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Exposure to ambient air pollution and risk of childhood cancers: A population-based study in Tehran, Iran

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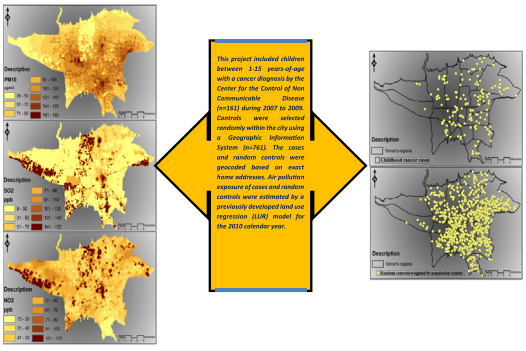
HIGHLIGHTS

- We observed a positive association between exposures to PM_{10} with childhood cancers.
- We did, however, observe a positive, but not statistically significant association between NO_2 exposure and childhood cancer.
- We did not find a positive association between exposures to SO_2 with childhood cancers.

GRAPHICAL ABSTRACT



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ABSTRACT

The relationship between air pollution and childhood cancer is inconclusive. We investigated the associations between exposure to ambient air pollution and childhood cancers in Tehran, Iran. This project included children between 1 and 15 years-of-age with a cancer diagnosis by the Center for the Control of Non Communicable Disease (n = 161) during 2007 to 2009. Controls were selected randomly within the city using a Geographic Information System (GIS) (n = 761). The cases were geocoded based on exact home addresses. Air pollution exposure of cases and random controls were estimated by a previously developed Land Use Regression (LUR) model for the 2010 calendar year. The annual mean concentrations of Particulate Matter ≤ 10 μm (PM_{10}), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) in the locations of cancer cases were 101.97 μg/m^3, 49.42 ppb and 38.92 ppb respectively, while in the random control group, respective mean exposures were 98.63 μg/m^3, 45.98 ppb and 38.95 ppb. A logistic regression model was used to find the probability of childhood cancer per unit increase in PM_{10}, NO_2 and SO_2. We observed a positive association between exposures to PM_{10} with childhood cancers. We did, however, observe a positive, but not statistically significant association between NO_2 exposure and childhood cancer. Our study is the first to highlight an association between air pollution exposure and childhood cancer risk in Iran, however these findings require replication through future studies.

1. Introduction

There is a growing body of literature describing the risks associated with proximity to urban air pollution (Brunekreef and Holgate, 2002;

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Raaschou-Nielsen and Reynolds, 2006; Forouzanfar et al., 2015). Air pollution exposure has been shown to have serious negative health consequences (Chen et al., 2016; Morawska et al., 1999). Cancer incidence and mortality rates in urban communities are far higher than in rural societies (Ziegler et al., 1993; Kunzli et al., 2000); with air pollution being recognized as one of the most important public health issues in an urban setting (Selden and Song, 1994).

Urban and industrial development and increasing economic activity tend to increase pollution levels in cities (Wheeler, 2001). In Tehran, as in many other industrial cities, the major sources of air pollutants include motor vehicles, industry and domestic sources (Asadollah-Fardi, 2008). Tehran acquires about 80–85% of its major air pollutants, which include PM_{10}, NO_2, SO_2, HC, O_3 and CO, from mobile sources (Naddafi et al., 2012).

