Association of fine particulate air pollution with cardiopulmonary morbidity in Western Coast of Saudi Arabia

Shedrack R. Nayebare, MS, PhD, Omar S. Aburizaiza, PhD, Azhar Siddique, PhD, David O. Carpenter, MD, Jahan Zeb, PhD, Abdullah J. Aburizaiza, MD, Cristian Pantea, MS, Mirza M. Hussain, PhD, Haider A. Khwaja, PhD.

ABSTRACT

الأهداف: دراسة الآثار الصحية المتعلقة ب $PM_{2.5}$ سابقا في المملكة العربية السعودية. قمنا بتقييم المراضة القلبية الرئوية المرتبطة التعرض اليومي ل $PM_{2.5}$ في رابغ.

الطريقة: رصدنا 24 ساعة $PM_{2.5}$ ومكوناتها بما في ذلك الكربون الأسود BC، وكبريتات الجسيمات $p–SO_4^{2-}$، والنترات $p–NO_3^-$، والأمونيوم $p=NH_4^+$ والعناصر النزرة TEs في موقع في رابغ من مايو – يونيو 2013 مع جمع في وقت واحد من بيانات المستشفى N=2513. تم تحديد مخاطر الاعتلال القلبي الرئوي في نموذج سلسل زمني خطي عام.

النتائج: ارتبط التعرض ل $PM_{2.5}$ مع 7.6% $p=0.056$ زيادة في خطر أمراض الجهاز التنفسي RD في الإناث. بك زيادة خطر الاعتلال أردي بنسبة 68.1% $p=0.056$ في الإناث. أدى التعرض إلى $p-SO_4^{2-}$ إلى زيادة خطر الإصابة بأمراض القلب والأوعية الدموية بنسبة تصل إلى 5.3% $p=0.048$ لدى الذكور؛ وRD بنسبة 2.9% $p=0.037$ و 2.5% $p=0.022$ في الإناث والذكور، على التوالي. يؤدي $p–NH_4^+$ إلى زيادة مخاطر الأمراض القلبية الوعائية بنسبة تصل إلى 20.3% ($p=0.033$) في الذكور؛ و RD بنسبة 10.7% $p=0.014$ و 8.0% $p=0.031$ في الإناث والذكور على التوالي. لم يلاحظ وجود ارتباط ذو دلالة إحصائية في التعرض ل $p–NO_3^-$ و TEs.

الخاتمة: عموما، تظهر النتائج زيادة خطر الإصابة بأمراض القلب والرئة بعد التعرض لتلوث الهواء.

Objectives: To assess cardiopulmonary morbidity associated with daily exposures to $PM_{2.5}$ in Western Coast of Saudi Arabia.

Methods: We monitored 24-h $PM_{2.5}$ and its constituents including black carbon (BC), particulate sulfate ($p-SO_4^{2-}$), nitrate ($p-NO_3^-$), ammonium ($p-NH_4^+$) and trace elements (TEs) at a site in Rabigh, Saudi Arabia from May to June 2013 with simultaneous collection of hospital data (N=2513). Cardiopulmonary morbidity risk was determined in a generalized linear time-series model.

Results: Exposure to $PM_{2.5}$ was associated with a 7.6% ($p=0.056$) increase in risk of respiratory disease (RD) in females. Black carbon increased RD morbidity risk by 68.1% ($p=0.056$) in females. Exposure to $p-SO_4^{2-}$ increased the cardiovascular disease (CVD) risk by up to 5.3% ($p=0.048$) in males; and RD by 2.9% ($p=0.037$) in females and 2.5% ($p=0.022$) in males. The $p-NH_4^+$ increased CVD risk by up to 20.3% ($p=0.033$) in males; and RD by 10.7% ($p=0.014$) in females and 8% ($p=0.031$) in males. No statistically significant association was observed for $p-NO_3^-$ and TEs exposure.

Conclusion: Overall, results show an increased risk for cardiopulmonary morbidity following exposure to air pollution.

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From the Department of Environmental Health Sciences (Nayebare, Carpenter, Hussain, Khwaja), School of Public Health, Institute for the Health and the Environment (Carpenter), University at Albany, from the Wadsworth Center (Nayebare, Hussain, Khwaja), Bureau of Occupational and Environmental Epidemiology (Pantea), New York State, the Department of Health, Albany, United States of America, from Ain Zubaida Rehabilitation & Ground Water Research Unit (Aburizaiza O, Zeb), King Abdulaziz University, Jeddah, School of Medicine (Aburizaiza A), Umm Ul Qura University, Mecca, Kingdom of Saudi Arabia, from Qatar Environment and Energy Research Institute (Siddique), Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar.

