Environmental Pollution 254 (2019) 113121

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Short-term associations between daily mortality and ambient particulate matter, nitrogen dioxide, and the air quality index in a Middle Eastern megacity☆

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ARTICLE INFO

Article history:
Received 28 February 2019
Received in revised form
23 August 2019
Accepted 25 August 2019
Available online 28 August 2019

Keywords:
Air pollution
Air quality index (AQI)
Mortality
Independent effect
Nitrogen dioxide (NO_2)
Particulate matter ($PM_{2.5}$)
Short-term

ABSTRACT

There is limited evidence for short-term association between mortality and ambient air pollution in the Middle East and no study has evaluated exposure windows of about a month prior to death. We investigated all-cause non-accidental daily mortality and its association with fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and the Air Quality Index (AQI) from March 2011 through March 2014 in the megacity of Tehran, Iran. Generalized additive quasi-Poisson models were used within a distributed lag linear modeling framework to estimate the cumulative effects of $PM_{2.5}$, NO_2, and the AQI up to a lag of 45 days. We further conducted multi-pollutant models and also stratified the analyses by sex, age group, and season. The relative risk (95% confidence interval (CI)) for all seasons, both sexes and all ages at lag 0 for $PM_{2.5}$, NO_2, and AQI were 1.004 (1.001, 1.007), 1.003 (0.999, 1.007), and 1.004 (1.001, 1.007), respectively, per inter-quartile range (IQR) increment (18.8 $\mu g/m^3$ for $PM_{2.5}$, 12.6 ppb for NO_2, and 31.5 for AQI). In multi-pollutant models, the $PM_{2.5}$ associations were almost independent from NO_2. However, the RRs for NO_2 were slightly attenuated after adjustment for $PM_{2.5}$ but they were still largely independent from $PM_{2.5}$. The cumulative relative risks (95% CI) per IQR increment reached maximum during the cooler months, including: 1.13 (1.06, 1.20) for $PM_{2.5}$ at lag 0–31 (for females, all ages); 1.17 (1.10, 1.25) for NO_2 at lag 0–45 (for males, all ages); and 1.13 (1.07, 1.20) for the AQI at lag 0–30 (for females, all ages). Generally, the RRs were slightly larger for NO_2 than $PM_{2.5}$ and AQI. We found somewhat larger RRs in

☆ This paper has been recommended for acceptance by Payam Dadvand.

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https://doi.org/10.1016/j.envpol.2019.113121

females, age group >65 years of age, and in cooler months. In summary, positive associations were found in most models. This is the first study to report short-term associations between all-cause non-accidental mortality and ambient $PM_{2.5}$ and NO_2 in Iran.

1. Introduction

Air pollution is composed of a complex mixture of gases and small particles and contributes to a range of health outcomes (Amini et al., 2017c; Künzli et al., 2000; Mousavi et al., 2018; Schwartz et al., 2018b). Of the outcomes associated with air pollution exposure, mortality has been most studied (Bell et al., 2013; Schwartz et al., 2018a; Vodonos et al., 2018). Of all of the constituents of the complex ambient air pollution mixture, the strongest and most consistent predictors of population mortality have been particulate matter with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) (Cohen et al., 2017; Katsouyanni et al., 2001; Mills et al., 2015). Although there is a large body of evidence on the associations between daily deaths and $PM_{2.5}$ and NO_2 concentrations, there are some important limitations of this literature when considering its generalizability for low- and middle-income countries (LMICs). First, the number of studies conducted in LMICs is small compared with high-income countries (HICs), meaning that meta-analyses are weighted towards the high-income context (Lu et al., 2015; Vodonos et al., 2018; West et al., 2016). In general, these are all lower exposure scenarios, and relationships may be nonlinear. Second, some studies have reported evidence of effect modification by age and sex (Clougherty, 2010; Yin et al., 2017; Zanobetti and Schwartz, 2000), but pooled estimates for gender-based effect modification have been weak and little is known in LMICs (Bell et al., 2013). Furthermore, not many studies on mortality have investigated the short-term associations beyond the window one week prior to death, and a few looked into lags of more than 30 days (Zanobetti et al., 2002; Zanobetti et al., 2003). From the current literature, the weight of the evidence suggests quite larger effects in long-term exposures (defined as the cumulated exposure experience over many months and years) than short-term (Künzli et al., 2001), and it is expected to also see larger effects in models that cumulate all short-term effects over longer short-term exposure periods, such as a few weeks. In addition, it is rare for studies to evaluate multi-pollutant models over distributed lags or the effects of widely-reported Air Quality Index (AQI) values.

Iran has currently a population of about 80 million people who are exposed to air pollution from natural dust storms and anthropogenic sources (Hosseini and Shahbazi, 2016). Although many studies have quantified the health burden attributable to air pollution in Iran (Faridi et al., 2018; Naddafi et al., 2012), the majority have been based on the World Health Organization (WHO) software called *AirQ* (which was recently upgraded to *AirQ+*). However, Iranian applications of *AirQ* have mostly used relative risks (RR) and 95% confidence intervals (CI) estimated from the international literature. These RRs and CIs are heavily driven by studies conducted in HICs (Burnett et al., 2014), which usually have much lower levels of air pollution than LMICs. In addition, they may have different sources of air pollution and their populations may have a different response due to difference in age structure, genetic factors, and baseline health. Furthermore, Iranian health impact assessments have mostly not accounted for lag structures that may differ between locations, nor have they considered effect modification by age, sex, and season. Indeed, recent studies in the capital city of Tehran showed that the composition of $PM_{2.5}$ varied substantially between colder and warmer seasons (Arhami et al., 2017; Taghvaee et al., 2018). So far, no time-series study in Iran has reported on the short-term association between daily all-cause non-accidental mortality and ambient $PM_{2.5}$ and NO_2, and only one recent study has evaluated the association with AQI (Khajavi et al., 2019).