A wide range of adverse health consequences due to short and long-term exposure to air pollutants have been recorded in urban populations throughout the world (Pope III and Dockery, 2006; Naddafi et al., 2012). Globally, cancer is one of the major causes of childhood death. Childhood cancer incidence rates among white children are 120–150 diagnoses per million boys and 110–140 per million girls annually within Europe, North and South America, Australia and New Zealand, all of which routinely register cancer cases (Parkin et al., 1988). In Iran, the third highest cause of deaths is cancer incidence, after coronary heart disease and accidents (Naghavi and Jafari, 2007). Cancer is responsible for 4% of the deaths in children under 5 years-of-age and 13% of deaths in children 5–15 years-of-age in the Iranian population; contributing to a total 15% of loss of life in the under 15-years-of-age population (Mosavi-Jarrahi et al., 2007). Some epidemiological studies have shown that an increase in childhood cancer risk is related to traffic exposure (Reynolds et al., 2002; Reynolds et al., 2004; Feychting et al., 1998; Raaschou-Nielsen et al., 2001; Elliott et al., 2017). Nevertheless, the evidence for an association between our air pollutants of interest and childhood cancer is weak; few positive findings were obtained in a small number of studies which featured small sample size, unreliable exposure assessment methods and other methodological limitations (Raaschou-Nielsen and Reynolds, 2006). The etiology of childhood cancers is to a great extent unknown, but a few risk factors have been confirmed, including environmental risk factors such as air pollution, traffic and electromagnetic radiation (Heck et al., 2013). It has been shown that environmental factors play an important causal role in childhood cancer, as cases of childhood cancer stemming from genetic alterations are responsible for only a small percentage of total cases (Parkin et al., 1988; Parsons et al., 2011). The aim of this study was to investigate the associations between exposure to ambient air pollution and childhood cancer incidence in Middle Eastern City of Tehran, Iran. Further research into and greater recognition of the effects of air pollutants in childhood cancer will help bring awareness to governments, medical professionals, and the public about the dangers of these pollutants to our health and economy.

2. Methods

2.1. Study area

This study was performed in Tehran, the capital of Iran. Tehran has a population of over 10 million (http://www.amar.org.ir, 2017). Tehran is located at the foot of the Alborz Mountains (Latitude: 35° North, Longitude: 51° East), south of the Caspian Sea. Tehran suffers from higher air pollution concentrations due to motorized traffic, industry and dust. There are many bus terminals within the city. There is also a wide range of heavy and light industries across the city, including production and manufacturing of inks, metals, machinery, roofing material, plastics, detergents and pharmaceuticals. Another source of air pollution is using natural gas for cooking and heating (Amini and Taghavi-Shahri, 2013). It is reported that childhood cancer in Tehran had a moderate incidence (176.3 cases/1,000,000 children under 15 years of age) (Mosavi-Jarrahi et al., 2007; Amini, 2014). However, more recent estimates of childhood cancer incidence are required.

2.2. Characterization of cases and random controls

Records of 64, 55 and 42 childhood cancer patients were obtained from the center for Non Communicable Disease (Ministry of Health and Medical Education) for years 2007, 2008 and 2009, respectively. All cancer cases were diagnosed during the years of 2007, 2008 and 2009, while our LUR model, based on air pollutant data from 2010, was used to estimate the exposure of patients. The limited number of cancer records available for 2007 did not permit a sufficiently powerful study size, so additional cancer cases were added from diagnoses in 2008 and 2009. These cases were geo-coded within the Tehran megacity by GIS based on their exact home addresses at diagnosis (Fig. 1). The postal code of each cancer patient was determined through the Bureau of Iran's Post Office. Each 10 digit postal code represented the exact cancer patient's place of living. Table 1 shows the age, gender and breakdown of cancer cases. We included cases that were of 1 to 15 years of age at cancer diagnosis, who permanently resided at their recorded addresses. We did not consider children <1 year of age in this study. The center for Non Communicable Disease has been recording each patient's residential situation (permanent and nonpermanent) and these details were used to geocode locations in our study. Given that people spend 90% or more of their time within indoor environments (Dockery and Spengler, 1981), we have assumed that our cases spend 90% of their time in their houses or schools. Because most children were enrolled in schools located close to their homes, their exposure to air pollutants was assumed to be the same during their journey to school and while at school. We did not have access to more information regarding

