results from the Tobit regression models (Table 4), the location of the attended school was a significant predictor of Cd, Hg, Ni and Ba concentrations, after adjusting for confounders. No significant effect on toenail metal concentrations derived from the analysis of covariates.

Considering the whole group of enrolled children, the Spearman's correlation matrix showed that toenail Cd concentration was correlated with Ni, Hg and As levels. Positive correlations were also shown between Ba, Ni, andAs concentrations (Table 5).

Discussion

The present study explored for the first time the chronic body accumulation of a wide panel of metals of anthropogenic origin in a cohort of children living and attending school in a populated urban area hosting a cement production plant.

In urban areas with pollution generated by multiple sources (i.e., natural sources, industrial facilities, vehicular traffic, domestic heating), monitoring air pollutants as unique technique of exposure assessment can underestimate the real individual exposure. Undervaluation can mainly derive from the multiple ways of intake of toxic chemicals (inhalation, oral ingestion, skin absorption), from the limited number of the air pollutants regularly monitored, from the effects of long-term exposure (i.e., accumulation of pollutants), and from the variable ground concentration of industrial pollutants generated by facilities located in urban areas

Table 4 Results of Tobit regression models on toenail metal concentrations in children attending control and exposed schools, and the effect of covariates

	Cd	Hg	Ni	Ba
Control vs. exposed	0.07* (− 0.12 to -0.018)	− 0.03** (− 0.05 to (− 0.02)	0.1* (0.03 to 0.18)	0.08** (0.03 to 0.13)
Domestic heating with biomass	−0.6 (−251.6 to 251.8)	0.08 (−0.09 to 0.3)	0.16 (−0.46 to 0.8)	0.008 (0.45 to 0.5)
Orthodontic treatments	0.0007 (−0.09 to 0.09)	0.007 (−0.03 to 0.04)	− 0.03 (0.04 to 0.5)	−0.04 (−0.14 to 0.05)
Outdoor sports	0.0004 (−0.06 to 0.06)	0.01 (−0.2 to 0.3)	−0.08 (−0.18 to 0.1)	−0.05 (−0.11 to 0.01)
Passive smoke	−0.8 (−250.1 to 251.8)	−0.08 (−0.008 to 0.04)	0.03 (−0.57 to 0.6)	−0.18 (−0.6 to 0.3)
Consumption of locally grown vegetables	− 3.3 (−0.1 to 0.05)	0.08 (−0.08 to 0.04)	0.5 (−0.1 to 1.1)	− 0.05 (−0.5 to 0.4)
Constant	− 1.67 (− 1.8 to − 1.5)	−2.31 (−2.4 to −2.2)	−1.03 (− 1.1 to −0.9)	−1.25 (− 1.3 to − 1.18)

Only significant results (metal concentration) are presented. Metal concentrations were log-transformed to meet the normal assumption. Results (β coefficients and 95% confidence intervals) have been adjusted for covariates and consider the left-censored data present in metals distribution

**P* < 0.05; ***P* < 0.01

Table 5 Spearman's correlation matrix considering the toenail concentrations of Ni, Cd, Ba, Hg, and as in the whole cohort of enrolled children

	Ni	Cd	Ba	Hg	As
Ni	–				
	–				
Cd	0.17				
	0.001	**–**			
Ba	0.21	0.089	–		
	0.0001	*ns*	–		
Hg	0.069	0.11	−0.03	–	
	ns	*0.03*	*ns*	–	
As	0.25	0.14	0.15	0.007	–
	0.000003	*0.008*	*0.005*	*ns*	–

Data are Spearman correlation coefficients (rho, normal text) and *P* values (in italic). Significant *P* values are marked in bold

with complex topography, inconstant wind directions and turbulence fields. Results from the present study point to the integration of environmental monitoring (i.e., the burden of specific pollutants in the environment) and biomonitoring techniques (i.e., the body burden of toxic chemicals) as a reliable method to assess the individual effects of environmental exposures, and the related health risk.