The Tehran Air Quality Control Company (AQCC), which is a subsidiary of the Tehran Municipality, measures hourly concentrations of criteria pollutants across the city. It also reports a daily air quality index (AQI) value to the public. Only one study to date has evaluated whether the AQI as reported by Tehran AQCC is an effective tool for risk communication by assessing whether it can predict daily morbidity or mortality (Khajavi et al., 2019). However, it has been conducted only in one out of 22 administrative districts of Tehran (District 13 with a population of about 276,000 people) and has important limitations. Indeed, such studies on the relationship between air quality indices and health outcomes are rare on the global scale. Our objective with this study is to address some of these research gaps by quantifying the short-term association between daily all-cause non-accidental mortality and $PM_{2.5}$, NO_2, and the AQI in the megacity of Tehran, Iran. In addition, we evaluate the cumulative effects of lags up to 45 days, the difference in associations by sex, age, and season, and evaluate multi-pollutant models.

2. Materials and methods

2.1. Study area

Tehran is the capital of Iran, with 22 administrative districts in an area of about 613 km^2. It is considered to be a megacity, with a resident population of almost 9 million people and a transient population of several million people who commute into the city daily from outside areas (Amini et al., 2014b). Tehran is surrounded by the Alborz Mountains in the north and a desert in the south (Amini et al., 2017b; Amini et al., 2014b). The climate is semi-arid, with an annual mean temperature of 18.3 °C for the study period of March 2011 to March 2014. The daily mean temperatures were 10.2 and 26.0 °C in the cooler (October to March) and warmer months (April to September), respectively, in the same period. The daily mean extremes rose up to 36.9 °C in July and went down to −5.7 °C in January for the same period (Table 1). The annual precipitation is approximately 220 mm (Amini et al., 2017a; Amini et al., 2016).

2.2. Mortality data

Daily counts of all-cause non-accidental mortality data by sex and age were obtained from the Behesht-e-Zahra Cemetery Organization, which is a subsidiary of Tehran Municipality, where almost all mortality data are registered (Mokhayeri et al., 2014).

2.3. Air quality data

Hourly $PM_{2.5}$ and NO_2 measurements for the period March 21, 2011 through March 20, 2014 were obtained from 40 air quality

Table 1
Summary statistics for daily all-cause non-accidental mortality, meteorological parameters, air pollutants, and the air quality index (AQI) from March 2011 through March 2014 in Tehran, Iran.

								Percentiles		
			Mean	SD	Min	Max	IQR	25th	50th	75th
Daily all-cause non-accidental mortality	Overall, both sexes; all ages		111.7	15.8	52	165	21	101	111	122
	Cooler months, both sexes; all ages		117.9	15.6	74	165	21	107	118	128
	Warmer months, both sexes; all ages		105.6	13.5	52	147	17	97	106	114
	Overall, males, all ages		61.2	10.3	29	95	14	54	61	68
	Overall, females, all ages		48.8	8.6	21	80	11	43	48	54
	Overall, both sexes, > 65 years of age		71.9	12.2	33	112	15	64	71	79
	Overall, both sexes, 18–65 years of age		33.9	6.8	16	56	9	29	34	38
	Overall, both sexes, < 18 years of age		6.0	3.5	1	22	5	3	5	8
Meteorological parameters	Temperature (°C)	All years	18.3	10.2	−5.7	36.9	18.5	9.1	18.8	27.6
		Cooler months	10.2	7.0	−5.7	27.9	9.5	5.0	9.0	14.5
		Warmer months	26.0	5.9	7.8	36.9	8.7	21.9	27.5	30.6
	Relative humidity (%)	All years	35.2	18.2	9.5	92.0	26.5	20.5	30.1	47.0
		Cooler months	46.5	17.8	12.3	92.0	26.6	33.4	45.0	60.0
		Warmer months	24.2	10.2	9.4	78.4	12.3	16.7	21.7	29.0
	Air pressure (hPa)	All years	880.0	4.6	868.4	893.6	6.5	876.8	879.8	883.3
		Cooler months	882.7	4.1	868.4	893.5	5.3	880.1	882.9	885.4
		Warmer months	877.3	3.3	868.5	889.6	4.4	875.2	877.4	879.6
Air pollutants	$PM_{2.5}$ ($\mu g/m^3$)	All years	40.0	15.4	10.1	126.9	18.8	29.1	37.7	47.9
		Cooler months	40.9	16	10.1	121.3	21.3	28.9	38.9	50.2
		Warmer months	39.0	14.8	13.3	126.9	16.7	29.2	37.0	45.9
	NO_2 (ppb)	All years	42.4	9.6	21.4	74.7	12.6	35.6	41.1	48.2
		Cooler months	45.2	10.1	22.3	74.7	14.4	37.9	43.8	52.3
		Warmer months	39.7	8.3	21.4	70.2	11	33.6	38.9	44.6
Air Quality Index (AQI)		All years	100.4	25.7	31	278	31.5	83.5	99.0	115.0
		Cooler months	102.8	26.4	31	180	34	85	102	119
		Warmer months	98.2	24.8	48	278	27	83	96	110

monitoring stations operated by the Tehran AQCC and the Tehran Department of Environment. We calculated the daily mean value for each site if at least 50% of the hourly measurements over the entire study period were available. This criterion led to the exclusion of eight stations, leaving 32 stations for all further analyses on $PM_{2.5}$ and NO_2. We obtained daily AQI values reported by Tehran AQCC for the study period. Noteworthy, the calculation method of AQCC slightly differs from the US EPA recommendations. The US EPA recommends calculation of AQI for each pollutant at each monitoring station in the study area, and finally reports the *maximum* of the maximum daily AQI values among all monitoring sites (U.S. Environmental Protection Agency, 2016) (Supplemental Information (SI), page S2). In Tehran, the AQCC reports the *mean* of the maximum daily AQI values among all monitoring sites as the AQI for the entire city (U.S. Environmental Protection Agency, 2016).