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Address correspondence and reprint request to: Dr. Haider A. Khwaja, Wadsworth Center, Empire State Plaza, New York State Department of Health, Albany, New York, United States of America. E-mail: haider.khwaja@health.ny.gov
ORICD ID: 0000-0002-0635-8447

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Epidemiological studies[1-4] continue to show that fine particulate ($PM_{2.5}$) air pollution increases the risk for morbidity and mortality from cardiopulmonary diseases. Exposure to $PM_{2.5}$ is believed to induce hypercoagulability, oxidative stress, pulmonary inflammation[5,6] and may alter cardiac autonomic function leading to changes in heart rate variability[7-10] and several severe cardiac events. The $PM_{2.5}$ constitutes a major portion of the overall particulate air pollution. While particulate air pollution is often monitored by only determining the levels of $PM_{2.5}$, it consists several different chemical species. We monitored the daily levels of $PM_{2.5}$ and determined its chemical components including black carbon (BC), particulate sulfate (p-SO_4^{2-}), nitrate (p-NO_3^-), ammonium (p-NH_4^+) and trace elements (TEs) at a site in Rabigh. Black carbon is primarily formed from incomplete combustion of bio-mass and fossil fuels; p-SO_4^{2-} and p-NO_3^- are formed by gas-phase oxidation of gaseous oxides of sulfur and nitrogen (SO_2 and NO_X) into sulfuric acid (H_2SO_4) and nitric acid (HNO_3) respectively.[11] The p-NH_4^+ typically exists as ammonium salts [$(NH_4)_2SO_4$ and NH_4NO_3] formed through the neutralization of H_2SO_4 and HNO_3 by atmospheric ammonia (NH_3).[12] Trace elements (TEs) will normally exist in ambient $PM_{2.5}$ aerosols in their most stable oxide forms. These aerosol species account for a significant portion of $PM_{2.5}$ and are toxic to human health and the environment. Rabigh is heavily industrialized (mostly petrochemical industry) plus its neighbored by Jeddah city that is also heavily industrialized. The major anthropogenic emission sources of air pollution in these cities are typically related to fossil fuels combustion and several other industrial processes, and vehicular emissions.[13,14] These sources are clearly depicted by the high levels of BC, p-SO_4^{2-}, p-NO_3^-, p-NH_4^+ and TEs observed in Rabigh. Industrialized cities in the Middle East[15,16] have high levels of $PM_{2.5}$. While the association between exposure to $PM_{2.5}$ and cardiopulmonary diseases has been well studied in developed countries of Europe[17-20] and North America,[21-24] limited or no research has been done for most countries in the Middle East, including Saudi Arabia. Cardiovascular diseases account for 35.9% of the overall 90,000 annual deaths in Saudi Arabia[25] and coronary heart disease is the third most common cause of hospital based mortality among the elderly.[26] Additionally, the burden of respiratory diseases is also significant. Chronic respiratory diseases account for more than 2% of the total deaths annually.[25] The hypothesis of this study is that air pollution is associated with an increased risk for cardiopulmonary diseases. We aimed to investigate the association of cardiopulmonary morbidity with the daily exposures to $PM_{2.5}$ in the urban population of Rabigh, Saudi Arabia.

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Methods.

$PM_{2.5}$ sample collection and analysis. A $PM_{2.5}$ sampler was installed for the period of 6 weeks from May to June 2013 at a fixed site in Rabigh city, Kingdom of Saudi Arabia. The 24-h samples of $PM_{2.5}$ were collected on pre-weighed and sequentially numbered polypropylene ring supported Whatman 2.0 µm pore-size PTFE 46.2 mm filters using a low volume air sampling pump operated at a flow rate of 16.7 L/min. The 24-h $PM_{2.5}$ samples were then analyzed for the overall mass concentrations of $PM_{2.5}$ and its chemical constituents including BC, NH_4^+, SO_4^{2-}, NO_3^- and trace elements (TEs). A detailed description of $PM_{2.5}$ sample collection and analysis, equipment and chemicals used, and the map of the study area has already been provided.[13,14]

Hospital data. The physicians at Rabigh General Hospital collected information on all patients with a primary or secondary diagnosis of either cardiovascular (CVD) or respiratory disease (RD) who visited the emergency room (ER) during the period from May 2013 to June 2013. Electronic hospital records were collected for each day of $PM_{2.5}$ sampling and organized in excel spread-sheets. The information collected on each hospital record included; date of admission, patient age, gender, nationality, diagnosis and the ICD-10 code for each diagnosis. All the patient records were coded with patient IDs to ensure patient confidentiality. Additionally, we further reviewed all the provided hospital records in electronic form crosschecking the diagnoses with the current ICD-10 codes. Patient records with missing diagnosis and gender, were excluded from further analyses. Institutional Review Board (IRB) approvals to use the collected hospital records were obtained from the Ministry of Health in Saudi Arabia, University at Albany, SUNY and the New York State Department of Health IRB committees.