Distinct Patterns of Bioaccumulation in the Exposed and Control Area

The present study shows at least two patterns of metal bioaccumulation, according to the location of the attended school and the home address of children in the exposed or in the control area. Children either attending school and living in the area of maximal ground-level concentration of pollutants produced by the cement plant were the most exposed group. These subjects showed a higher accumulation of Ni, Cd, Hg and As, when compared to those living and attending schools in the control area. These metals correlated each other, indicating the possibility of a common source of emission.

On the other hand, children either attending school and living in the control area (i.e., the subgroup less exposed to plant emissions) showed a prevalent bioaccumulation of Ba. The concentration of this metal positively correlated with that of Ni, and previous evidence indicates that both Ba (Birmili et al., 2006; Figueiredo et al., 2007; Godri Pollitt et al., 2016) and Ni (Canteras et al., 2019) are markers of metal accumulation mainly deriving from vehicular traffic. These data confirm that vehicular traffic and home heating can be considered important sources of metal bioaccumulation in urban areas, besides industrial emissions. This hypothesis is in line with data deriving, in the present study, from the environmental monitoring of air pollutants. In this case, higher levels of NO_2 were present in the control, than in the exposed area. Of note, as Ba and Ni accumulation, also NO_2 air concentration is a well-known environmental marker of traffic density in an urban context (da Silveira Fleck et al., 2017).

Conversely, the increased body accumulation of Ni, Cd, Hg and As in the exposed area seems to be mainly related to the industrial emissions produced by the cement plant.

Cement Production as a Source of Pollution of Specific Metals

Raw material and fuels commonly employed for clinker/cement production (mainly fossil fuels as pet-coke and coal, but also waste-derived fuels), contain large amounts of heavy metals (in particular Hg, Co, Cd, Ni and Tl) (Gendebien et al. 2003; Genon and Brizio 2008; Zemba et al., 2011), and the emission of pollutants from cement kilns strongly depends on the primary fuel used (Zemba et al., 2011).

Mercury, in particular, is typically present in the emissions from cement kilns alimented with coal or pet-coke, supplemented or not with waste-derived fuels. This is due to the presence of Hg in elemental vapor form, which is less captured by the pollution control devices employed in kilns for cement production (Zemba et al., 2011).

Additional risk could derive from the presence of heavy metals (in particular the more volatile ones, as Hg) in substitution fuels (i.e., waste derived fuels), and from their transfer factors to gaseous emissions (Genon and Brizio 2008). Previous evidence showed that the substitution in cement kilns of fossil fuels with waste-derived fuels might have a negative impact on the emissions of heavy metals, and in particular Hg (Genon and Brizio 2008). This might be the case of the cement plant examined in the present study, in which an additional activity is the incineration of non-hazardous waste, which partially substituted fossil fuels to power the kiln.

A previous study exploring air pollutants generated from three commercially operating cement kilns co-burning waste, confirmed that Ni, Cd, Hg and As were among the predominant heavy metals emitted (Pudasainee et al., 2009). In the cited study, bag filters were able to remove above 98.5% of all heavy metals except Hg, which showed a removal above 60%. In the case of Hg, the removal efficiency ranged in the cited study from 77 to 28%. Thus, on average, about 40% of Hg was released into the atmosphere, as compared with 3.3% of Ni, 0.14% of Cd and 0.01% of As entering bag filters (Pudasainee et al., 2009).

Of note, these proportions (i.e., release of Hg and Ni higher than those of Cd and As) are comparable with those deriving, in the present study, from toenail concentration of the same metals in exposed children. In fact, children in the exposed area showed, on average, relatively higher concentrations of Hg (0.15 ± 0.02 μg/g) and Ni (0.97 ± 0.7 μg/g), as compared with those of Cd (0.08 ± 0.03 μg/g) and As (0.12 ± 0.07 μg/g).

The Accumulation of Metals in the Environment and in Biological Samples Surrounding Cement Plants

The presence of higher toenail concentrations of Ni, Cd, Hg and As in the exposed, than in control area is in line with previous observations confirming the accumulation of these metals in environmental matrices or in biological samples collected in geographical areas surrounding cement plants.