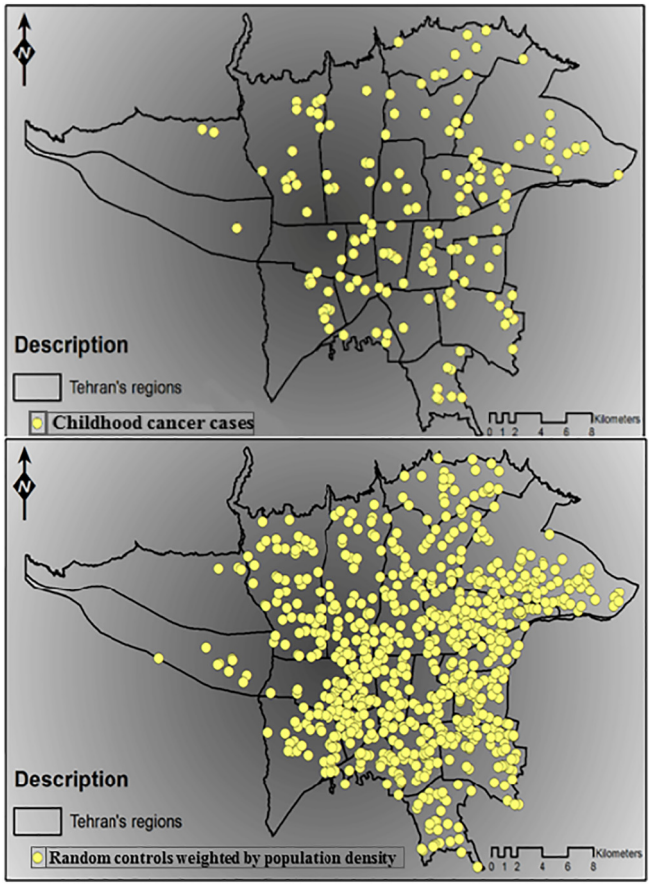

Fig. 1. Map illustrating the distribution of cancer cases and their random controls within the Tehran area.

Table 1
Characterization of cancer patient age, gender and cancer type.

Subjects	Variables	Mean ± SD
Leukemia (all types, n = 63)	Male	35
	Female	28
	Age (years)	8.19 ± 4.74
Sarcoma (all types, n = 39)	Male	20
	Female	19
	Age (years)	7.67 ± 4.22
Neuroblastoma (n = 25)	Male	14
	Female	11
	Age (years)	5.16 ± 4.65
Retinoblastoma (n = 16)	Male	7
	Female	9
	Age (years)	6.11 ± 4.32
Germ cell tumors (n = 10)	Male	5
	Female	5
	Age (years)	5.23 ± 4.71
Other cancers (n = 8)	Male	5
	Female	3
	Age (years)	6.11 ± 3.51

movement patterns of children, but assumed that based on our eligibility criteria, the mobility was minimal. Additionally, 761 random control points were selected by population density in each region, irrespective of exposure status, and then geo-coded within Tehran megacity by GIS (Fig. 1). It was not possible to use real non-cancer patient controls in this study, due to our limitation in having access to more information about cases, and controls. We therefore included around four-times the number of controls to every cancer case. The annual exposure of cases and random controls has been estimated by a previously developed LUR model for the 2010 calendar year. We used the annual average of each pollutant in each station to estimate the average concentrations in locations using the LUR model based on air pollutant data from 2010. According to Wang et al. (Wang et al., 2013) the results from the LUR model can be extrapolated to at least 7 years before and after the year of model construction provided there are no major changes in urban structure. Within Tehran, these large urban structural changes were not observed. Therefore it is likely that large fluctuations in the concentration of air pollutants over time were avoided.

2.3. Air pollution exposure assessment

Air pollution exposure of cases and random controls was estimated by a previously developed LUR model for the 2010 calendar year (Amini et al., 2014; Amini and Taghavi-Shahri, 2013). LUR is a geospatial technique that has been used to model within-city spatial and spatio-temporal variability for a variety of air pollutants (Hoek et al., 2008; Dons et al., 2014). Briefly, several sites measure pollutant concentrations around a city (Fig. 2).