Statistical analysis. We utilized a generalized linear time-series model (GLM) to investigate the association of exposure to $PM_{2.5}$ and its constituents (BC, p-NH_4^+, p-SO_4^{2-}, p-NO_3^- and TEs) with daily ER visits for cardiopulmonary diseases among the urban population of Rabigh. Due to significant correlations between the different air pollutant species analyzed, the health risk associated with exposure to each pollutant specie was modeled separately in single pollutant and single lag

models, to avoid introducing errors associated with collinearity. The models were adjusted for the day of the week effects and confounding due to meteorology (average daily temperature, relative humidity and wind speed). Effect modification related to personal life styles (such as diet, exercise and smoking) were not controlled for, since there were no data on these variables. The period between exposure and outcome was evaluated using time lags going up to 6 days post exposure (lags 0–6), where "lag 0" means the same day effects; "lag 1", the effects after one day and so on. Equation 1 is the general form of the time–series model used to analyze the data, with health outcome counts variances Vt = ϕμt

$$\eta_t = \ln(\mu_t) = \ln[E(Y_t)] = a_0 + \sum_{j=1}^{q} f_i(X_{tj}) + \beta_t(E_t) + \sum_{d=1}^{p} \beta_d(Z_d)$$

(Equation 1)

where Y_t=observed health outcome counts on day t; E_t=exposure of interest, β_t=effect estimate for Et on day t; X_t=time–varying predictor variables and potential confounders, f_i=smooth/spline functions of these variables to allow for non–linear relationships; Z_d=any other non–time varying factors; μ_t=expected count of the health outcome [$E(Y_t)$]; and ϕ=the over–dispersion parameter estimated from the Pearson's χ^2 statistic. Depending on the specifications of the spline function (parametric and non-parametric), the model in **Equation 1** can lead to GLM (parametric functions) and Generalized Additive Models (GAM) (non-parametric functions). Since we applied a GLM with a negative binomial distribution, the spline function on the non-linear predictor variables could not be included in the regression analysis. The spline function for this model is not supported by the SAS software currently in use. However, the results from this GLM model were the same when compared to GAM model with spline function on the non-linear covariates. The analyses were only stratified by gender and diagnosis category. We did not assess the health risk by age-group and individual diagnosis due to a limitation on sample size. All statistical analyses were performed using SAS 9.4 version. Our single pollutant and single lag model is as shown in Equation 2.

$$\ln(Y_t) = \beta_0 + \beta_1 (Lag_\chi P_i) + \beta_2 (Sun) + \beta_3 (Mon) + \beta_4 (Tue) + \beta_5 (Wed) + \beta_6 (Thu) + \beta_7 (Fri) + \beta_8 (Mean\ daily\ temp.) + \beta_9 (Humidity) + \beta_{10} (Wind\ Speed) \quad \textbf{(Equation 2)}$$

where, Y_t=the number of ER visits for either CVD or RD; Lag_χ=the time lag (lag 0 – lag 6); and P_i = the air pollutant specie ($PM_{2.5}$, BC, SO_4^{2-}, NO_3^- and NH_4^+).

Table 1 - Pearson correlation between different pollutant species measured from $PM_{2.5}$ and with daily visits for cardiopulmonary diseases (combined CVD and RD).

	$PM_{2.5}$	BC	SO_4^{2-}	NO_3^-	NH_4^+	MT	RH	WS
DV	0.001	0.043	0.064	-0.029	0.060	-0.050	0.061	-0.075
$PM_{2.5}$	1.00	0.473**	0.110	0.299*	-0.131	0.331*	-0.22*	-0.069
BC		1.00	0.41**	0.168*	0.288*	-0.093	0.061	-0.172*
SO_4^{2-}			1.00	-0.067	0.940***	-0.307*	0.489**	-0.581**
NO_3^-				1.00	-0.281*	-0.102	0.056	0.019
NH_4^+					1.00	-0.364*	0.524**	-0.535**
MT						1.00	-0.734***	0.245*
RH							1.00	-0.290*
WS								1.00

DV-Daily visits for cardiopulmonary diseases; MT-Mean daily temperature (°F); RH-Relative humidity; WS-Wind speed. Only *p*-values ≤ 0.05 were considered statistically significant. Alfa (∝) was set at 5%. Correlations= r*-Moderate/ low correlation (0.2-0.4), r**-High correlation (>0.4-0.7), r***-Very high correlation (>0.7-1.0)

Results. Significant correlations between different pollutant species and with meteorology were observed. Daily $PM_{2.5}$ was moderately correlated with BC (r=

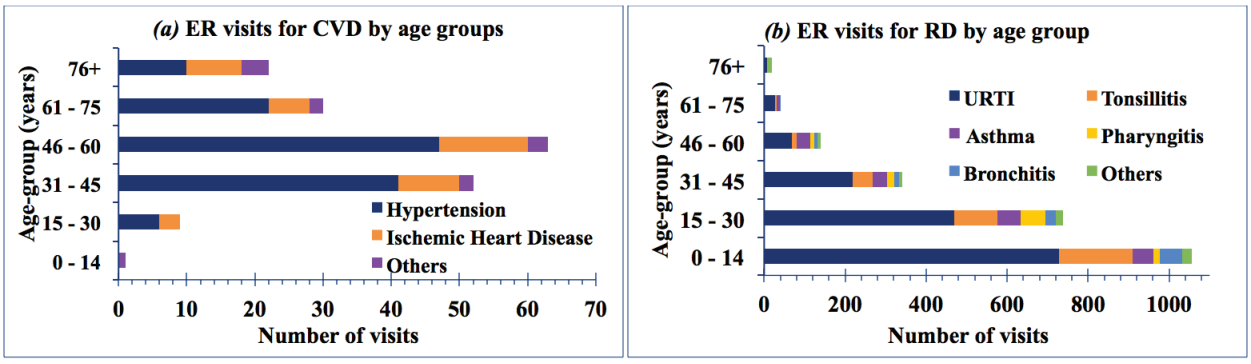

Figure 1 - Bar graphs showing the top diseases by age-groups in the emergency room (ER) visits for **a**) cardiovascular (CVD) and **b**) respiratory diseases (RD) during the study period.