2.4. Meteorology data

The meteorology variables including temperature, relative humidity (RH), and air pressure (AP) for Tehran-Mehrabad station (station identifier: OIII, station number: 40,754, latitude: 35.68, longitude: 51.35) located at Mehrabad International Airport were obtained from the Iran's Meteorological Organization data archived in the University of Wyoming repository (http://weather.uwyo.edu/upperair).

2.5. Statistical analyses

We first calculated descriptive statistics for daily all-cause non-accidental mortality, weather parameters, air pollutants, and the AQI. The same statistics were calculated separately for the warmer (April–September) and cooler months (October–March). We also calculated the temporal Spearman correlations for daily $PM_{2.5}$, NO_2, AQI, and weather parameters.

Generalized additive quasi-Poisson models were used within a distributed lag linear modeling framework to estimate the effects of NO_2, $PM_{2.5}$, and the AQI on all-cause non-accidental mortality. The models were run for a lag period of 0–45 days, controlling for measured and unmeasured time-varying covariates. The unmeasured confounders were seasonality and temporal trend, which we captured by thin plate spline functions with six degrees of freedom (df) per year. The appropriate df value was selected based on visual inspection of the residual partial autocorrelation function plots (PACF) and lower generalized cross-validation (GCV) values. We added an autoregressive term to the model if we were unable to adequately remove partial autocorrelation at lag 0.

For the measured meteorological variables we included temperature, RH, and AP. We evaluated the effect of temperature on overall mortality for single lags and cumulative lags up to seven days, and found the highest impact for a cumulative lag of 0–4 days. This is consistent with findings of a multi-country multi-community study of the effects of heat waves on mortality (Guo et al., 2017). We used three df per year and found that adaptive smoothers provided better results for meteorological variables with lower GCV values. In addition, we included day-of-week as a categorical variable and created a Boolean indicator for all holidays.

One important covariate that was missing in our dataset was influenza epidemics. Because we had access to respiratory mortality data for the same period, we created a dummy variable to flag those days when respiratory mortality was above percentile 90 of overall respiratory mortality. This variable turned out to be significant in the models, so we adjusted the air pollutant and AQI models with this proxy.

After building core models that removed the effect of relevant covariates, the $PM_{2.5}$, NO_2, and AQI variables were added separately. Multi-pollutant models were also run for the combined effects of NO_2 and $PM_{2.5}$. Finally, the effect estimates for lag 0 and the cumulative estimates for the preceding 45 days were extracted for an interquartile range (IQR) increase in each of $PM_{2.5}$, NO_2, and the

AQI. Estimates for a 10-unit increase were also calculated and are reported in the SI.

In addition to the overall analyses, all models were also stratified by sex (males vs females), age groups (>65, 18–65, and <18), and season (cooler *vs* warmer months). It is noteworthy that in the seasonal models, seasonality and temporal trend were captured by adaptive smoothers with four degrees of freedom (df) for both cooler and warmer season. In the cooler months, the temperature was controlled up to a lag of 0–7 days while in warmer months it was controlled up to a lag of 0–4 days both by adaptive smoothers and using three df. In addition, the RH was controlled up to a lag of 0–3 days and using three df in the cooler months while in the warmer months it was controlled for a log of 0–4 days and using four df, both by adaptive smoothers. The AP was controlled up to a lag of 0–4 days and using three df in both cooler and warmer months. These choices were chosen based lower GCV values in the respective models. Differences between the sub-group estimates were assessed using a *t*-test to test the effect modification.

Regarding AQI, we also assessed the dose-response curve for the association been the AQI at lag 0 with overall, males, and females mortality.

All analysis were performed and plotted in R environment (Gasparrini, 2011; R Core Team, 2017).

2.6. Sensitivity analyses

Ultimately, we conducted multiple sensitivity analyses to ensure that our results were robust. We ran the overall alternative models for $PM_{2.5}$, NO_2, and AQI with natural cubic spline functions with eight knots per year to capture trends and seasonal variations, and four df per year for temperature, RH and AP.

3. Results

3.1. Description of mortality data

Over the March 2011–March 2014 study period, 122,376 individuals deceased in Tehran. The mean (SD) daily death count in Tehran was 111.7 (15.8) with a range from 52 to 165 (Table 1). This value increased to 117.9 (15.6) during the cooler months compared with 105.6 (13.5) in the warmer months. The daily number of deaths was higher for males than females, at 61 compared with 49.

3.2. Description of air quality data

The overall daily mean (SD) $PM_{2.5}$ and NO_2 concentrations and AQI value were 40.0 (15.4) $\mu g/m^3$, 42.4 (9.6) ppb, and 100.4 (25.7), respectively. The average concentrations were slightly higher in the cooler months (Table 1).

3.3. Description of meteorology data

The overall daily mean (SD) temperature (°C), RH (%), and AP (hPa) were 18.3 (10.2), 35.2% (18.2%), 880.0 (4.6), respectively. These values in cooler vs warmer months were 10.2 (7.0) vs 26.0 (5.9), 46.5% (17.8%) vs 24.2% (10.2%), and 882.7 (4.1) vs 877.3 (3.3), respectively (Table 1).

3.4. Correlation of air quality and meteorology data

The Spearman correlation between daily $PM_{2.5}$ and NO_2 was 0.53; between $PM_{2.5}$ and the AQI it was 0.83, and between NO_2 and the AQI it was 0.40. The temporal correlations between markers of pollution and weather parameters were very low (Table 2).

3.5. Core main model description

Our model demonstrated that time, temperature, day of the week, holidays, and the proxy influenza variable were all significant explanatory covariates for overall mortality in Tehran, but relative humidity and air pressure were not. However, we kept them in the core model.

