





BMJ Open Multiple air pollutants exposure and leukaemia incidence in Tehran, Iran from 2010 to 2016: a retrospective cohort study

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ABSTRACT

Objective Leukaemia is one of the most common cancers and may be associated with exposure to environmental carcinogens, especially outdoor air pollutants. The objective of this study was to investigate the association of ambient air pollution and leukaemia in Tehran, Iran.

Design In this retrospective cohort study, data about the residential district of leukaemia cases diagnosed from 2010 to 2016 were inquired from the Ministry of Health cancer database. Data from a previous study were used to determine long-term average exposure to different air pollutants in 22 districts of Tehran. Latent profile analysis (LPA) was used to classify pollutants in two exposure profiles. The association between air pollutants and leukaemia incidence was analysed by negative binomial regression.

Setting Twenty-two districts of Tehran megacity.

Participants Patients with leukaemia.

Outcome measures The outcome variables were incidence rate ratios (IRR) of acute myeloid and lymphoid leukaemia across the districts of Tehran.

Results The districts with higher concentrations for all pollutants were near the city centre. The IRR was positive but non-significant for most of the air pollutants. However, annual mean NO_x was directly and significantly associated with total leukaemia incidence in the fully adjusted model (IRR (95% CI): 1.03 (1.003 to 1.06) per 10 ppb increase). Based on LPA, districts with a higher multiple air-pollutants profile were also associated with higher leukaemia incidence (IRR (95% CI): 1.003 (0.99 to 1.007) per 1 ppb increase).

Conclusions Our study shows that districts with higher air pollution (nitrogen oxides and multipollutants) have higher incidence rates of leukaemia in Tehran, Iran. This study warrants conducting further research with individual human data and better control of confounding.

BACKGROUND

Leukaemia is one of the most common haematological malignancies among adults and children.¹ In 2020, leukaemia was among the 15 more common cancers worldwide and

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first study for estimating the simultaneous effect of single and multiple ambient air pollutants on the incidence of leukaemia in Iran.
- ⇒ We included potential confounding covariates at area level based on administrative survey data.
- ⇒ However, control for confounding variables was not done at the individual level.
- ⇒ We were not able to adjust for human relocation or migration.

contributed to 2.5% of all new cases of cancer and 3.1% of all cancer death. Worldwide, the age standardised incidence and mortality rates of leukaemia are 6.3 per 100 000 and 4.0 per 100 000 for men and 4.5 per 100 000 and 2.7 per 100 000 in women, respectively. In countries with low and medium human development index, the age-standardised incidence and mortality rates of leukaemia are, respectively, 3.8 per 100 000 and 3.0 per 100 000 for men, and 2.9 per 100 000 and 2.0 per 100 000 for women.² In Iran where cancer is the third leading cause of death after cardiovascular disease mortality and traffic accidents, leukaemia is the sixth most common cancer in men with age standardised rates of 8.32 per 100 000, and the fifth in women with age-standardised rates of 5.40 per 100 000.³

Outdoor air pollution may have serious adverse effects on human health, including cancer.⁴ It has been proven that some environmental factors including ambient air pollution are carcinogenic to humans.⁵

The aetiology of leukaemia remains mostly unknown. Some studies have reported that adverse gene-environment interactions may lead to leukaemia.¹ A recent meta-analysis on the association between outdoor air

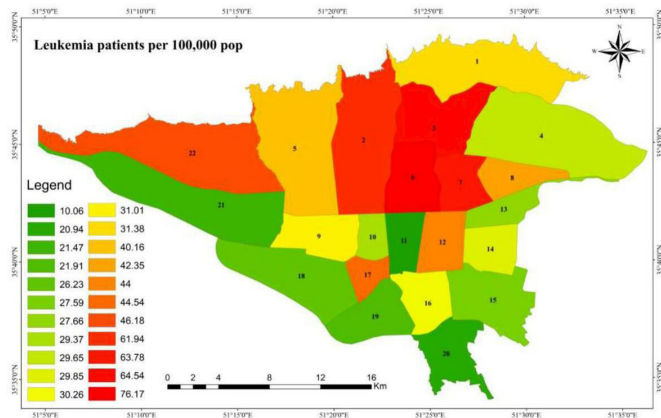


Figure 1 Spatial distribution of patients with leukaemia (number of cases in 100 000) in different areas of Tehran in 2014–2016 (the labels on the map are district numbers).

pollution and childhood leukaemia showed a positive linear association between benzene exposure and risk of childhood leukaemia, particularly for acute myeloid leukaemia (AML), among children under 6 years of age, and nitrogen dioxide at high levels was associated with leukaemia.⁶

In the current study, we aimed to examine the association between estimates of district level averages of multiple ambient air pollutants and acute leukaemia incidence across Tehran districts using LPA method. LPA is a robust technique, mainly used to identify subtypes of homogeneous latent classes or subgroups within a large heterogeneous group. This iterative process clusters similar profiles together to generate distinct subgroups/classes.⁷

METHODOLOGY

Research location

The present retrospective cohort study was carried out based on annual mean air pollution levels in 22 districts of Tehran megacity, which is the capital of Iran. According to the World Population Review report, Tehran's 2021 population was estimated to be 9.2 million inhabitants. Tehran includes 22 districts in which each include from 174 239

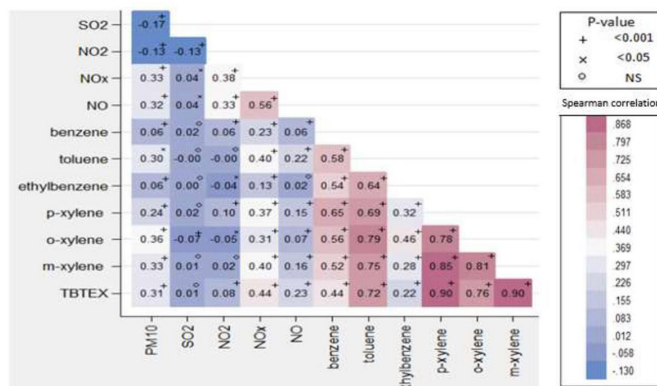


Figure 2 Spearman correlation matrix of air pollutants in the 22 districts of Tehran, Iran, in 2014–2016.