Table 2 - Summary of the overall ER visits by diagnosis category, diagnosis and age-groups collected over the study period (7th May – 17th June 2013) from Rabigh hospital, Kingdom of Saudi Arabia.

CVD			RD			CVD			RD		
Diagnosis	**n**	**(%)**	**Diagnosis**	**n**	**(%)**	**Age group**	**n**	**(%)**	**Age group**	**n**	**(%)**
HTN	127	(71.3)	URTI	1521	(65.1)	0-14	1	(0.60)	0-14	1056	(45.2)
IHD	43	(24.2)	Tonsillitis	351	(15.0)	15-30	9	(5.10)	15- 30	738	(31.6)
Others	8	(4.50)	Asthma	189	(8.10)	31-45	52	(29.2)	31-45	341	(14.6)
			Pharyngitis	105	(4.50)	46-60	64	(36.0)	46 -60	141	(6.04)
			Bronchitis	103	(4.43)	61-75	30	(16.9)	61-75	40	(1.71)
			Others	66	(2.83)	76+	22	(12.4)	76+	19	(0.81)
Total	**178**	**(100)**		**2335**	**(100)**		**178**	**(100)**		**2335**	**(100)**

HTN - Hypertension; IHD – Ischemic Heart Disease; URTI - Upper Respiratory Tract Infection; IHD - Ischemic Heart Disease and Myocardial Infarction; HTN - Hypertension and Pulmonary Hypertension; Other CVD - cerebrovascular accident, ACS, Atrial Fibrillation, Infective Endocarditis and Symptomatic Bradycardia; Asthma - bronchial asthma, asthma, exacerbated bronchial asthma, chronic bronchial asthma; Tonsillitis - tonsillitis, acute and chronic tonsillitis and acute follicular tonsillitis; Pharyngitis - pharyngitis and acute pharyngitis; Bronchitis - bronchitis and acute bronchitis; Other RD - chest infection, rhinitis, bronchiolitis, croup, pneumonia, pulmonary congestion, sinusitis, allergic rhinitis, lung fibrosis, and respiratory distress

Table 3 - Relative risk (RR) estimates per 10 μg/m^3 increments in $PM_{2.5}$ and 1.0 μg/m^3 increments in BC.