A recent study measuring heavy metals in the surrounding soil of a Chinese cement plant reported levels of Cd and Hg which were, respectively, two- and six times higher than background levels, thus generating a high ecological risk (Wang et al., 2018a). In France, cement plants in the Paris region have been identified as significant secondary source of soil contamination by Cd (Foti, 2017). A Turkish cement plant has been indicated as a significant contributor to depositions of trace elements, in particular Cd, in the surrounding area (Yatkin and Bayram 2010). Finally, in an Italian study, elevated Ni concentration were detected in leaves from trees close to a cement plant, as an effect of clinker production and storage (Baldantoni et al., 2014).

Similarly to studies which measured metal concentration in environmental matrices, previous biomonitoring studies showed, in biological samples from adult subjects, higher concentration of Cd in blood (Afridi et al., 2011; Isikli et al., 2006), hair(Afridi et al., 2011), and urine(Cha, 2011), higher Ni levels in blood (Afridi et al., 2011; Demir et al., 2005), and hair (Afridi et al., 2011), and higher Hg concentrations in blood (Dong et al., 2015), and urine(Cha et al., 2011) from subjects exposed to cement plant emissions, as compared with non-exposed subjects.

The Bioaccumulation of Specific Metals in Exposed Children

Our study shows, for the first time in pediatric age, higher Hg bioaccumulation in the area of maximal exposure to the emissions from the cement plant, as compared with the control area.

Cement production has been indicated as the largest Hg emission source in China, with considerable increase in Hg emissions in the last years (Chen et al., 2020). A recent study exploring positive effects of the COVID-19 lockdown on atmospheric Hg concentrations identified cement clinker production as the main responsible for Hg emission during the pre-lockdown period. In this study, the Hg emission from cement clinker production decreased markedly during the lockdown (Wu et al., 2021).

In a U.S. study, blood Hg levels measured in subjects living closer to a cement plant were associated with $PM_{2.5}$ modeling, and were significantly and positively correlated with As blood concentrations (Dong et al., 2015).

Approximately 80% of inhaled mercury is absorbed via the lungs and retained in the body (World Health Organization 1976). Although ingestion of contaminated food is a major source of Hg body levels (European Food Safety Authority (EFSA) 2012; European Food Safety Authority (EFSA) 2015), ground-level ambient air concentration of Hg is a significant predictor of body metal levels, also after controlling for covariates and other exposure variables (Hill 2020). Furthermore, in children living in industrial areas, a relatively high risk of exposure from hand-to-mouth intake is also possible (Abuduwailil et al., 2015).

These findings are in line with results from our study since, according to Tobit regression analysis, attending school in the exposed area was a significant predictor of increased Hg body levels.

Moreover, the average toenail Hg concentration recorded in the most exposed subgroup of children (0.16 ± 0.03 μg/g), was about three-times higher than that measured in a cohort of 290 children aged three years and enrolled in the New Hampshire Birth Cohort Study (0.055 ± 0.087SD) (Farzan 2021), and about 2.2-times higher than in a cohort of 222 U.S. healthy term newborns (0.07 ± 0.1SD) (Appleton et al., 2017).

A large biomonitoring survey involving, in 17 European countries, 1844 children aged 5–11 years participating in the DEMOCOPHES study, showed an average Hg concentration in hair (weighted geometric mean) of 0.145 μg/g (95% CI 0.139–0.151) (Hond 2015). Although a conversion ratio between Hg concentration in hair and in toenail has not been fully validated, according to a previous evidence this value should be equivalent to 0.05 μg/g in toenails (Choi 2009), a concentration about 3-times lower that that observed, in the present series, in the subgroup of the most exposed children.

Mercury is highly toxic to humans, in particular in terms of negative effects on the developing nervous system, and for exposures occurring in utero and during childhood (Rice et al., 2014). Thus, it has been strongly recommended to avoid Hg exposure during pregnancy and childhood as much as possible (European Food Safety Authority (EFSA) 2012; European Food Safety Authority (EFSA) 2015).

We found that the mean toenail Ni concentration measured in the whole population (0.8 ± 0.3 μg/g) was almost in the same range previously detected in other cohorts of children from Brazil (1.3 ± 1.0 μg/g, mean ± SD(da Silveira Fleck et al., 2017)), Italy (0.43 ± 0.18 μg/g, mean ± SE (Ciaula et al., 2020)), New Zealand (mean 1.08 μg/g, range 0.01–71.84 (Karatela et al., 2018)), and Pakistan (0.91 ± 0.1 μg/g mean ± SE (Bibi et al., 2016)). However, when the most exposed subgroup of children was considered (i.e., those living and attending school in the exposed area), the average Ni concentration was the highest (2.0 ± 1.7). Although a large variability existed, the maximal recorded value reached, in an exposed child, the value of 109.2 μg/g.