Table 1 Description of characteristics of patients, air pollution and district-level covariates

Individual-level variables	
Number of patients with leukaemia patients	3237
Age of patients (year)	
Median (1st–3rd quartile range)	55 (16–69.1)
Gender of patients (male)	
Per cent (number)	59.7 (1934)
Grading	
I	4.8 (156)
II	33.2 (1076)
III	2.8 (90)
IV	1 (32)
Unknown	58.2 (1883)
Topography	
Lymphoid	68.9 (2231)
Myeloid	31.1 (1006)
Air pollutants	Median (1st–3rd quartile range)
PM ₁₀ (µg/m ³)	101.32 (82.35–123.82)
SO ₂ (ppb)	52.42 (26.38–77.19)
NO ₂ (ppb)	46.43 (39.95–55.74)
NO (ppb)	78.13 (44.47–118.84)
NO _x (ppb)	112.12 (83.24–158.49)
Benzene (µg/m ³)	8.12 (7.02–9.85)
Toluene (µg/m ³)	24.96 (20.85–29.45)
Ethylbenzene (µg/m ³)	5.90 (4.97–6.94)
p-xylene (µg/m ³)	5.71 (4.88–6.52)
o-xylene (µg/m ³)	5.84 (4.86–7.46)
m-xylene (µg/m ³)	10.71 (9.06–12.81)
TBTEX (µg/m ³)	60.57 (52.29–70.15)
District-level variables	Median (1st–3rd quartile range)
Number of districts	22
Total population (persons)	319 443 (263 536–421 225)
Urban green space, per capita (m ² per 1000 people)	13.9 (10.7–18)
Life expectancy (year)	75.9 (75.4–76.7)
Socioeconomic status *	49.95 (44.21–53.34)

*Socioeconomic status score according to the 16 variables mentioned in the Method section. This variable does not have a unit. The lowest value of this score was 36.6 and the highest was 67.4.

to 9 19 001 residents according to the latest 2016 census.⁸ Population density is higher in the central, western and southern regions.⁹ Tehran suffers from severe ambient air pollution as documented by numerous studies.^{9–12} The central districts with higher population densities (five districts of 2, 6, 10, 11 and 12 in central Tehran) have more air pollution.⁹

Table 2 Fit indices for different latent profile models with number of profiles ranging from 2 to 5

Profile	Log-likelihood	AIC	BIC	a-BIC	LMR-LRT	VLMR-LRT	Entropy
2 profile	-35505.2	71 084.5	71 309.6	71 192	13 725.8*	13 856.4*	0.908
3 profile	-31630.4	63 360.8	63 665	63 506.1	7676.6	7749.6	0.941
4 profile	-29593.4	59 312.9	59 696.1	59 495.9	4035.5	4073.9	0.951
5 profile	-27590.1	55 332.2	55 794.5	55 553	3968.9	4006.7	0.968

*P<0.001.

Models with a significant Lo-Mendell-Rubin likelihood ratio test and Vuong-Lo-Mendell-Rubin likelihood ratio test were preferred. The bolded fit indices indicate that profile 2 was the optimal latent profile model.

a-BIC, sample size adjusted BIC; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LMR-LRT, Lo-Mendell-Rubin likelihood ratio test; VLMR-LRT, Vuong-Lo-Mendell-Rubin likelihood ratio test.

Data sources

Leukaemia data

Information about patients with leukaemia (acute lymphoblastic leukaemia (ALL) and AML) residing in Tehran, diagnosed between 2010 and 2016 and their residential address (on a district basis) were obtained from the Ministry of Health's Cancer Registry.