The sites are specifically selected to adjust the spatial variability in pollutant concentrations (Gulliver et al., 2013; Amini et al., 2014; Lee et al., 2014). 210 potentially predictive variables in six classes and seventy-three sub-classes were generated within GIS and used as spatial predictors. The potentially predictive variables usually define site location, surrounding land use, traffic patterns, point sources, and population density. Multiple linear regression is used to associate the calculations with the most anticipating variables, and the resulting equation can be used to account for pollutant concentrations in each point. Physical and geographic characteristics that might be associated with the pollutant concentrations are then measured around each site using a GIS (Amini et al., 2014). A standard approach was expanded for the LUR model building and finally the resulting equation was used to estimate the outdoor pollutant concentrations at the residential address for cases and random controls within the city. These estimates aimed to reliably reflect the spatial distribution of pollution during the entire seven-year period, as has been reported elsewhere (Wang et al., 2013).

2.4. PM_{10}, NO_2 and SO_2 levels estimated by land use regression models

The concentrations of criteria air pollutants (PM_{10}, SO_2 and NO_2) are shown in Fig. 3. In some locations, emissions of these pollutants exceed the EPA and WHO standards (Schnelle and Brown, 2016) due to their proximity to industry, highways and city center traffic. The first map shows the concentration of PM_{10} (μg/m^3); the light yellow region corresponds the minimum concentration of PM_{10} (39–50 μg/m^3) with color darkening as concentration increases. It can be seen that the PM_{10} concentrations were as high as 180 μg/m^3 in the east, south, west of the city and within the city center; this concentration is much higher than the

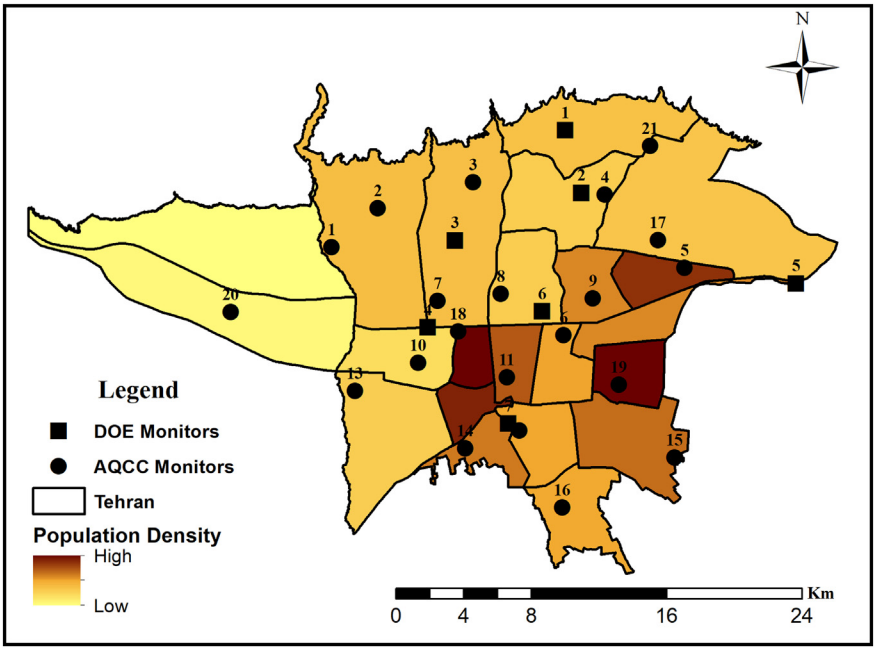

Fig. 2. Locations of Air Quality Control Company (AQCC) and the department of environment (DOE) air quality monitoring stations in 2010 in Tehran, Iran.