According to the International Agency for Research on Cancer (IARC), Ni is classified in group A1, i.e., "carcinogenic to humans". Besides the carcinogenic risk, Ni exposure can increase the risk of low birth weight (Sun 2018), preterm delivery(Chen 2018), and congenital malformations (Xu et al., 2021; Zhang, 2019b). In a cohort of adult patients with Mesoamerican nephropathy, average toenail Ni concentration (1.55 μg/g, range 0.18–42.65) was similar to that measured, in the present series, in children living and attending school in the exposed area (2.0 ± 1.7 μg/g). In the same study, control subjects showed a mean toenail Ni concentration of 0.21 μg/g (range 0.06–51.24), and the concentrations of this toxic metal were negatively correlated with the estimated glomerular filtration rate (Zhang et al., 2019b).

Cadmium has been identified as a biomarker of emissions from cement plants by biomonitoring techniques and atmospheric dispersion models (Abril et al., 2014).

In a previous Italian cohort of adult subjects, toenail Cd levels in the third (i.e., 0.0145–0.0306 μg/g) and in the fourth quartiles (i.e., ≥ 0.0306 μg/g) have been linked with an increased risk of prostate cancer, with ORs of 1.3 (95% CI 0.3–4.9) and 4.7 (95% CI 1.3–17.5), respectively (Vinceti 2007). In our study, the average toenail Cd concentration measured in children living and attending school in the exposed area was about 3-times higher than the threshold for the 4th quartile of Cd toenail concentration reported in the cited study. The average Cd toenail concentration measured in this subgroup of children (0.1 ± 0.07 μg/g) was also higher than the average value reported by the Italian National Institute of Health in another cohort of Italian subjects (0.041 ± 0.1)(Alimonti et al., 2010).

Cadmium levels have been also linked with exocrine pancreatic cancer (Kriegel 2006). A study assessing metal toenail concentrations in adult subjects with or without exocrine pancreatic cancer, demonstrated higher Cd concentrations in patients than in controls, and a significantly increased risk of pancreatic cancer in subjects with toenail Cd and As concentrations above 0.029 μg/g, and 0.1061 μg/g, respectively (Amaral 2012). Of note, in the present study, both average Cd (0.1 ± 0.07 μg/g) and As (0.25 ± 0.18 μg/g) toenail concentrations in children living and attending school in the exposed area were above the values reported in the cited study.

Besides the risk of cancer, previous studies linked increased Cd exposure in children with learning disability and cognitive delay (Ciesielski et al., 2012; Rodriguez-Barranco, 2014), altered immune response and inflammatory regulation(Zhang et al., 2020), altered renal function (Sanders et al., 2019), altered metabolic homeostasis(Pizzino et al., 2017).

Different Air Pollutants Concentration in Control and Exposed Areas

Heavy metals present in emissions generated by cement plants are vehiculated by particulate matter. Cement plants can increase atmospheric concentrations of particulate matter by both direct (Baroutian et al., 2006; Mohebbi and Baroutian 2007; Yatkin and Bayram 2010) and fugitive emissions from stocked materials (clinker and pet-coke materials) (Moreno 2009). Previous studies indicate these industrial facilities as a major source of PM_{10} in urban areas, being also responsible for the deterioration of air quality (Leone et al., 2016). This evidence is confirmed by results from the present study, which showed significantly increased air levels of PM_{10} in the exposed, as compared with the control area.

Previous authors found that the amount of particles emitted by a cement plant may be higher than levels recommended by WHO guidelines at a distance of about 600–1400 m from the plant stacks (Mohebbi and Baroutian 2007). In the present study, the distance from the cement plant and the two exposed schools is less than 1 km, and the annual average exposure to PM_{10} was above the limit set by World Health Organization (20 µg/m^3) (World Health Organization 2006) in all the examined areas. However, the highest annual mean PM_{10} level was present in the high exposure area, as compared with both control and intermediate exposure area.

