Air Pollution and Hospital Admission for Epilepsy in Kerman, Iran

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Abstract

Background: There is little information about air pollution and epilepsy attacks. The aim of this study was to investigate the relation between air pollution and epilepsy admission in Kerman, Iran.

Methods: This was an ecological study, in which the concentrations of ambient air pollutants and meteorological data were inquired from the Kerman Environmental Protection Agency and the Kerman Meteorology Organization respectively, and epilepsy admission data were obtained from Kerman's Shafa hospital Epilepsy Registry. Generalized Additive Models (GAM) with lags up to 7 days were used for estimating the Relative Risks (RR).

Results: During 2008 until 2020, 894 epilepsy admission occurred in Kerman which 498 (55.7%) were male. The strongest relation between epilepsy admission was seen in the over 59 years group for CO in lag 0 (RR = 2.1455, 95% CI: 1.5823–2.9091), for NO_2 in lag 0 (RR =1.0409, 95% CI: 1.0282–1.0537), and for $PM_{2.5}$ in lag 5 (RR =1.0157, 95% CI: 1.0062–1.0252). Also for PM_{10} in the under 18 year's group in lag 2 (RR =1.0064, 95% CI: 1.0029–1.0098), for O_3 in lag 0 (RR =0.9671, 95% CI: 0.9581–0.9761) and for SO_2 in lag 5 (RR = 0.9937, 95% CI: 0.9891–0.9983).

Conclusion: The findings of this study showed that CO, NO_2, $PM_{2.5}$, and PM_{10} air pollutants might be risk factors for epilepsy admission in Kerman.

Background

Epilepsy is one of the most common serious neurological problems and occurs because of sudden, severe and intermittent disturbance of the nervous system due to abnormal electrical activity of the neurons (1).

Air pollution may be able to cause CNS damage and neurodegenerative disorders (2). The occurrence of seizures may be affected by the interaction of internal and pathologic factors as well as extrinsic factors, including medication and environmental factors (3, 4). Studies have shown that Parkinson's disease (PD), Alzheimer's disease (AD), Multiple Sclerosis (MS) and stroke may be related to ambient air pollution (5, 6). Calderon et al. conducted a study in Mexico and report that exposure to air pollutants can seriously affect children's central nervous system (7). Another study from China also shows the possible relation between air pollution and neurodegenerative diseases (8). Fluegge et al. reported hospitalization for epilepsy associated with changes in the concentrations of various pollutants including nitrogen dioxides (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), ozone (O_3), and particulate matter (PM_{10}, $PM_{2.5}$), and showed that air pollutants might be a risk factor for hospital admission for epilepsy (9).

However, the effect of air pollution on the central nervous system (CNS) has not been thoroughly studied. The prevalence of epilepsy in Kerman city was 7.87 per 1000 people in 2011 (1). Kerman city has a population of about 740,000 people according to the 2016 census and is located in Kerman province in southeastern Iran (10). In addition to man-made air pollution, Kerman city faces sandstorms and

increased ambient dust in specific seasons. The aim of this study was to investigate the relation between air pollution and epilepsy admissions in Kerman.

Methods

Concentrations of ambient air pollutants (CO, O_3, NO_2, SO_2, PM_{10}, $PM_{2.5}$) were inquired from the Kerman Environmental Protection Agency, from September 2008 to March 2020.

Meteorological data including temperature and relative humidity were inquired from the Kerman Meteorological Organization. These variables were adjusted for as confounders.

Epilepsy hospitalization data were obtained from Kerman's Shafa hospital Epilepsy Registry and according to the International Classification of Diseases (ICD10) which was code G40. Data were inquired in gender and age subgroups (under 18 years, between 18–59 years and over 59 years). Patients that had stayed in the hospital for more than one day were included.

Statistical analysis

Generalized Additive Models (GAM) similar to the equation below were used for estimating the Rate Ratio (RR) of air pollutants and epilepsy admission, and up to 7 day lags.

Several studies have shown that meteorological factors such as temperature are associated with hospital admissions for epilepsy attacks (3, 11–14), therefore we adjusted for average daily temperature and relative humidity. The degree of freedom (df) for the smoothers is determined with Generalized Cross Validation (GCV) and by using the mgcv package in R software. The time unit used in the analysis was day.

Microsoft Office Excel 2010 and SPSS 22 software were used for primary analysis then, the 'mgcv' package in R i386 4.0.3 software was used for GAM analysis.

Results

In the less than 12-year period under study, 894 epilepsy admissions occurred in Kerman, in which 498 (57.7%) cases were male and 396 (44.3%) were female. The male to female sex ratio was 1.25. The number of epilepsy admission from 2008 to 2020, in different population subgroups are shown in Table 1.