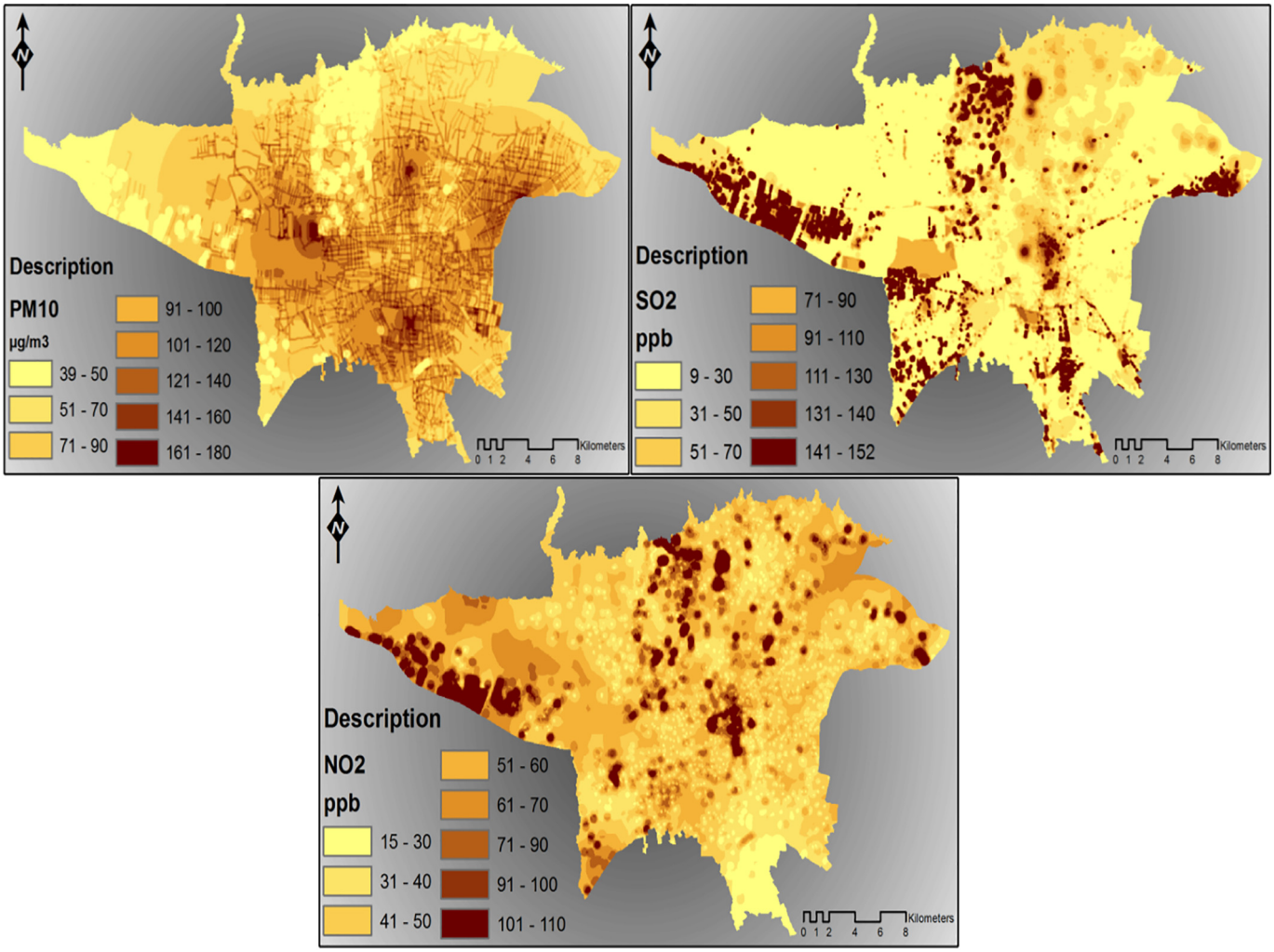

Fig. 3. Particulate matter ≤ 10 μm (PM_{10}), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) levels estimated by land use regression models.

EPA permissible limit. The minimum SO_2 concentration was 9–30 ppb in the west and north-west of the city map (Fig. 3). This may be due to a lack of heavy industry within the area. Other areas of Tehran demonstrate SO_2 concentrations generally higher than PM_{10} and NO_2. NO_2 concentrations were also lower than SO_2 (Fig. 3).

2.5. Data analysis

Collected data were analyzed by SPSS software version 20. One sample Kolmogorov-Smirnov tests were performed to determine the normality of data. Descriptive statistics were calculated and then the associations between childhood cancer and PM_{10} (μg/m^3), and NO_2 (ppb), SO_2 (ppb) concentration were assessed using the logistic regression model in 2010. Unadjusted Odds ratio (OR) with 95% confidence interval (CI) were reported.