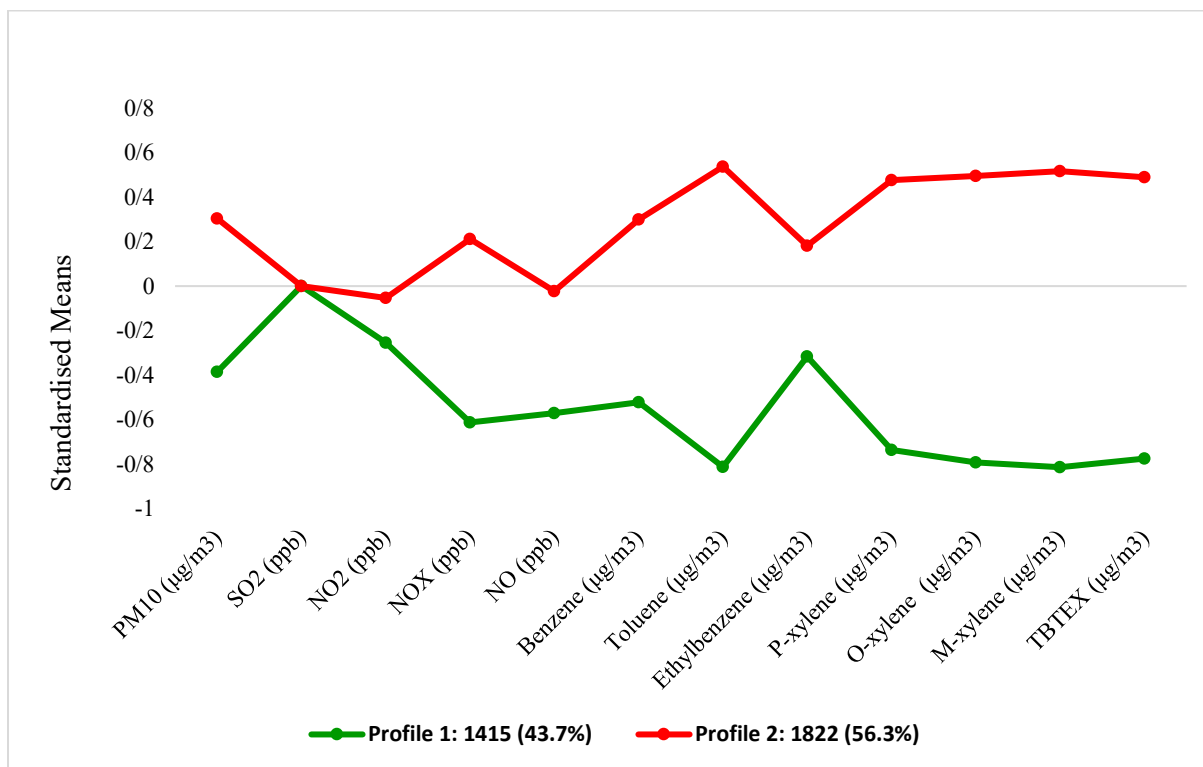
Exposure assessment

The annual mean concentrations of several pollutants in the 22 districts of Tehran were obtained from land use regression models developed in previous studies, for PM₁₀, SO₂, NO, NO₂ and NO_x in Tehran, which were based on measurements conducted at 23 regulatory network monitoring sites in 2010.^{10 11} Data about volatile

organic compounds (VOCs) were taken from a previous study.¹² The average of sampling site estimates for each pollutant, in each district was determined and included in the analyses of this study.

Covariates

District level data including urban green space per capita, life expectancy and socioeconomic status were extracted from the Urban Health Equity Assessment and Response Tool (Urban HEART-2), which has been conducted in the 22 districts of Tehran. A detailed description of the Urban HEART-2 study can be found elsewhere.¹³ The socioeconomic indicators of the 22 districts of Tehran was extracted from a study conducted by Sadeghi *et al.*¹⁴


Figure 3 Standard mean values of pollutants in the two latent profiles in different areas of Tehran, Iran, in 2014–2016.

**Table 3** The mean of air pollutants in different profiles

Pollutant	Profile	Mean	SD	T	P value
PM10 ($\mu\text{g}/\text{m}^3$)	Profile 1	87.2	38.3	-21.6	<0.001
	Profile 2	114.2	31.1		
SO ₂ (ppb)	Profile 1	54.8	45.7	-0.32	0.74
	Profile 2	55.3	53.7		
NO ₂ (ppb)	Profile 1	48.4	18.2	-3.84	<0.001
	Profile 2	50.7	15.7		
NO (ppb)	Profile 1	68.9	51.6	-19.8	<0.001
	Profile 2	108.9	63.5		
NO _x (ppb)	Profile 1	91.6	38.8	-33.55	<0.001
	Profile 2	163.8	80.7		
Benzene ($\mu\text{g}/\text{m}^3$)	Profile 1	8.9	3.2	-26.3	<0.001
	Profile 2	10.1	3.6		
Toluene ($\mu\text{g}/\text{m}^3$)	Profile 1	19.6	3.5	-56.9	<0.001
	Profile 2	30.2	6.8		
Ethylbenzene ($\mu\text{g}/\text{m}^3$)	Profile 1	4.7	1.1	-17.4	<0.001
	Profile 2	7.3	6.1		
p-xylene ($\mu\text{g}/\text{m}^3$)	Profile 1	4.7	0.6	-49.9	<0.001
	Profile 2	6.7	1.5		
o-xylene ($\mu\text{g}/\text{m}^3$)	Profile 1	4.8	0.8	-53.8	<0.001
	Profile 2	7.4	1.7		
m-xylene ($\mu\text{g}/\text{m}^3$)	Profile 1	8.6	1.5	-57.1	<0.001
	Profile 2	13.2	2.9		
TBTEX ($\mu\text{g}/\text{m}^3$)	Profile 1	49.5	7.8	-53.1	<0.001
	Profile 2	72.9	16.5		

Statistical analyses

This study used LPA to investigate the patterns of multiple air pollutants exposure. LPA is a statistical method to identify unobserved subgroups (profile) within populations based on observed variables. LPA has several advantages over traditional methods, such as cluster analysis, for example, it does not require researchers to specify the number of profiles in advance, which is more suitable for addressing research questions that are exploratory in nature. Moreover, unlike cluster analysis that assigns individuals to clusters absolutely, LPA assigns individuals to subgroups probabilistically.¹⁵

LPA as a person-centred approach can be used to examine the patterns of multiple air pollutants. LPA is a statistical method for identifying unobserved subgroups within populations based on observed indicators. In contrast to traditional methods, such as cluster analysis, LPA has several advantages. LPA does not require researchers to determine the number of profiles beforehand, and this is more suitable to answer research questions that are exploratory in nature. Also, empirical indicators are available to determine the optimal number of profiles. In addition, LPA allocates individuals to subgroups probabilistically, taking into account the rate of classification uncertainty, and uses multiple statistical indices for determining the optimal number of subgroups.