	$PM_{2.5}$				BC			
	CVD		**RD**		**CVD**		**RD**	
	RR (95% CIs)	***P*-value**	**RR (95% CIs)**	***P*-value**	**RR (95% CIs)**	***P*-value**	**RR (95% CIs)**	***P*-value**
Combined age groups and gender								
Lag_0	0.941 (0.831, 1.065)	0.3340	0.990 (0.936, 1.047)	0.7271	0.838 (0.370, 1.900)	0.6729	1.279 (0.894, 1.830)	0.1779
Lag_1	0.979 (0.848, 1.130)	0.7700	0.968 (0.911, 1.027)	0.2781	0.917 (0.413, 2.032)	0.8303	0.914 (0.643, 1.299)	0.6162
Lag_2	0.941 (0.818, 1.082)	0.3939	1.017 (0.963, 1.074)	0.5550	0.810 (0.351, 1.868)	0.6206	1.048 (0.741, 1.481)	0.7925
Lag_3	0.922 (0.801, 1.060)	0.2547	1.007 (0.948, 1.070)	0.8211	0.732 (0.332, 1.614)	0.4389	1.150 (0.832, 1.590)	0.3980
Lag_4	1.046 (0.913, 1.197)	0.5178	0.973 (0.916, 1.034)	0.3826	1.506 (0.682, 3.325)	0.3109	1.143 (0.807, 1.619)	0.4515
Lag_5	0.900 (0.768, 1.056)	0.1957	0.978 (0.919, 1.040)	0.4758	0.966 (0.425, 2.200)	0.9351	1.154 (0.807, 1.648)	0.4330
Lag_6	0.992 (0.859, 1.145)	0.9132	1.030 (0.970, 1.094)	0.3314	1.504 (0.700, 3.231)	0.3784	1.420 (1.017, 1.984)	0.0397
CVD (stratified by gender)								
	Female		**Male**		**Female**		**Male**	
Lag_0	1.019 (0.860, 1.206)	0.8315	0.944 (0.826, 1.078)	0.3942	0.407 (0.066, 2.531)	0.3352	1.060 (0.413, 2.720)	0.9037
Lag_1	0.943 (0.756, 1.177)	0.6026	1.029 (0.883, 1.198)	0.7157	0.640 (0.171, 2.397)	0.5082	0.979 (0.334, 2.868)	0.9694
Lag_2	0.936 (0.760, 1.152)	0.5302	0.916 (0.789, 1.063)	0.2481	0.873 (0.201, 3.796)	0.8560	0.748 (0.266, 2.102)	0.5820
Lag_3	0.944 (0.752, 1.185)	0.6200	0.919 (0.782, 1.081)	0.3104	1.408 (0.278, 7.139)	0.6794	0.452 (0.167, 1.228)	0.1194
Lag_4	1.063 (0.892, 1.268)	0.4941	1.056 (0.906, 1.230)	0.4858	1.321 (0.366, 4.771)	0.6712	1.613 (0.534, 4.877)	0.3969
Lag_5	0.859 (0.656, 1.126)	0.2714	0.926 (0.791, 1.085)	0.3415	0.496 (0.103, 2.398)	0.3832	1.120 (0.410, 3.057)	0.8248
Lag_6	0.949 (0.779, 1.155)	0.5998	0.987 (0.854, 1.139)	0.8532	1.866 (0.464, 7.508)	0.3796	1.911 (0.702, 5.201)	0.2047
RD (stratified by gender)								
	Female		**Male**		**Female**		**Male**	
Lag_0	1.030 (0.959, 1.107)	0.4201	0.979 (0.920, 1.041)	0.4943	1.524 (0.880, 2.638)	0.1326	1.135 (0.707, 1.822)	0.6012
Lag_1	0.950 (0.870, 1.036)	0.2438	1.003 (0.932, 1.078)	0.9425	0.799 (0.464, 1.377)	0.4191	0.988 (0.623, 1.569)	0.9605
Lag_2	1.076 (0.998, 1.161)	0.0561	1.013 (0.951, 1.080)	0.6904	1.202 (0.706, 2.044)	0.4980	0.942 (0.597, 1.489)	0.7994
Lag_3	0.976 (0.899, 1.060)	0.5673	1.009 (0.945, 1.078)	0.7850	0.878 (0.526, 1.466)	0.6201	1.362 (0.895, 2.072)	0.1497
Lag_4	0.947 (0.870, 1.031)	0.2083	0.982 (0.917, 1.051)	0.5946	1.022 (0.588, 1.775)	0.9397	1.246 (0.795, 1.954)	0.9678
Lag_5	0.942 (0.866, 1.025)	0.1653	0.983 (0.919, 1.052)	0.9162	1.003 (0.571, 1.760)	0.9929	1.267 (0.798, 2.012)	0.3153
Lag_6	0.989 (0.913, 1.071)	0.7877	1.026 (0.961, 1.095)	0.4468	1.681 (0.987, 2.862)	0.0557	1.291 (0.838, 1.989)	0.2474

BC - Black carbon, CVD - Cardiovascular disease, RD - Respiratory disease

0.47, *p*-value<.0001), *p*-SO_4^{2-} was highly correlated with *p*-NH_4^+ (r=0.94, *p*-value <.0001), *p*-NO_3^- had moderate negative correlation with *p*-NH_4^+ (r=–0.28, *p*-value <.0001) and was not significantly correlated with *p*-SO_4^{2-} (**Table 1**). The average levels of daily $PM_{2.5}$ and its components during the entire study period were as follows; $PM_{2.5}$ (37.0±16.2 μg/m^3), BC (1.11±0.38 μg/m^3), *p*-SO_4^{2-} (7.01±4.79 μg/m^3), *p*-NO_3^- (2.28±1.36

Table 4 - Relative risk estimates per 1.0 μg/m³ increment in exposure to *p*-SO_4^{2-}, *p*-NO_3^-, and *p*-NH_4^+.