3.6. Overall association of mortality and $PM_{2.5}$

After adding air pollution terms to the core model, an IQR increase in $PM_{2.5}$ (18.8 $\mu g/m^3$) was associated with a small increase in same day (lag 0) all-cause non-accidental mortality, with an RR (CI) of 1.004 (1.001, 1.007). At longer lags the cumulative RR rose steadily until lag 0–36, reaching a maximum value of 1.036 (1.0005, 1.073) per 18.8 $\mu g/m^3$ before decreasing (Figs. 1 and SI, Table S1).

3.7. Overall association of mortality and NO_2

An IQR increase in NO_2 (12.6 ppb) had an RR (CI) of 1.003 (0.999, 1.007) at lag 0, which rose steadily to a maximum of 1.049 (1.003, 1.096) at lag 0–30. Generally, the RRs were slightly larger for NO_2 than $PM_{2.5}$ (Figs. 1 and SI, Table S2).

3.8. Overall association of mortality and AQI

Similar to $PM_{2.5}$ and NO_2, an IQR increase in the AQI (31.5 units) had an RR (CI) of 1.0037 (1.0007, 1.0067) at lag 0, which rose steadily to a maximum of 1.035 (1.002, 1.070) at lag 0–38 (Figs. 1 and SI, Table S3)

The dose-response curves for the association between the AQI at lag 0 with overall, males, and females mortality in Tehran were close to linear down to the lowest observed values (Fig. 2).

3.9. Multi-pollutant models

In multi-pollutant models, the $PM_{2.5}$ associations were almost independent from NO_2. For example, the RR (CI) at lag 0 for an IQR increase in $PM_{2.5}$ was 1.004 (1.001, 1.007) in single pollutant model, while it was 1.004 (1.001, 1.007) in the multi-pollutant model where it was adjusted for NO_2 (SI, Fig. S2 and Table S4). However,

Table 2
Spearman correlation between $PM_{2.5}$, NO_2, the air quality index (AQI), and meteorological parameters during the March 2011 to March 2014 study period in Tehran, Iran.

	$PM_{2.5}$	NO_2	AQI	Temperature	Relative humidity	Air pressure
$PM_{2.5}$	1					
NO_2	0.53*	1				
AQI	0.83*	0.40*	1			
Temperature	0.11*	−0.16*	0.04	1		
Relative humidity	−0.11*	0.06*	−0.04	−0.81*	1	
Air pressure	0.01	0.21*	0.002	−0.62*	0.49*	1

*$p < 0.05$.

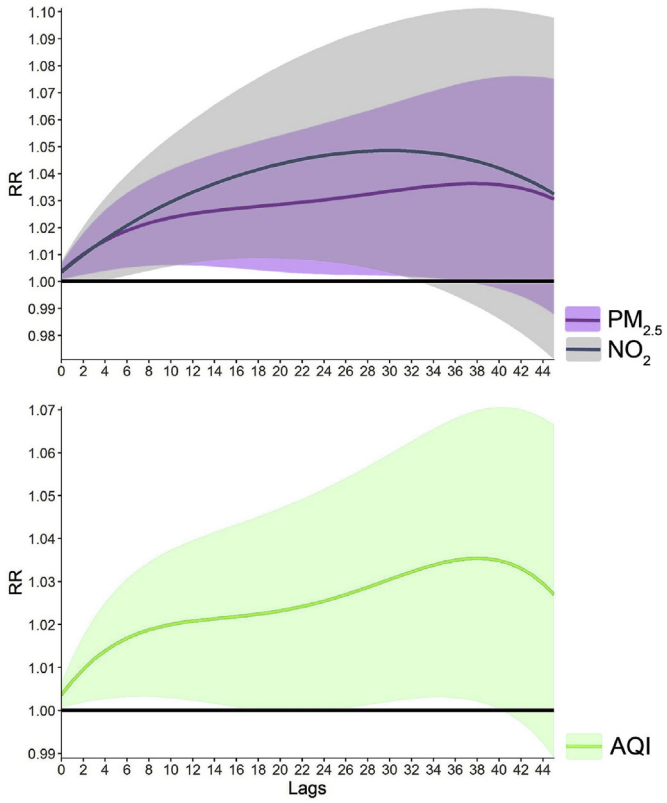

Fig. 1. The cumulative associations (lag 0 to lag 45 days) between overall all-cause non-accidental mortality and $PM_{2.5}$, NO_2, and AQI (per IQR) from March 2011 to March 2014 in Tehran, Iran. In general, we did not see that the cumulative effects vanish or get negative (harvesting). This indicates that air pollution in Tehran does not just affect the frailest individuals. All point estimates for increments of 10 μg/m^3 of $PM_{2.5}$, 10 ppb of NO_2, 10 units of AQI, and per IQR are available in the Supplemental Information.