Most air pollutants in this study had a skewed distribution and were transformed by natural logarithm before LPA, except PM₁₀ and SO₂. Several latent profile models were performed, ranging from two to five latent profiles. The most appropriate number of subgroups was identified based on statistical criteria and profile interpretability. The statistical criteria included the Akaike's Information Criterion (AIC), the Bayesian Information Criterion (BIC) and the sample-size adjusted Bayesian information criterion (a-BIC), the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) and the Vuong-Lo-Mendell-Rubin likelihood ratio tests (VLMR-LRT). Smaller values of the AIC, BIC and aBIC indicate a better fit model.¹⁶

A significant p value of the LMR LRT and VLMR LRT (ie, $p < 0.05$) indicates a significant improvement in model fit in the k-class model compared with the (k - 1)-class model and thus rejects the (k - 1)-class model and suggests choosing a model with k classes.

In other words, each number of classes (or profiles, shown as k) is compared with the number of classes which is 1 unit less (k - 1), and if the VLRT and LMRT values are not significant for higher classes, the model with less classes (k - 1) is preferred and will get chosen.¹⁷

Data preparation was done in Stata V.14. LPA was conducted using Mplus V.7.4. One-way analysis of variance and posthoc follow-up tests were used to investigate the differences between profiles of multiple pollutions in

terms of each component of air pollution. Management of missing data and other statistical preparation details have been mentioned in our previous publication.⁸

Kolmogorov-Smirnov test was used to test the normality of the pollutants data and because the data were not normally distributed, Spearman's correlation test was used to estimate the correlation between pollutants. As the number of leukaemia cases was overdispersed, negative binomial (NB) regression was performed to estimate the incidence rate ratios (IRR) and their 95% CI for each air pollutant and multiple pollution profiles, adjusted for age, sex and district level (by using them as a covariate). Statistical analyses were performed using Mplus V.7.4 and Stata V.14 (Stata; College Station, Texas, USA). ArcGIS V.10.8 was used for exposure assignment to districts and data visualisation.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

RESULTS

Summary statistics of patients, air pollutants and information about the area under study are shown in table 1. The total number of leukaemia cases in 2010–2016 in all districts of Tehran was 3237. The distribution of patients with leukaemia in different districts of Tehran is shown in figure 1. The highest numbers of patients with leukaemia per 100 000 people were in districts 6, 3, 7 and 2, respectively (figure 1).

As shown in figure 2, there was a strong correlation between pollutants, most notably for VOCs (benzene, toluene, m-xylene, p-xylene, o-xylene and TBTEX) ($p < 0.001$). The positive correlation between NO and NO_x was weaker ($r = 0.56$).

Fit indices for the different LPA models are displayed in table 2. Several latent profile models were considered. Although the AIC, BIC and a-BIC of the two-profile were more than other models, the LMR of LRT (Lo-Mendell-Rubin likelihood ratio test) and VLMR (Vuong-Lo-Mendell-Rubin likelihood ratio test) were significant in the two-profile model.

Figure 3 shows the multipollution profiles. Profile 1 had the lowest scores for all pollutants including (PM₁₀, SO₂, NO, NO₂, NO_x, benzene, toluene, ethylbenzene, m-xylene, p-xylene, o-xylene and TBTEX). We labelled this profile as 'low multiple-pollution'. Summary statistics for each pollutant in different profiles are shown in table 3. There was a significant difference between the means of all pollutants in the two profiles, except for SO₂.

Table 4 shows the IRR estimates and 95% CI by single-pollutant and multiple-pollutant multivariable NB regression models, adjusted for age, gender, socioeconomic status and life expectancy.

In single-pollutant models, NO₂ and NO_x were significantly associated with increased leukaemia incidence in model 1 (adjusted for age and gender) and also in

model 2 (adjusted in addition for urban green space per capita) with IRR (95% CI) of model 2, respectively, 1.35 (1.11–1.64) and 1.07 (1.03–1.11) per 10 ppb increase in pollutants. In model 3, after adjustment for age, gender, socioeconomic status and life expectancy, only NO_x was significantly associated with increased leukaemia incidence with an IRR (95% CI) of 1.03 (1.003–1.06) per 10 ppb increase in NO_x. However, NO₂ was borderline significantly associated with increased leukaemia incidence (IRR=1.19, CI 95%=0.99–1.43) in this model.

In multipollutant models, the high multiple-air-pollutants profile was associated with higher leukaemia incidence when compared with the low multiple-air-pollutants profile, but this association did not reach significance.

Tables 5 and 6 show the IRR (95% CI) estimates by single-pollutant and multiple-pollutant multivariable NB regression models for acute myeloid and lymphoid leukaemia incidence, respectively. NO, NO₂ and NO_x were related to acute increased lymphoid leukaemia incidence, while NO₂ and TBTEX were related to increased AML incidence.

Tables 7 and 8 show the IRR (95% CI) estimates by single-pollutant and multiple-pollutant multivariable NB regression models for total acute leukaemia incidence, respectively, in children and adults. Increase in all single pollutants except SO₂ and high multiple pollutants were related to increased acute leukaemia incidence in children (≤ 14 years old), while nitrogen oxides, toluene, ethylbenzene, o-xylene and TBTEX were related to increased acute leukaemia incidence among adults.

DISCUSSION

The findings of our study show that exposure to air pollutants, such as nitrogen oxides and VOCs, may be associated with the incidence of leukaemia. Our study was the first to investigate the effect of single and multiple ambient air pollutants on leukaemia in Iran.