3. Result

3.1. Exposure of cases and random controls

Table 2 gives information on the mean, standard deviation, maximum and minimum exposure to PM_{10}, SO_2 and NO_2 of cancer cases and random controls. It is clear that cancer patients' exposure to PM_{10} and NO_2 was higher than that of random controls, with 101.97 μg/m^3 and 49.21 ppb, respectively. Meanwhile, both of groups' exposure to SO_2 was at same level overall.

3.2. Unconditional logistic regression

Table 3 demonstrates the logistic regression results. In this study based on the data provided in Table 3, we observed a positive association between our childhood cancer cases and PM_{10} (OR = 1.008; 95% CI: 1.001, 1.015). Regarding SO_2 exposure, we found no association (OR = 1.000; 95% CI: 0.999, 1.001) between exposure to this pollutant and case control status. We did, however, observe a positive, but not statistically significant association between NO_2 exposure and childhood cancer.

4. Discussion

In this population-based study in the largest city of Iran we examined the associations between exposure to ambient air pollutants

Table 2
Air pollution (PM_{10}, NO_2 and SO_2) exposure in cancer cases and random controls.

	Groups					
	Cases			Random controls		
	Min	Mean ± SD	Max	Min	Mean ± SD	Max
PM_{10} (μg/m^3)	41.52	101.97 ± 25	142.7	39	98.63 ± 26.03	165.14
SO_2 (ppb)	9	38.92 ± 30.7	152	9	38.95 ± 38.86	152
NO_2 (ppb)	89.21	49.42 ± 15.34	155.5	18.05	45.98 ± 16.98	114

Table 3
ORs (95% CIs) for cancer risk for 1 unit increase in PM_{10}, SO_2 and NO_2.

Outcome	n cases	Controls	Average PM_{10}, SO_2 and NO_2 exposure after cancer diagnosis		
			PM_{10} model	SO_2 model	NO_2 model
All cancer types	161	761	1. 008 (1.001, 1.015)	1.00 (0.999, 1.001)	1.05 (0.989, 1.013)

(PM_{10}, SO_2 and NO_2) and childhood cancers. Our results showed that there is significant association between PM_{10} and childhood cancer incidence overall.

Some earlier studies relied on traffic exposure during the childhood period, but excluded the prenatal period (Boothe et al., 2014; Sun et al., 2014). More recent projects have considered prenatal or early life exposure to specific pollutants in association with childhood cancers (Heck et al., 2014; von Ehrenstein et al., 2016). Boothe et al. conduced that childhood leukemia was associated with residential traffic exposure during childhood, but not during the prenatal period (Boothe et al., 2014). While Julia E. Heck et al. found weak associations between Pregnancy and early life exposure to traffic pollution and several childhood cancers (Heck et al., 2013). We hypothesize that it is meaningful to consider the importance of later childhood exposures for cancer risk in comparison to exposures occurring during pregnancy or very early life, however it is not known which are more relevant for cancer risk.

The most prevalent childhood cancer types in Tehran are leukemia, Lymphoma and CNS tumors, respectively and the ratio of Childhood Cancer to All Cancer (%) in Tehran is higher than other regions in Iran (Mousavi et al., 2010). Acute lymphoblastic leukemia (ALL) is the most frequently diagnosed cancer among children and a large number of studies have investigated the association between air pollution and the risk of its development among children (Sun et al., 2014). However, little is known about other rarer cancer types (Gruzieva et al., 2017). The major cancer types considered in our study were leukemia and Sarcoma (all types), neuroblastoma, retinoblastoma and germ cell tumors but it is not possible to attribute significant associations to specific cancer types. Compare to other studies neuroblastoma and retinoblastoma have a higher average age. This is because we excluded cases diagnosed <1 year of age and also cases who are not permanently resided at the location of their addresses. This exclusion gives us more unusual sample of neuroblastoma and retinoblastoma cases.