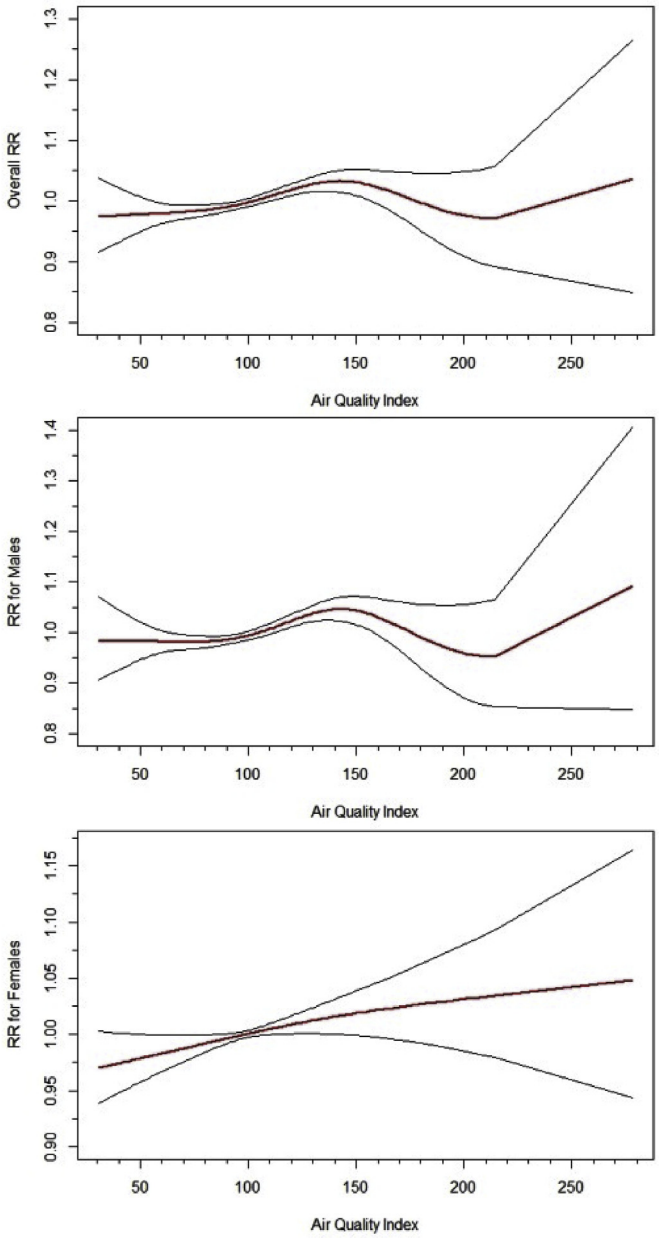

Fig. 2. The dose-response curves for the association of Air Quality Index at lag 0 with overall, males, and females' mortality in Tehran, Iran.

the RRs for NO_2 were slightly attenuated after adjustment for $PM_{2.5}$ but still they were largely independent from $PM_{2.5}$ (SI, Fig. S2 and Table S5).

3.10. Effect modification by sex

Overall, we found somewhat larger RRs in females than males (Fig. 3). For example, for overall $PM_{2.5}$ at lag 0–45 per an IQR increase, the cumulative RR (CI) for females was 1.053 (0.994, 1.115) while it was 1.003 (0.951, 1.058) for males. However, the p-value for the difference was >0.05. The values at lag 0 were slightly larger in males for NO_2. The cumulative RR (CI) for males at lag 0 for NO_2 was 1.005 (1.0002, 1.010) while for females it was 1.001 (0.995, 1.006) (p-value > 0.05).

For females (all ages), the maximum RR (CI) for an IQR increase were: 1.059 (1.015, 1.106) at lag 0–32 for $PM_{2.5}$; 1.071 (1.017, 1.127) at lag 0–27 for NO_2; and 1.054 (1.011, 1.099) at lag 0–36 for the AQI. These values for males were: 1.008 (0.968, 1.045) at lag 0–32 for $PM_{2.5}$; 1.033 (0.982, 1.088) at lag 0–27 for NO_2; and 1.012 (0.972, 1.054) at lag 0–36 for the AQI (Figs. 3 and SI, Tables S6–S11). The p-values for all of these differences were >0.05.

3.11. Effect modification by age group

As shown in Fig. 4, somewhat larger RRs were observed in the age group >65 years of age. However, for NO_2, larger RRs were found for age group <18 at early lags up to a cumulative lag of 0–23 where again the RRs for the age group >65 years of age became larger.

For the age group >65 years (both sexes), the maximum RRs (CI) per IQR increases were: 1.044 (1.005, 1.084) at lag 0–31 for $PM_{2.5}$; 1.071 (1.014, 1.131) at lag 0–31 for NO_2; and 1.047 (1.007, 1.088) at lag 0–36 for AQI. These corresponding lag values for the age group 18–65 were: 1.036 (0.999, 1.073) for $PM_{2.5}$; 1.046 (0.999, 1.094) for NO_2; and 1.019 (0.974, 1.066) for the AQI. They were 1.010 (0.916, 1.112) for $PM_{2.5}$; 1.014 (0.922, 1.114) for NO_2; and 1.0003 (0.907, 1.102) for the AQI for the age group <18 years of age at these corresponding cumulative lags (Figs. 4 and SI, Tables S12–S20). Again, the p-values for all of these differences were >0.05.