	p-SO_4^{2-}				p-NO_3^-				p-NH_4^+			
	CVD		RD		CVD		RD		CVD			RD
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Combined age groups and gender												
Lag_0	0.98 (0.94, 1.03)	0.520	1.000 (0.98, 1.02)	0.795	0.95 (0.84, 1.08)	0.453	0.96 (0.91, 1.01)	0.146	0.990 (0.85, 1.15)	0.891	1.010 (0.95, 1.08)	0.662
Lag_1	0.99 (0.95, 1.03)	0.532	1.010 (0.99, 1.03)	0.401	1.01 (0.89, 1.16)	0.826	0.96 (0.91, 1.02)	0.202	0.970 (0.87, 1.10)	0.676	1.040 (0.98, 1.10)	0.197
Lag_2	1.01 (0.97, 1.05)	0.646	1.020 (1.01, 1.04)	0.017	0.95 (0.83, 1.08)	0.421	0.97 (0.91, 1.02)	0.239	1.020 (0.90, 1.16)	0.728	1.058 (1.01, 1.11)	0.033
Lag_3	1.01 (0.97, 1.05)	0.569	1.020 (1.01, 1.03)	0.026	0.93 (0.81, 1.06)	0.290	0.92 (0.87, 0.98)	0.007	1.050 (0.93, 1.18)	0.411	1.060 (1.01, 1.11)	0.017
Lag_4	1.03 (1.00, 1.07)	0.080	1.020 (1.00, 1.03)	0.061	0.97 (0.83, 1.12)	0.654	0.90 (0.85, 0.95)	0.0004	1.101 (0.98, 1.23)	0.093	1.064 (1.01, 1.12)	0.011
Lag_5	1.02 (0.97, 1.08)	0.407	1.020 (1.01, 1.04)	0.012	0.84 (0.71, 1.00)	0.047	0.94 (0.88, 1.01)	0.080	1.100 (0.96, 1.25)	0.174	1.069 (1.02, 1.12)	0.009
Lag_6	1.04 (1.00, 1.09)	0.052	1.030 (1.01, 1.04)	0.004	1.06 (0.87, 1.29)	0.583	0.94 (0.88, 1.01)	0.109	1.125 (0.99, 1.28)	0.072	1.088 (1.03, 1.15)	0.001
CVD (stratified by gender)												
	Female		Male		Female		Male		Female		Male	
Lag_0	1.01 (0.93, 1.10)	0.776	0.96 (0.90, 1.030)	0.270	0.98 (0.79, 1.23)	0.869	0.95 (0.80, 1.12)	0.508	1.030 (0.80, 1.33)	0.815	0.950 (0.78, 1.16)	0.630
Lag_1	0.98 (0.91, 1.05)	0.520	0.99 (0.94, 1.040)	0.784	0.92 (0.72, 1.16)	0.478	1.06 (0.91, 1.24)	0.473	0.960 (0.78, 1.18)	0.710	0.980 (0.85, 1.14)	0.829
Lag_2	1.02 (0.92, 1.13)	0.704	1.01 (0.96, 1.06)	0.716	1.00 (0.78, 1.29)	0.996	0.90 (0.76, 1.07)	0.221	1.070 (0.82, 1.39)	0.627	1.020 (0.88, 1.18)	0.826
Lag_3	1.03 (0.97, 1.09)	0.366	1.00 (0.95, 1.06)	0.881	1.05 (0.83, 1.33)	0.662	0.84 (0.70, 1.01)	0.063	1.070 (0.88, 1.29)	0.522	1.050 (0.89, 1.23)	0.567
Lag_4	1.02 (0.96, 1.09)	0.481	1.051 (1.01, 1.10)	0.034	1.05 (0.78, 1.43)	0.739	0.90 (0.74, 1.10)	0.312	1.090 (0.88, 1.35)	0.442	1.168 (1.01, 1.35)	0.036
Lag_5	1.00 (0.92, 1.08)	0.949	1.06 (0.98, 1.14)	0.131	0.93 (0.69, 1.25)	0.641	0.79 (0.63, 0.98)	0.034	0.860 (0.40, 1.86)	0.697	1.191 (0.99, 1.43)	0.061
Lag_6	1.06 (0.96, 1.18)	0.235	1.053 (1.01, 1.11)	0.048	1.29 (0.92, 1.80)	0.137	0.98 (0.74, 1.29)	0.860	1.140 (0.85, 1.53)	0.392	1.203 (1.01, 1.43)	0.033
RD (stratified by gender)												
	Female		Male		Female		Male		Female		Male	
Lag_0	1.01 (0.97, 1.04)	0.665	1.00 (0.97, 1.03)	0.912	1.00 (0.92, 1.09)	0.993	0.93 (0.87, 1.00)	0.065	1.020 (0.92, 1.13)	0.702	1.010 (0.92, 1.10)	0.872
Lag_1	0.99 (0.96, 1.03)	0.667	1.020 (0.99, 1.04)	0.167	0.97 (0.88, 1.06)	0.489	0.96 (0.89, 1.04)	0.286	1.000 (0.91, 1.09)	0.913	1.060 (0.99, 1.14)	0.090
Lag_2	1.01 (0.99, 1.04)	0.310	1.025 (1.01, 1.05)	0.022	1.02 (0.93, 1.11)	0.702	0.93 (0.86, 1.01)	0.067	1.040 (0.96, 1.13)	0.367	1.070 (1.01, 1.15)	0.044
Lag_3	1.01 (0.99, 1.04)	0.389	1.023 (1.01, 1.05)	0.030	0.92 (0.84, 1.00)	0.064	0.93 (0.86, 1.00)	0.047	1.030 (0.95, 1.11)	0.448	1.080 (1.02, 1.15)	0.014
Lag_4	1.02 (0.99, 1.04)	0.245	1.020 (0.99, 1.04)	0.117	0.92 (0.84, 1.01)	0.089	0.88 (0.82, 0.95)	0.001	1.060 (0.98, 1.14)	0.122	1.070 (1.01, 1.14)	0.033
Lag_5	1.026 (1.0, 1.06)	0.069	1.021 (0.99, 1.04)	0.076	0.98 (0.88, 1.09)	0.723	0.92 (0.84, 1.00)	0.046	1.071 (0.99, 1.16)	0.095	1.070 (1.01, 1.14)	0.048
Lag_6	1.029 (1.0, 1.06)	0.037	1.024 (1.01, 1.05)	0.034	0.92 (0.82, 1.03)	0.148	0.96 (0.87, 1.05)	0.366	1.107 (1.02, 1.20)	0.014	1.080 (1.01, 1.15)	0.031

CVD - Cardiovascular disease, RD - Respiratory disease

μg/m³) and *p*-NH_4^+ (1.89±1.51 μg/m³). Previously, we provided a comparison of $PM_{2.5}$ levels observed in Rabigh with other cities around the world.[13] The daily $PM_{2.5}$ levels in Rabigh did not only exceed the WHO guideline (25.0 μg/m³) but were also higher than for most cities considered.