Leukaemia is one of the most common cancers in children and adults. The cause of leukaemia is currently unknown.¹⁸ However, some sources have suggested that genetic and transgenic mutations due to environmental factors may contribute to leukaemia.^{1 19} A study in Shanghai, China showed that air pollution from industrial waste gas emissions was associated with the incidence of several cancers including leukaemia.²⁰

Many experimental studies have shown that air pollutants may be carcinogenic by causing DNA damage and mutations.^{21–26}

A review indicated that exposure to air pollutants is associated with leukaemia stronger than other cancers.¹⁸ Carlos-Wallace *et al* also conducted a meta-analysis and reported associations between childhood leukaemia and benzene exposure. They indicated that in studies that evaluated benzene versus all solvents, the pooled RR (relative risk from meta-analysis) was higher for maternal exposure compared with paternal exposure. For NO₂,

Table 4 The estimated incidence rate ratios using negative binomial regression analyses for the effect of each 10 unit increase in air pollutants on total leukaemia incidence across the districts of Tehran

Pollutant	Model 1		Model 2		Model 3	
	IRR (95% CI)	P value	IRR (95% CI)	P-value	IRR (95% CI)	P value
<i>Single-pollutant</i>						
Annual PM ₁₀ (µg/m ³)	0.95 (0.87 to 1.05)	0.352	0.92 (0.82 to 1.03)	0.165	1.03 (0.95 to 1.12)	0.376
Annual SO ₂ (ppb)	0.99 (0.89 to 1.09)	0.901	0.99 (0.98 to 1.01)	0.775	0.97 (0.91 to 1.05)	0.575
Annual NO ₂ (ppb)	1.35 (1.11 to 1.64)	0.002	1.35 (1.11 to 1.64)	0.002	1.19 (0.99 to 1.43)	0.062
Annual NO (ppb)	1.02 (0.98 to 1.07)	0.238	1.03 (0.97 to 1.08)	0.235	1.02 (0.99 to 1.06)	0.130
Annual NO _x (ppb)	1.04 (1.01 to 1.08)	0.003	1.07 (1.03 to 1.11)	<0.001	1.03 (1.003 to 1.06)	0.029
Benzene (µg/m ³)	0.97 (0.85 to 1.11)	0.696	0.97 (0.85 to 1.11)	0.965	0.92 (0.83 to 1.02)	0.119
Toluene (µg/m ³)	1.11 (0.78 to 1.56)	0.550	1.14 (0.71 to 1.85)	0.570	1.11 (0.85 to 1.44)	0.436
Ethylbenzene (µg/m ³)	1.08 (0.27 to 4.28)	0.906	0.97 (0.19 to 4.91)	0.974	1.09 (0.38 to 3.16)	0.865
p-xylene (µg/m ³)	1.23 (0.14 to 10.23)	0.844	1.002 (0.04 to 22.77)	0.999	1.24 (0.23 to 6.42)	0.797
o-xylene (µg/m ³)	0.48 (0.09 to 2.57)	0.397	0.29 (0.04 to 2.03)	0.214	0.77 (0.21 to 2.84)	0.705
m-xylene (µg/m ³)	1.14 (0.48 to 2.72)	0.760	1.11 (0.28 to 4.36)	0.876	1.20 (0.61 to 2.34)	0.589
TBTEX (µg/m ³)	1.04 (0.89 to 1.23)	0.561	1.07 (0.84 to 1.36)	0.575	1.03 (0.91 to 1.17)	0.564
<i>Multipollutant</i>						
Profile 1 (low pollution)	Ref		Ref		Ref	
Profile 2 (high pollution)	1.003 (0.99 to 1.009)	0.227	1.005 (0.99 to 1.01)	0.168	1.003 (0.99 to 1.007)	0.168

Model 1: Adjusted for age and gender.

Model 2: Adjusted for age, gender and urban green space per capita (m² per 1000 people).

Model 3: Adjusted for age, gender, socioeconomic status, life expectancy.

The incidence rate ratio of leukaemia is estimated for each 10 unit increase in pollutants.

Statistically significant IRRs are bolded.

IRR, incidence rate ratio.

an excess risk was reported in concentration-response meta-analysis from 40 µg/m³ to 60 µg/m³; however, the increase was not statistically significant and was mainly related to ALL.⁶

Our study showed some associations between benzene and leukaemia incidence among children. Similarly, a study in the UK revealed that there was an increased risk of leukaemia from low-level exposure to benzene from smoking and that benzene may contribute to up to a third of smoking-induced leukaemia. The contribution of benzene to smoking-induced leukaemia was estimated to be between 9% and 24%. For AML, this contribution was estimated as 11%–30%.²⁷ Janitz *et al* conducted a case-control study between 1997 and 2012 including 307 patients with acute leukaemia from the Oklahoma Central Cancer Registry and 1013 controls matched on week of birth from birth certificates and showed no association between benzene and childhood leukaemia, in Oklahoma. However, based on the analysis of quartiles, they indicated that there was a positive concentration-response relation between benzene and AML.²⁸