In the exposed area, besides the possible health effects directly deriving by chronic bioaccumulation of heavy metals, the combined exposure to elevated PM_{10} and NO_2 air levels per se can be responsible for additional health risk. Children are particularly vulnerable to these pollutants, which can promote a number of health effects in the short term (i.e. asthma attacks and allergies Penard-Morand et al., 2010; Zhang, 2019c), and following chronic exposures (i.e., poorer performance in working memory, inhibitory control, behavioural regulation, and metacognition(Gui 2020a), reduced lung function(He et al., 2019; Oftedal et al., 2008; Xing, 2020), sleep disorders(Lawrence, 2018), altered lipid metabolism (Gui, 2020b; Kim et al., 2019)).

Limitations of the study

A limitation of the present study is the lack of evaluation of biological and epidemiological effects deriving from PM_{10} and NO_2 exposure, and from bioaccumulation of metals in enrolled children. These aspects should be investigated by future studies specifically designed to evaluate, in this geographical area, acute and chronic health effects possibly linked with a complex environmental exposure.

Inhalation of metals was the only exposure way considered in the present study. This can be identified as another limitation, since anthropogenic sources can contaminate vegetable-growing soils (Gan et al., 2018), water, and edible fish (Ramos-Miras et al., 2019), and the possible ingestion of contaminated food has not been comprehensively quantified in enrolled children. However, the consumption of locally grown vegetables has been considered as a possible confounder in the statistical analysis, and a significant role for this factor has been excluded. On the other hand, although not quantified, water composition and the average amount of fish consumption should be comparable in children living in the same city, with similar dietary habits. Furthermore, the cement plant was the only significant anthropogenic source of Hg in the explored area. Finally, it has been suggested that air concentration of metals can be considered a predictor of body metal levels, independently from other exposure variables (Hill et al., 2020). The separate role of different ways of exposure to environmental metals, however, should be better examined by further investigations.

Conclusions

The present study demonstrates, for the first time in pediatric age, a long-term body accumulation of toxic metals (i.e., Hg, Ni, Cd, As) in children living and attending school in an urban area with the maximal estimated ground concentration of PM_{10}, as calculated by a specific pollutant dispersion model. According to previous environmental and biomonitoring evidence, the distinct panel of metals chronically bioaccumulating in children is compatible with the emission pattern of metals generated by cement plants powered with fossil fuels and waste-derived fuels. The specific bioaccumulation pattern documented in the area mainly exposed to cement plant emissions is different from that found in children in the control area, which appears to be primarily related to vehicular traffic. Evidence from the present study also confirms the role of a cement plant located in a populated urban area as a significant contributor to urban PM_{10} pollution and, thus, to related health risk, in particular during childhood. Thus, the location of cement production plants in the context of an urban area seems particularly harmful, since the negative effects produced by the plant add up to those generated by other typical sources of urban pollution. Besides the previously documented health risk in adult age, the high vulnerability of children to this toxic and chronic exposure might generate significant consequences in the short and in the long term, and suggest the need of adequate primary prevention policies. Specific strategies, in particular, should be oriented to the relocation of cement production facilities away from urban centers, and to more strict regulations for the use of fossil fuels. Combustion of pet-coke and coal, in particular, should be discouraged, and more sustainable energy sources (i.e., natural gas, renewable energy sources, biomaterials) should be preferred. More strict regulation of fossil replacement with alternative fuels should also be useful, with limitation of waste-derived fuels containing a significant burden of heavy metals. Furthermore, in the case of cement plants located in urban areas at high population density, an implementation of health education programs at all scales (schools, mass media, political sectors) might be necessary to improve resilience in subjects at risk.

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Data Availability The data are not publicly available due to the presence of information that could compromise the privacy of research participants. Data are available after reasonable and motivated request to the corresponding author.

Declarations

Conflicts of interest The authors declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local, institutional research ethics committee (inter-provincial ethics committee, ASL FG/ASL BAT authorization n. 108/CE/2019).

Consent to Participate and to Publish Data All children were enrolled after parents signed written informed consent. Children also agreed to participate as volunteers. A consent to publish individual data after anonymization was also obtained by all participants.

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