Overall, there were 2513 ER visits collected over a period of May 2013 to June 2013. These have been summarized by diagnosis category and age–group in **Table 2** and presented in **Figure 1**. The most frequent forms of cardiovascular diseases were hypertension (HTN) (71.3%) and ischemic heart disease (IHD) (24.2%). The prevalence of CVD increased with age peaking at age-group (46–60) years (**Figure 1a**). Respiratory diseases were mostly upper respiratory tract infections (URTIs), tonsillitis, asthma, pharyngitis and bronchitis. The prevalence of RD decreased with age. People below 30 years had the highest rate with children (0-14) years being the most vulnerable (**Figure 1b**).

The relative risk (RR) estimates for cardiopulmonary morbidity at 95% CI associated with a 10 μg/m³ increase in $PM_{2.5}$ and a unit (1.0 μg/m³) increase in BC, *p*-SO_4^{2-}, *p*-NO_3^- and *p*-NH_4^+ have been determined and presented in **Tables 3 & 4**. A 10 μg/m³ increase in exposure to $PM_{2.5}$ was associated with a 7.6% increased risk for RD in females, with a marginal statistical significance. A unit (1.0 μg/m³) increase in exposure to BC was significantly associated with a 42.0% (95% CI: 1.017, 1.984) increased risk for RD with combined genders, and 68.1% (95% CI: 0.987, 2.862) in females, with a marginal statistical significance. Increased risk estimates were also observed for both CVD and RD at several lags but with no statistical significance (**Table 3**).

A unit increase in exposure to *p*-SO_4^{2-} was significantly associated with a 5.1–5.3% increased risk for CVD in males; and a 2.9% increased risk for RD in females and 2.3–2.5% in males (**Table 4**). A similar increase in exposure to *p*-NO_3^- was associated with 29% increased risk for CVD in females and 6.0% in males but with no statistical significance as shown in **Table 4**. Exposure to *p*-NH_4^+ was significantly associated with a 5.8–8.8% increased risk for RD with combined

genders; males 7.0–8.0% and females 10.7% (95% CIs: 1.02, 1.20). A similar exposure significantly increased the risk for CVD in males by 16.8–20.3% at lags 4 and 6 as shown in **Table 4**.

Discussion. The outcome on RD was relatively earlier than the CVD for most part. We observed an increased risk for RD at later lags too. This could possibly be clarified with longer sampling duration and larger sample size study. Much of the risk on RD became more apparent within the first two days following exposure (lags 1–2). In contrast CVD risk was mostly observed several later lags. These observations are biologically plausible given that RD often have a short incubation period of a few hours to days[27] while CVD tend to have longer incubation periods following exposure.[28] The observed increased CVD risk at lags 0–1 could imply exacerbation of preexisting illnesses since the outcomes on CVD usually take longer incubation periods to manifest. Also, majority of RD recorded were URTIs, which would be mostly acute and thus the increased RR at lags 0–1. This may also suggest that the subject had an existing URTI that was adversely impacted by the air pollution. Health issues related to CVD normally appear later in life since the behavioral risks associated with heart diseases such as smoking, diet, exercise and occupational exposures are mostly experienced in adulthood. These in addition to air pollution exposure, may pose a significant risk for adverse cardiovascular health outcomes. Moreover, HTN and IHD diagnoses tend to be more prevalent among middle-aged adults and the elderly due to cumulative lifestyle risks.

Though these findings are consistent with results from previous studies especially for exposures to $PM_{2.5}$ and BC, the observed associations between air pollution and cardiopulmonary morbidity are relatively higher than previously reported data.[22,29] This may be primarily attributed to the higher levels of particulate air pollution observed in this study as compared to the levels measured in cities of the developed nations. Another factor is that this study did not focus only on the primary diagnosis of RD and CVD, which may have led to detection of associations that were not found in studies looking only at primary diagnoses. Future studies may need to focus more on the health effects associated with elevated levels of particulate air pollution, as this seems to be the major environmental issue in heavily industrialized countries such as Saudi Arabia. Furthermore, though results on the health risk associated with exposure to p-SO_4^{2-} and p-NO_3^- are consistent with some previous studies[30,31] findings from majority of epidemiologic studies that assessed the risk of exposure to p-SO_4^{2-} are still inconsistent and the data on p-NO_3^- are very limited.[32] However, the RR estimates for exposure to p-NO_3^- were not statistically significant which may be due to a small sample size. Also, the effect of exposure to p-NH_4^+ on cardiopulmonary health outcomes has not been studied previously in either epidemiologic or toxicological studies. However, a significant risk on exposure to p-NH_4^+ for both RD and CVD has been observed (**Table 4**).