3.12. Effect modification by season

In the cooler months, the associations were positive and

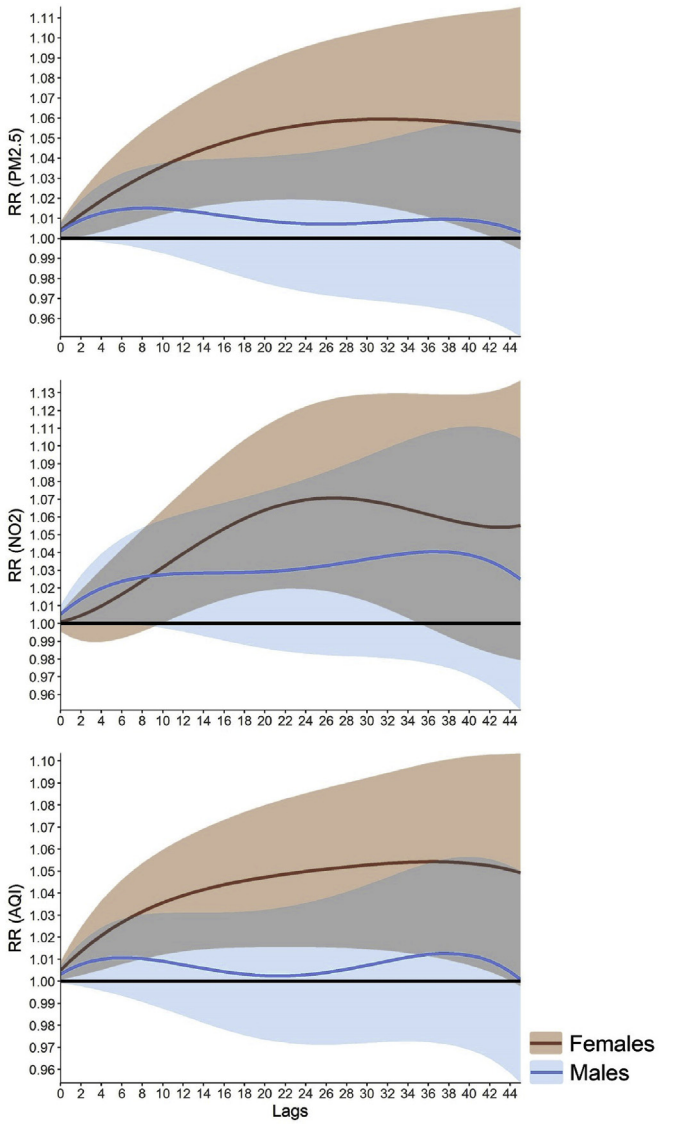

Fig. 3. The cumulative associations (lag 0 to lag 45 days) between sex-specific all-ages all-cause non-accidental mortality and $PM_{2.5}$, NO_2, and AQI (per IQR) from March 2011 to March 2014 in Tehran, Iran. All point estimates for increments of 10 μg/m^3 of $PM_{2.5}$, 10 ppb of NO_2, 10 units of AQI, and per IQR are available in the Supplemental Information.

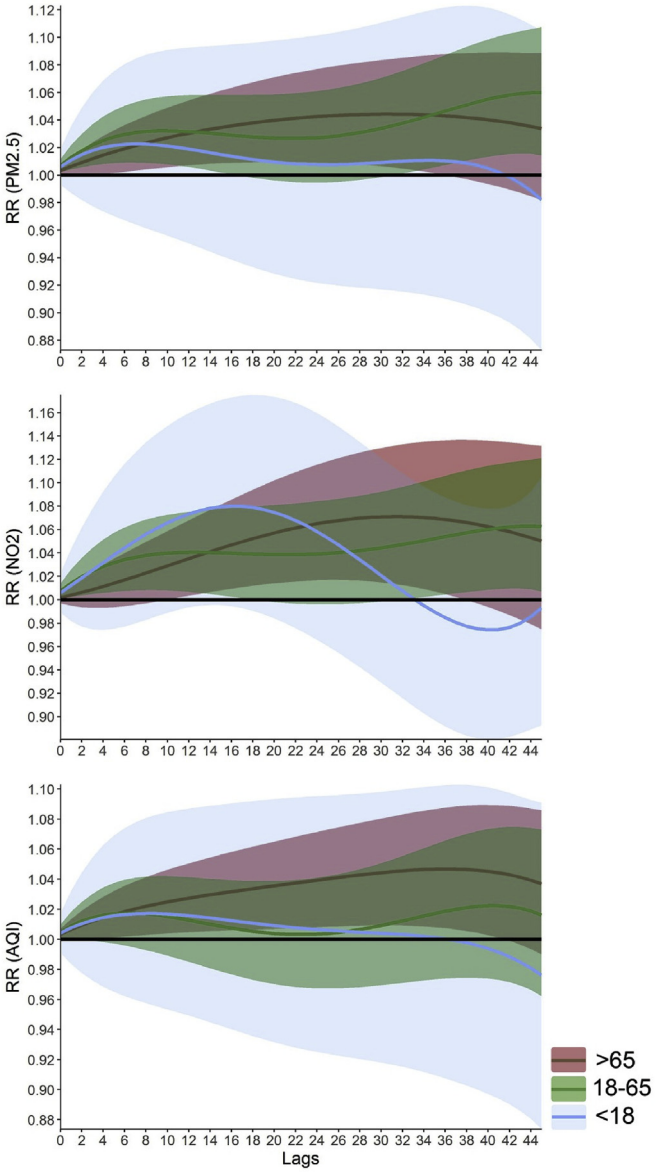

Fig. 4. The cumulative associations (lag 0 to lag 45 days) between age-specific (>65, 18–65, and <18 years of age) all-cause non-accidental mortality and $PM_{2.5}$, NO_2, and the AQI (per IQR) from March 2011 to March 2014 in Tehran, Iran. All point estimates for increments of 10 μg/m^3 of $PM_{2.5}$, 10 ppb of NO_2, 10 units of AQI, and per IQR are available in the Supplemental Information.

stronger than the associations during the warmer months for most models. In the warmer months, the associations remained positive up to a lag of ~20 days for most models. Noteworthy, positive associations were also found for males, especially for NO_2 in the cooler months, and for the younger age categories. Overall, the maximum cumulative RRs (CIs) per IQR were found during the cooler months, which were 1.13 (1.06, 1.20) among females at lag 0–31 for $PM_{2.5}$; 1.17 (1.10, 1.25) among males at lag 0–45 for NO_2; and 1.13 (1.07, 1.20) among females at lag 0–30 for the AQI (SI, Tables S21–S60). Overall, the p-values for these differences were also >0.05.

3.13. Sensitivity analyses

The results of sensitivity analysis showed that our results were robust. However, the confidence intervals, especially for NO_2, became slightly wider if we would have chosen different spline functions and larger df for capturing trend and meteorological variables (SI, Fig. S2).

4. Discussion

Herein we provided the first-ever report on the association between daily all-cause non-accidental mortality and ambient $PM_{2.5}$ and NO_2 in Tehran, Iran, including evaluation of the local AQI. Availability of these local RRs for Tehran and Iran in general, may assist many future health impact assessment studies, such as National and Subnational Environmental Burden of Disease Study in Iran (Amini et al., 2014a). Although the previous research on PM_{10} has shown that the short-term effects on mortality can persist up to 30–40 days (Zanobetti et al., 2002; Zanobetti et al., 2003), to the best of our knowledge, no study reported lag structures of acute effects up to 45 days for $PM_{2.5}$, NO_2, and the AQI.