Our study indicated that NO₂ increased the incidence of acute lymphoid leukaemia, and total leukaemia among children and adults. Similarly, findings of the population-based study by Ribeiro *et al* in São Paulo, Brazil has shown

that NO₂ and traffic density were associated with Hodgkin lymphoma and lymphoid leukaemia in children; and the variations in the IRR in gender and SES groups may be because of differences in underlying risk and exposure profiles.²⁹ In addition, Raaschou-Nielsen *et al* conducted a nationwide case-control study in Denmark and indicated that long-term exposure to traffic-related air pollutants (NO_x and NO₂) was associated with AML, but not other subtypes of leukaemia, in the general population.³⁰ Our study revealed that NO, NO₂ and NO_x are related to increased acute lymphoid leukaemia incidence, while NO₂ and TBTEX are related to increased AML incidence, while a Canadian population-based case-control study revealed a weak association between all forms of leukaemia only at low concentrations of NO₂. The study showed an ‘n-shaped’ response function between exposure to NO₂ and all forms of leukaemia. The OR was 1.20 (95% CI 0.97 to 1.48) from the 10th percentile (4.51 ppb) to the median (14.66 ppb), then the OR decreased to 0.79 (95% CI 0.68, 0.93) from the 75th percentile (22.75) to the 90th (29.7 ppb) range.³¹ Some differences in results may be attributable to differences in settings and population characteristics.

In a large nationwide population-based case-control study in Denmark, Taj *et al* showed a high risk for overall

Table 5 The estimated incidence rate ratios using negative binomial regression analyses for the effect of each 10 unit increase in air pollutants on acute myeloid leukaemia incidence in the districts of Tehran

Pollutant	Model 1		Model 2		Model 3	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
<i>Single-pollutant</i>						
Annual PM10 (µg/m ³)	0.97 (0.88 to 1.06)	0.547	0.94 (0.82 to 1.08)	0.542	1.01 (0.89 to 1.14)	0.846
Annual SO ₂ (ppb)	1.004 (0.88 to 1.13)	0.949	1.008 (0.88 to 1.15)	0.904	1.01 (0.91 to 1.11)	0.814
Annual NO ₂ (ppb)	1.35 (1.11 to 1.63)	0.002	1.35 (1.11 to 1.63)	0.002	1.22 (0.98 to 1.52)	0.068
Annual NO (ppb)	1.02 (0.98 to 1.07)	0.260	1.03 (0.98 to 1.09)	0.172	0.99 (0.94 to 1.05)	0.966
Annual NO _x (ppb)	0.96 (0.93 to 1.001)	0.057	0.95 (0.92 to 0.99)	0.035	0.97 (0.939 to 1.01)	0.240
Benzene (µg/m ³)	1.71 (0.44 to 6.66)	0.436	4.93 (0.60 to 40.17)	0.136	1.46 (0.38 to 5.47)	0.574
Toluene (µg/m ³)	1.19 (0.83 to 1.71)	0.334	1.71 (0.97 to 3.02)	0.061	1.23 (0.85 to 1.77)	0.254
Ethylbenzene (µg/m ³)	1.52 (0.27 to 8.53)	0.634	4.59 (0.25 to 82.81)	0.301	1.68 (0.31 to 9.03)	0.545
p-xylene (µg/m ³)	1.08 (0.87 to 1.35)	0.454	23.75 (0.55 to 102.3)	0.099	1.78 (0.18 to 17.66)	0.620
o-xylene (µg/m ³)	0.81 (0.15 to 4.31)	0.804	0.77 (0.06 to 8.66)	0.837	0.71 (0.13 to 3.87)	0.701
m-xylene (µg/m ³)	1.63 (0.61 to 4.31)	0.324	3.03 (0.78 to 11.69)	0.107	1.83 (0.74 to 4.52)	0.190
TBTEX (µg/m ³)	1.11 (0.92 to 1.31)	0.255	1.41 (1.07 to 1.85)	0.014	1.09 (0.91 to 1.32)	0.314
<i>Multipollutant</i>						
Profile 1 (low pollution)	Ref		Ref		Ref	
Profile 2 (high pollution)	1.003 (0.99 to 1.01)	0.265	1.003 (0.99 to 1.01)	0.259	1.004 (0.99 to 1.01)	0.113

Model 1: Adjusted for age and gender.
 Model 2: Adjusted for age, gender and urban green space per capita (m² per 1000 people).
 Model 3: Adjusted for age, gender, socioeconomic status, life expectancy.
 The incidence rate ratio of leukaemia is estimated for each 10 unit increase in pollutants.
 Statistically significant IRRs are bolded.
 IRR, incidence rate ratio.

leukaemia in association with secondary inorganic aerosols including nitrate (NO₃) and that AML was associated with NO₃,³² which was similar to our findings.

Studies focusing on the association between childhood leukaemia and exposure to air pollutants have had inconsistent results. Ghosh *et al* in California revealed that prenatal exposure to traffic-related air pollution was associated with the risk of ALL.³³ A population-based study from Canada suggested that exposure to ambient air pollution during the first trimester of pregnancy may cause astrocytoma and ALL.³⁴ However, Peckham-Gregory *et al* conducted a population-based case-control study in Texas to evaluate the association between maternal residential proximity to major roadways and developing ALL and AML in children, and reached different results. They indicated that mothers who lived closer than 500 m to a major roadway and mothers who lived in high roadway density areas were not more likely to have a child with ALL or AML.³⁵

Although many studies have shown a possible relation between air pollution and leukaemia, there is still a need for more high-quality studies with higher sample sizes, and better control of confounders.

Strengths and limitation

In this study, we estimated the simultaneous effect of several different air pollutants on the incidence of leukaemia. However, our study had several limitations. We did not use individual-level data; thus, we were not

able to control for confounding variables at individual-level, such as blood group, family history of cancer, taking medicine during pregnancy, parents' job, history of radiation, smoking and other factors such as genetics, nutrition status, cultural context and behavioural patterns. But we did include potential confounding covariates at regional level.