Reiss et al[32] (2007) noted that the existing epidemiologic and toxicological data provide little or no support for a causal association between p-$SO4^{2-}$ exposure and health risk at ambient concentrations. It should be noted that the ambient concentrations of p-SO_4^{2-} vary significantly from place to place. Thus, it is difficult to establish a baseline on this observation. Also, the ambient p-SO_4^{2-} concentrations authors referred to were from the developed nations, which tend to be much lower than what is measured in heavily industrialized cities of developing nations. Results are indeed quite intriguing when the effects on exposure to p-SO_4^{2-} are assessed using high ambient concentrations such as those determined in this study. Reiss and his colleagues further noted that there were virtually no epidemiologic data on p-NO_3^- and that the little existing toxicological data did not support any causal association between p-NO_3^- and the health risks. To fully understand the health effects of exposure to particulate p-SO_4^{2-}, p-NO_3^- and p-NH_4^+ on cardiopulmonary health outcomes, it requires long-term monitoring. However, results from this study clearly show that exposure to these pollutant species potentially increases the risk for morbidity due to both CVD and RD at several lags. This may be attributable to the relatively higher fine particulate pollutants concentrations observed in this study, as compared to what has been previously reported from cities of developed nations in Europe and N. America.

A substantial morbidity risk but with no statistical significance was observed for daily exposures to p-NO_3^- and CVD in females. However, much of the exposures to p-NO_3^- showed a significant protective effect on morbidity due to RD (**Table 4**). It is possible that the association between p-NO_3– exposure and cardiopulmonary morbidity may have been affected by the prevailing meteorology during the study period. As discussed earlier, p-NO_3^- may exist as either NH_4NO_3 or $NaNO_3$ depending on the prevailing environmental factors such as meteorology, sampling location and emission sources. For example, the existence of ambient NH_4NO_3 is strongly influenced by ambient temperature.[33] This further warrants long-term monitoring to assess the influence of seasonal variations

in meteorology on the health risk associated with *p*-NO_3^- exposure.

Overall, results clearly indicate that daily exposures to elevated levels of fine particulate pollutant species significantly increases the risk for cardiopulmonary morbidity. There are some major strengths of this study, especially in having direct measurements of different components of particulate air pollution, including some pollutants such as *p*-NH_4^+, that have not previously been reported. There are also some limitations in that only particulates were monitored, and did not include other gaseous air pollutants. Moreover, sampling was done only during summer (May to June 2013). Thus, the influence of seasonality on the association of exposure to air pollutants and cardiopulmonary morbidity could not be assessed. Also, since we had only one sampling site, there was a potential for exposure misclassification, particularly for those patients that lived far from the monitoring site. Furthermore, the health data besides having a small sample size, included all RD and CVD diagnoses, not only those that were the primary diagnosis and reason for visit to the ER. It was also difficult to ascertain the representatives of the patients at Rabigh General Hospital to the general Rabigh population. Besides, the risk estimates provided in studies of this nature, are on a population level. Thus, they may not be extrapolatable directly to individual level due to interindividual differences such as age, gender, socio-economic status, etcetera. Nevertheless, results from this study can be used as a basis for further studies with longer duration of sampling and larger sample size.

Summary and conclusions. This is the first study to assess the effect of exposure to particulate air pollution and cardiopulmonary health in Rabigh, Saudi Arabia. Health effects associated with higher ambient particulate air pollution than what has been previously reported in several studies, were assessed. Results clearly showed that daily exposures to elevated levels of $PM_{2.5}$ and its components including BC, *p*-SO_4^{2-}, *p*-NO_3^- and *p*-NH_4^+ significantly increased the rates of ER visits for CVD and RD morbidity in Rabigh with the strongest association observed for exposures to BC. Age is clearly an important factor. Children aged 0 to 14 years dominated the ER visits for RD. Children are normally very active, have a high metabolism and an increased air intake. Besides, their lungs and other biological systems are still undergoing rapid development which makes them more vulnerable to the damaging effects of air pollution. Adults above 30 years dominated the CVD category. Factors such as diet, exercise, pre-existing medical conditions, as well as social economic status may perhaps be significantly influencing the observed prevalence rates for CVD in Rabigh. These in addition to high levels of $PM_{2.5}$, may provide the most plausible explanation as to why the CVD peak at age-groups above 30 years. It is recommendable that future studies with larger sample sizes, consider determining the associations among different age-groups, to clearly identify the most vulnerable sub-groups. Though the high ambient concentrations of these pollutant species could be a major factor that influenced the observed health outcomes, more studies are obviously needed to affirm this supposition.

Cardiopulmonary health outcomes especially for CVD can be due to a range of other factors especially those closely linked to diet, exercise, pre-existing medical conditions, and social economic status (SES). It would be recommendable if future studies controlled for these factors to accurately determine the cardiopulmonary risk associated with exposure to elevated levels of particulate air pollution in Saudi Arabia and the rest of the Middle East region. Moreover, several long-term exposure studies will be necessary to assess the health risk associated with air pollutant species such as *p*-NO_3^- that showed inconsistent associations in this study. Exposure to TEs did not show any increased risk for this analysis. The health risk for exposure to TEs could also be effectively assessed with long-term monitoring.

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