4.1. Overall association of mortality and $PM_{2.5}$

The RR (CI) for the association between $PM_{2.5}$ and overall all-cause non-accidental mortality in Tehran at lag 0 was 1.002 (1.0005, 1.0036) per each 10 $\mu g/m^3$ increase, which is consistent with the pooled global findings. Atkinson et al. (2014) conducted a systematic review and meta-analysis of the association between $PM_{2.5}$ and all-cause mortality in 23 studies and reported an RR (CI) of 1.010 (1.005, 1.056) per each 10 $\mu g/m^3$ increment. However, most of the assessed studies were conducted in high income countries where age distribution, genetic factors, response of their population, and air pollution concentrations could be different than Tehran (Atkinson et al., 2014). Another meta-analysis conducted only on studies from Chinese cities reported a RR (CI) of 1.004 (1.002, 1.006) for the same association, which is more comparable with our results (Lu et al., 2015).

Most studies conducted to date have considered short lag periods, and studies that have evaluated the effect of $PM_{2.5}$ beyond seven days are rare. Neuberger et al. (2007) evaluated the association between $PM_{2.5}$ and mortality in Vienna (Austria) for lags 0–1, 0–7, and 0–14 days. Similar to our results, the RR (CI) values rose steadily with the longer lags, increasing from 1.005 (0.994, 1.015) for 0–1, to 1.018 (1.000, 1.037) for 0–7, to 1.026 (1.011, 1.041) for 0–14 per each 10 $\mu g/m^3$ increment (Neuberger et al., 2007). The equivalent values in Tehran were 1.004 (1.001, 1.007) for 0–1 days, 1.011 (1.003, 1.020) for 0–7 days, and 1.014 (1.003, 1.025) for 0–14 days. They did not reach a maximum of 1.019 (1.0003, 1.038) until the 0–36 day lag. Again, the slightly higher values in Vienna could be due to the abovementioned differences in these two contexts, and maybe also due to the fact that in our study we used respiratory mortality as proxy for influenza, which may have attenuated our results. Two other studies, both within Air Pollution and Health: A European Approach (APHEA-2) project, have reported on the relationship between PM_{10} and mortality for lags of up to 0–40 days. They both observed that effect estimates were more than doubled for the longest lags (Zanobetti et al., 2002; Zanobetti et al., 2003). We did not find any other studies that considered the effects of $PM_{2.5}$ on mortality for lags as long as 0–45 days.

Support for these associations comes from extensive toxicological literature on their biological plausibility where multiple pathways have been proposed. Roy et al. (2014) suggested that the first pathways to ambient air pollution exposure within 24 h are through pulmonary inflammation and oxidative stress while after two to three days of exposure gradually hemostasis pathway responds (Roy et al., 2014). Other studies have reported that selective activation of endoplasmic reticulum stress response in the lung and liver tissues (Laing et al., 2010), adverse effects on inflammatory and hemostatic markers, such as high-sensitivity C-reactive protein, tissue-type plasminogen activator antigen, and plasminogen activator inhibitor (Green et al., 2016), sustained oxidative stress and inflammation, and increased autonomic nervous system activation (Fiordelisi et al., 2017), induction of endothelial cells apoptosis (Wang et al., 2017), pollution-mediated thrombosis through oxidative stress, platelet activation, interplay between interleukin-6 and tissue factor, circulating microvesicles and epigenetic changes (Robertson and Miller, 2018) are the possible pathways, and it is most likely that they act in concert.

4.2. Overall association of mortality and NO_2

The RR (CI) for the association between NO_2 and overall all-cause non-accidental mortality in Tehran at lag 0 was 1.003 (0.999, 1.006) for a 10 ppb increase, with the cumulative effects increasing steadily to 1.038 (1.003, 1.076) at a lag of 0–32 days. The aforementioned study in Vienna also considered NO_2 in the lagged mortality analyses, and reported an RR (CI) of 1.008 (1.000, 1.016) for 0–1 days, 1.021 (1.008, 1.035) for 0–7 days, and 1.029 (1.016, 1.041) for 0–14 days per each 10 $\mu g/m^3$ increment (Neuberger et al., 2007). These equivalent values in Tehran were 1.005 (0.999, 1.011) for 0–1 days, 1.018 (1.002, 1.035) for 0–7 days, and 1.029 (1.006, 1.052) for 0–14 days per each 10 ppb increment. Again, we did not find any other studies to consider longer cumulative lags for the association between NO_2 and mortality.

Fewer studies have reported the biological pathways for adverse effects of NO_2 compared to $PM_{2.5}$. The current toxicology literature suggests that when NO_2 is inhaled in large amounts, in the respiratory tract and lungs, it can react with constituents in the airway surface fluids, result in highly reactive protein and lipid oxidation products, which could through secondary reactions subsequently damage the epithelial cells and cause inflammation (Gamon and Wille, 2016). A study in the United States on older Americans by Honda et al. (2017) has shown that NO_2 was significantly associated with increased glycosylated hemoglobin (HbA1c) levels, leading to abnormal glucose metabolism and diabetes (Honda et al., 2017). Another study by van Veldhoven et al. (2019) also have done research on the short-term impact of NO_2 on the metabolome and suggested acyl-carnitine pathway, which has been previously found to be associated with cardio-respiratory disease (van Veldhoven et al., 2019). A recent study on the NO_2-related FEV1 responses, further suggested pathways involved in cellular adhesion, oxidative stress, inflammation, and metabolic responses (Ierodiakonou et al., 2019).