PM_{10} shows the strongest association with childhood cancer incidence compared to NO_2 and SO_2. Children who lived in the group of municipalities characterized by the highest levels of PM_{10} had a significantly higher risk of childhood cancer than the group that lived in municipalities with the lowest PM_{10} levels. Few studies have tested this association using estimated PM_{10} exposure. The Research by Lacasaña and et al. (Lacasana et al., 2005) indicated that the greater the increase in PM_{10}, the higher the risk of childhood cancer. Furthermore, they found that an increase of 10 $\mu g/m^3$ in PM_{10} lead to an approximate 5% increase in mortality among children. In a study conducted in Italy, Marco Vinceti reported that exposure to PM_{10} appeared to be independently associated with an increase in leukemia risk (Vinceti et al., 2012). Exposure to PM stimulates an immune response with increasing TLR (toll-like receptor) and RAGE (advanced glycation end-products) reception (Shoenfelt et al., 2009; Reynolds et al., 2011). These signalling routes have been demonstrated to significantly impact tumor growth and metastasis (Heck et al., 2013).

We also demonstrated that another pollutant factor, NO_2, exhibited a weak positive association with childhood cancer. In Sweden, NO_2 levels were shown to be higher than 80 $\mu g/m^3$ in the environment surrounding family homes based on the modeling of NO_2 emissions from motor vehicles. Here they reported a total childhood cancer odds ratio of 3.8 (95% CI 1.2–12.1) (Feychting et al., 1998). Another study confirmed that in Great Britain exposure to PM_{10}, VOCs, NO_2, benzene, dioxins, 1,3-butadiene, and benz(*a*)pyrene increased the risk of childhood cancer (Knox, 2005). In France, Amigou et al. demonstrated an odds ratio of 1.20 (95% CI: 0.96–1.47) when evaluating the association between modeled exposure to NO_2 during childhood and risk of ALL up to age 14 (Amigou et al., 2011). A study performed in California by Ghosh et al. reported an odds ratio of 1.23 (95% CI: 0.98–1.53) per 25 ppb rise in exposure to NO_2 during the pregnancy on the risk of ALL before 6 years of age (Ghosh et al., 2013). An association between NO_2 and childhood ALL is biologically applicable (Folinsbee, 1993; Cancer, 2015). DNA breakage in cultured cells as well as in alveolar macrophages has been found following controlled exposure to NO_2 (Görsdorf et al., 1990).

Based on our observation, SO_2 exposure was similar between childhood cancer cases and random controls during the entire period of interest. However, our study is the first study to consider SO_2 as a risk factor for childhood cancer. Further studies will be needed to confirm the effect of this pollutant.

Using LUR to model PM_{10}, SO_2 and NO_2 allows for extrapolation to at least 7 years before and after the year of model construction provided that there are no large changes in urban structure (Wang et al., 2013) however we wish to acknowledge some limitations of this study. Firstly, we did not have access to information about certain potential confounding influences. For example, we did not have access to the lifestyle and exposures to other risk factors experienced by cases and controls. Such information might provide interesting insights if factored into our model. Nor can we exclude the possibility that the observed relationship between childhood cancers and PM is due to exposure to other air pollutants such as BTEX (benzene, toluene, ethylbenzene and xylene) which can be highly correlated with PM. This possibility exists due to the common source of these air pollutants, however the importance of our results for policy makers remains. Another limitation is related to the fact that due to limited access to the type of patient data that would give a meaningful sample size for individual childhood cancer types, we had to evaluate the associations between overall childhood cancer (irrespective of cancer site/type) with concentration of PM_{10}, NO_2 and SO_2.

5. Conclusion

This is the first study to evaluate associations between exposure to air pollutants and the risk of childhood cancer in Iran. Our results provide evidence that the levels of air pollution and childhood cancer increase with increasing proximity to industrial areas, highways and city traffic. The exposure of 161 childhood cancer cases to criteria pollutants (PM_{10} and NO_2) was higher than that of random controls. According to our logistic regression data there were positive associations between total childhood cancer and increasing PM_{10}. Many childhood cancer risk factors are linked to environmental factors, but few studies have reported that higher exposure to air pollutants plays an important role in the increased incidence of childhood cancer. We suggest that these findings warrant replication in future studies.

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