The other major limitation of this study is our estimates of exposure. First, our study used some more recent air pollution data, not past life-time exposure estimates, because we did not have a better option. In addition, we did not have data on the length of residence of patients in the study regions, and life-time relocation or migration. Second, we assigned the same exposure concentrations to all people living in the same area. Although the mean area level values may well reflect the average exposure levels of the inhabitants, our approach ignored within-area variation, which has been demonstrated in previous studies in Tehran.¹⁰⁻¹²

CONCLUSION

This is the first study to examine the association between multiple air pollutants and leukaemia incidence in Iran. Our findings suggest that exposure to VOCs, nitrogen oxides and/or multiple ambient air pollutants may be associated with increased leukaemia incidence in Tehran. Further research with individual data and better control

Table 6 The estimated incidence rate ratios using negative binomial regression analyses for the effect of each 10 unit increase in air pollutants on acute lymphoid leukaemia incidence in the districts of Tehran

Pollutant	Model 1		Model 2		Model 3	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
<i>Single-pollutant</i>						
Annual PM ₁₀ (µg/m ³)	0.94 (0.87 to 1.02)	0.207	0.91 (0.83 to 1.01)	0.096	0.99 (0.91 to 1.07)	0.822
Annual SO ₂ (ppb)	1.08 (0.96 to 1.21)	0.181	1.08 (0.96 to 1.22)	0.172	1.03 (0.95 to 1.12)	0.428
Annual NO ₂ (ppb)	1.29 (1.07 to 1.55)	0.006	1.29 (1.07 to 1.54)	0.006	1.07 (0.90 to 1.27)	0.425
Annual NO (ppb)	1.03 (0.98 to 1.08)	0.157	1.04 (0.99 to 1.10)	0.101	1.04 (0.99 to 1.08)	0.052
Annual NO _x (ppb)	1.04 (1.01 to 1.08)	0.010	1.06 (1.02 to 1.10)	0.002	1.01 (0.98 to 1.05)	0.310
Benzene (µg/m ³)	1.21 (0.36 to 4.01)	0.754	1.33 (0.27 to 6.48)	0.722	0.46 (0.17 to 1.24)	0.129
Toluene (µg/m ³)	1.01 (0.72 to 1.41)	0.949	1.006 (0.65 to 1.54)	0.978	0.92 (0.71 to 1.21)	0.585
Ethylbenzene (µg/m ³)	0.84 (0.33 to 2.13)	0.723	0.78 (0.27 to 2.24)	0.658	0.69 (0.32 to 1.46)	0.336
p-xylene (µg/m ³)	0.41 (0.04 to 3.51)	0.422	0.21 (0.01 to 3.13)	0.258	0.28 (0.05 to 1.42)	0.126
o-xylene (µg/m ³)	0.36 (0.08 to 1.57)	0.175	0.23 (0.04 to 1.26)	0.091	0.32 (0.10 to 1.03)	0.058
m-xylene (µg/m ³)	0.83 (0.31 to 2.16)	0.705	0.64 (0.16 to 2.55)	0.533	0.58 (0.28 to 1.20)	0.144
TBTEX (µg/m ³)	1.001 (0.85 to 1.17)	0.988	0.99 (0.80 to 1.23)	0.971	0.95 (0.84 to 1.08)	0.433
<i>Multipollutant</i>						
Profile 1 (low pollution)	Ref		Ref		Ref	
Profile 2 (high pollution)	1.002 (0.99 to 1.009)	0.427	1.003 (0.99 to 1.01)	0.343	0.99 (0.99 to 1.004)	0.884

Model 1: Adjusted for age and gender.
 Model 2: Adjusted for age, gender and urban green space, per capita (m² per 1000 people).
 Model 3: Adjusted for age, gender, socioeconomic status life expectancy.
 The incidence rate ratio of leukaemia is estimated for each 10 unit increase in pollutants.
 Statistically significant IRRs are bolded.
 IRR, incidence rate ratio.

of confounding covariates is needed to confirm the role of air pollution in human leukaemia.

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Table 7 The estimated incidence rate ratios using negative binomial regression analyses for the effect of each 10 unit increase in air pollutants on total leukaemia incidence in children (≤ 14 years old) across the districts of Tehran