4.3. Overall association of mortality and AQI

The RR (CI) for the association between AQI and overall all-cause non-accidental mortality in Tehran was 1.001 (1.0002, 1.002) at lag 0, and the cumulative effect had an upward trend to 40 days, where the RR (CI) was 1.011 (1.001, 1.022) for a 10-unit increase—these values for an IQR increase in the AQI (31.5) were 1.004 (1.0007, 1.008) at lag 0 and 1.035 (1.0003, 1.071) at lag 40. To date, very few studies have reported on the association between air quality indices and mortality (Khajavi et al., 2019; Li et al., 2015), and none have considered long lag periods. Li et al. (2015) evaluated the association between mortality and the AQI (calculated using an approach similar to the US EPA) in Guangzhou (China), and reported RRs (CI) of 1.006 (1.003, 1.008) at lag 0 and 1.010 (1.003, 1.018) at lag 0–15 for each 10-unit increase (Li et al., 2015). Khajavi et al. (2019) have also investigated the association between mortality and AQI in Tehran using data from longitudinal Tehran Lipid and Glucose Study (TLGS) (Khajavi et al., 2019). They reported RR of 2.40 (1.03, 5.59) for lag 1 at AQI = 180. The RR reported by Khajavi et al. (2019) is larger than what we report here. However, there are important limitations to be highlighted for the study by Khajavi et al. (2019). First, their study area was limited only to one out of 22 administrative districts of Tehran megacity. Second, they created a time series of death events within a cohort study and therefore ended up in small sample size. In fact, they observed total of 725 deaths in their study from 1999 to 2014, which is quite smaller than our study with >122,000 deaths within three years. Third, they studied a maximum exposure window of six days (Khajavi et al., 2019). Two other studies have evaluated the Canadian Air Quality Health Index (AQHI), but they are not directly comparable with our findings because the index construction and communication are different from the AQI used here (Chen et al., 2013; Li et al., 2017b).

The AQI values below 50 are considered as good condition for air quality (U.S. Environmental Protection Agency, 2016). However, as shown in Fig. 2, the dose-response curve indicates that the lower the AQI, the better for health status of general population as the associations were close to linear down to the lowest observed

values. It also raises fundamental questions about the current color-concept used in the communication of the AQI. Given the observed increase in mortality at levels <50 AQI, it is problematic to label such days as having "good/healthy" conditions. This problem is underscored by the fact that the annual mean concentrations can be far above the air quality guideline values proposed by WHO to protect public health, even in a scenario where the majority of days would currently be considered "good/healthy".

4.4. Multi-pollutant models

The $PM_{2.5}$ effect estimates from the multi-pollutant models ($PM_{2.5}$ + NO_2) were similar to those from the single-pollutant model, with an overall RR (CI) of 1.002 (1.0003, 1.0037) at lag 0 up to a maximum significant cumulative RR (CI) of 1.018 (1.00004, 1.037) at lag 0–36 per each 10 $\mu g/m^3$ increment (Figs. 2 and SI, Table S4 and Table S5). Mills et al. (2016) conducted a systematic review and meta-analysis to distinguish associations between $PM_{2.5}$ and NO_2 and mortality (Mills et al., 2016). They found that short-term exposure to NO_2 and mortality was largely independent of PM mass, which supports our results.

4.5. Effect modification by sex, age group, and season

We generally found larger effects in females, in those older than 65 years, and in the cooler months (Figs. 3 and 4, and SI, Table S21 to Table S60), which is consistent with the findings of several other studies (Bell et al., 2015; Clougherty, 2010; Franklin et al., 2007; Li et al., 2017a; Li et al., 2015). Franklin et al. (2007) evaluated the association between $PM_{2.5}$ and mortality in 27 US communities and reported that the pooled RR (CI) for lag 1 in females was 1.013 (1.004, 1.023) compared with 1.011 (1.007, 1.021) in males. For the >75 age group the value was 1.017 (1.006, 1.027) compared with 1.006 (0.997, 1.015) in age group <75 (Franklin et al., 2007). Similar estimates have been found in several studies for NO_2 and the AQI (Li et al., 2015; Qin et al., 2017). The role of season has been evaluated in a number of studies and estimates depend on local conditions. In Tehran we found larger estimates in cooler months, when the organic matter and elemental carbon components of $PM_{2.5}$ are increased and the dust component is decreased (Arhami et al., 2017). Studies in the US have reported higher estimates in the warmer season for Detroit, but for the cooler season in Seattle (Zhou et al., 2011).

4.6. Strengths and limitations

Our study benefitted from the fact it was conducted in all districts of Tehran megacity in the Middle East, used air quality data from all 32 available monitoring stations, studied cumulative lags up to 45 prior days, considered single-pollutant and multi-pollutant modeling, used AQI as an exposure metric, which remains relatively under-researched compared to pollutant concentrations, and finally conducted several sub-group and sensitivity analyses.

It also suffered from a number of limitations. First of all, the mortality data was not coded by the ICD codes. Instead, the cause of death was recorded by several local codes in Farsi language by the staff of the Behesht-e-Zahra Cemetery Organization. This caused the process of data cleaning challenging to exclude accidents and extract respiratory mortality as well. However, it is very unlikely that our results would be affected by this limitation. Another limitation was that in fact, we used percentile 90 of respiratory mortality as a proxy for influenza and controlled that in our models. This may have attenuated our results in general. The fact that we have seen mostly non-significant results for <18 years of age group might be due to the inclusion of this variable in the models.

5. Conclusions

In conclusion, we found that the effects of $PM_{2.5}$, NO_2, and the AQI on mortality in Tehran were immediate, and that they increased steadily over a period of weeks. We further observed stronger associations in females, older age groups, and the cooler months. On the communication side, we did find that the reported AQI showed similar association with mortality as those measured by $PM_{2.5}$ and NO_2. However, the communication strategy could focus on reporting 30–45 day moving averages of AQI. This has important implications for risk communication, impact assessment, and health protection.

Conflicts of interest

All authors declare that they have no actual or potential financial competing interests.

Acknowledgment

Heresh Amini received a Swiss Government Excellence Scholarship (ESKAS) for PhD in Epidemiology and a project stipend of the PhD Program Health Sciences (PPHS) at the Faculty of Medicine, the University of Basel, Switzerland. The authors would like to thank the editor and four anonymous reviewers for their excellent comments and suggestions, which truly improved our work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2019.113121.

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