Pollutant	Model 1		Model 2		Model 3	
	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
<i>Single-pollutant</i>						
Annual PM ₁₀ ($\mu\text{g}/\text{m}^3$)	0.87 (0.84 to 0.92)	<0.001	0.78 (0.74 to 0.82)	<0.001	1.11 (1.03 to 1.18)	0.003
Annual SO ₂ (ppb)	0.95 (0.91 to 0.99)	0.036	0.96 (0.92 to 1.008)	0.106	0.99 (0.95 to 1.04)	0.712
Annual NO ₂ (ppb)	1.45 (1.32 to 1.61)	<0.001	1.45 (1.31 to 1.60)	<0.001	1.21 (1.08 to 1.35)	0.001
Annual NO (ppb)	0.93 (0.91 to 0.96)	<0.001	0.90 (0.88 to 0.93)	<0.001	1.05 (1.02 to 1.09)	0.005
Annual NO _x (ppb)	1.04 (1.02 to 1.07)	<0.001	1.04 (1.01 to 1.07)	0.004	1.08 (1.05 to 1.10)	<0.001
Benzene ($\mu\text{g}/\text{m}^3$)	0.49 (0.23 to 1.05)	0.068	0.30 (0.14 to 0.67)	0.003	5.87 (2.43 to 14.16)	<0.001
Toluene ($\mu\text{g}/\text{m}^3$)	0.75 (0.63 to 0.89)	0.001	0.63 (0.52 to 0.76)	<0.001	1.77 (1.42 to 2.22)	<0.001
Ethylbenzene ($\mu\text{g}/\text{m}^3$)	0.17 (0.07 to 0.42)	<0.001	0.06 (0.02 to 0.16)	<0.001	21.78 (6.02 to 78.85)	<0.001
p-xylene ($\mu\text{g}/\text{m}^3$)	0.14 (0.05 to 0.43)	0.001	0.02 (0.01 to 0.08)	<0.001	17.83 (4.22 to 75.29)	<0.001
o-xylene ($\mu\text{g}/\text{m}^3$)	0.11 (0.05 to 0.24)	0.001	0.04 (0.01 to 0.08)	<0.001	19.89 (5.19 to 76.24)	<0.001
m-xylene ($\mu\text{g}/\text{m}^3$)	0.37 (0.24 to 0.58)	<0.001	0.20 (0.12 to 0.33)	<0.001	4.08 (2.13 to 7.80)	<0.001
TBTEX ($\mu\text{g}/\text{m}^3$)	0.89 (0.82 to 0.97)	0.007	0.79 (0.73 to 0.87)	<0.001	1.29 (1.16 to 1.44)	<0.001
<i>Multipollutant</i>						
Profile 1 (low pollution)	Ref		Ref		Ref	
Profile 2 (high pollution)	1.003 (1.001 to 1.006)	0.001	1.004 (1.001 to 1.007)	0.016	1.008 (1.005 to 1.01)	<0.001

Model 1: Adjusted for age and gender.
 Model 2: Adjusted for age, gender and urban green space per capita (m^2 per 1000 people).
 Model 3: Adjusted for age, gender, socioeconomic status, life expectancy.
 The incidence rate ratio of leukaemia is estimated for each 10 unit increase in pollutants.
 Statistically significant IRRs are bolded.
 IRR, incidence rate ratio.

Table 8 The estimated incidence rate ratios using negative binomial regression analyses for the effect of each 10 unit increase in air pollutants on total leukaemia incidence in adults across the districts of Tehran

Pollutant	Model 1		Model 2		Model 3	
	IRR (95% CI)	P value	IRR (95% CI)	P value	IRR (95% CI)	P value
<i>Single-pollutant</i>						
Annual PM ₁₀ ($\mu\text{g}/\text{m}^3$)	0.92 (0.90 to 0.95)	<0.001	0.89 (0.87 to 0.92)	<0.001	1.01 (0.97 to 1.05)	0.479
Annual SO ₂ (ppb)	0.96 (0.94 to 0.99)	0.012	0.97 (0.95 to 1.01)	0.109	0.98 (0.96 to 1.02)	0.390
Annual NO ₂ (ppb)	1.21 (1.14 to 1.27)	<0.001	1.19 (1.13 to 1.26)	<0.001	1.10 (1.03 to 1.18)	0.003
Annual NO (ppb)	0.98 (0.97 to 0.99)	0.028	0.97 (0.95 to 0.98)	<0.001	1.03 (1.01 to 1.05)	0.005
Annual NO _x (ppb)	1.02 (1.00 to 1.03)	0.008	1.01 (0.99 to 1.02)	0.338	1.03 (1.01 to 1.04)	<0.001
Benzene ($\mu\text{g}/\text{m}^3$)	0.66 (0.42 to 1.05)	0.078	0.44 (0.27 to 0.72)	0.001	1.44 (0.87 to 2.40)	0.158
Toluene ($\mu\text{g}/\text{m}^3$)	0.87 (0.78 to 0.97)	0.017	0.79 (0.71 to 0.89)	<0.001	1.19 (1.05 to 1.37)	0.008
Ethylbenzene ($\mu\text{g}/\text{m}^3$)	0.36 (0.19 to 0.67)	0.001	0.20 (0.11 to 0.38)	<0.001	2.28 (1.05 to 4.94)	0.037
p-xylene ($\mu\text{g}/\text{m}^3$)	0.39 (0.19 to 0.80)	0.010	0.14 (0.06 to 0.30)	<0.001	1.98 (0.86 to 4.55)	0.106
o-xylene ($\mu\text{g}/\text{m}^3$)	0.33 (0.19 to 0.55)	<0.001	0.22 (0.13 to 0.37)	<0.001	3.03 (1.36 to 6.74)	0.006
m-xylene ($\mu\text{g}/\text{m}^3$)	0.59 (0.44 to 0.78)	<0.001	0.43 (0.31 to 0.58)	<0.001	1.39 (0.95 to 2.02)	0.085
TBTEX ($\mu\text{g}/\text{m}^3$)	0.94 (0.89 to 0.99)	0.042	0.88 (0.83 to 0.94)	<0.001	1.08 (1.01 to 1.15)	0.019
<i>Multipollutant</i>						
Profile 1 (low pollution)	Ref		Ref		Ref	
Profile 2 (high pollution)	1.002 (1.00 to 1.003)	0.017	0.99 (0.99 to 1.001)	0.892	1.003 (1.001 to 1.005)	<0.001

Model 1: Adjusted for age and gender.
 Model 2: Adjusted for age, gender and urban green space per capita (m^2 per 1000 people).
 Model 3: Adjusted for age, gender, socioeconomic status, life expectancy.
 The incidence rate ratio of leukaemia is estimated for each 10 unit increase in pollutants.
 Statistically significant IRRs are bolded.
 IRR, incidence rate ratio.

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