Table 1
The number of epilepsy admission from 2008 to 2020, in different population subgroups

Year	Male	Female	Male/Female ratio	< 18 years	18–59 years	> 59 years
2008	17	10	1.7	5	20	2
2009	61	52	1.17	21	69	23
2010	53	37	1.43	20	59	11
2011	39	40	0.97	27	47	5
2012	37	35	1.05	11	56	5
2013	54	38	1.42	18	61	13
2014	52	36	1.44	14	64	10
2015	31	18	1.72	15	28	6
2016	41	41	1	16	57	9
2017	33	21	1.57	6	39	9
2018	25	21	1.19	7	27	12
2019	54	47	1.14	10	67	24
2020 (only 3 months)	1	0	-	0	0	1
Total	498	396	1.25	170	594	130

Table 2 shows descriptive statistics of daily air pollution, meteorological variables and epilepsy admission in 2008–2020. The findings show that the mean daily concentrations of PM_{10}, $PM_{2.5}$, and SO_2 were higher than the WHO daily thresholds which are respectively 50, 25 and 20 $\mu g/m^3$ (15).

Table 2
Descriptive statistics of daily air pollution, meteorological variables and epilepsy admissions

	Mean	SD	Median	Minimum	Maximum
O_3(ppb)	30.21	11.91	29.72	1.92	79
CO(ppm)	1.07	0.69	0.92	0.03	12.27
NO_2(ppb)	15.82	7.96	15.41	0	78.45
SO_2(ppb)	26.12	20.64	21	0	128.46
PM_{10}(μg/m^3)	71.11	47.45	63.48	0	382.76
$PM_{2.5}$(μg/m^3)	27.47	16.18	24.20	0	112
Temperature(°C)	16.75	8.10	17.2	0	41
Humidity (%)	31.15	17.30	27	3.5	100
Male attack(N)	0.11	0.35	0	0	3
Female attack(N)	0.09	0.31	0	0	3
Total attack(N)	0.21	0.48	0	0	4
< 18 years	0.04	0.20	0	0	2
18–59 years	0.14	0.39	0	0	3
> 59 years	0.03	0.17	0	0	2

Table 3 shows the results of the adjusted Generalized Additive Model, about the effect of air pollutants on overall epilepsy admission, in male, female and age groups adjusted for average daily relative humidity and temperature. Increased epilepsy admission in the total population were seen in various lags for CO, NO_2, PM_{10}, and $PM_{2.5}$.

Table 3
Results of adjusted Generalized Additive Model about the effect of air pollutants on epilepsy admission in total, male, female and age groups adjusted for relative humidity and temperature

Lag 0				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9816	0.9756, 0.9877	0.0001
	CO	0.9008	0.7906, 1.0263	0.315
	NO2	**1.0266**	**1.0168, 1.0364**	0.001
	SO2	0.9978	0.9945, 1.0011	0.178
	PM10	**1.0037**	**1.0024, 1.0050**	0.0001
	PM2.5	1.0017	0.9977, 1.0057	0.402
Male	O3	0.9942	0.9854, 1.0029	0.718
	CO	0.9543	0.8015, 1.1360	0.598
	NO2	**1.0409**	**1.0282, 1.0537**	0.001
	SO2	0.9967	0.9923, 1.0012	0.234
	PM10	**1.0057**	**1.0039, 1.0075**	0.001
	PM2.5	1.0001	0.9949, 1.0054	0.581
Female	O3	0.9671	0.9581, 0.9761	0.001
	CO	0.8665	0.7119, 1.0547	0.240
	NO2	1.0049	0.9894, 1.0206	0.533
	SO2	0.9988	0.9938, 1.0038	0.560
	PM10	**1.0023**	**1.0002, 1.0044**	0.015
	PM2.5	1.0042	0.9981, 1.0104	0.215
< 18 years	O3	1.0062	0.9913, 1.0212	0.089
	CO	0.5803	0.4138, 0.8139	0.001
	NO2	**1.0213**	**1.0000, 1.0435**	0.004
	SO2	0.9985	0.9906, 1.0064	0.510
	PM10	**1.0051**	**1.0021, 1.0081**	0.0001
	PM2.5	1.0007	0.9915, 1.0099	0.510

Lag 0				
18–59 years	O3	0.9812	0.9736, 0.9888	0.0001
	CO	0.8188	0.6961, 0.9632	0.015
	NO2	**1.0243**	**1.0123, 1.0365**	0.0001
	SO2	0.9963	0.9922, 1.0004	0.520
	PM10	**1.0039**	**1.0022, 1.0056**	0.0001
	PM2.5	1.0005	0.9956, 1.0053	0.540
> 59 years	O3	0.9545	0.9404, 0.9689	0.0001
	CO	**2.1455**	**1.5823, 2.9091**	0.0001
	NO2	**1.0407**	**1.0139 ,1.0681**	0.002
	SO2	1.0031	0.9948, 1.0115	0.151
	PM10	1.0022	0.9990, 1.0054	0.216
	PM2.5	**1.0148**	**1.0038, 1.0259**	0.0001
Lag 1				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9908	0.9844, 0.9972	0.0002
	CO	1.0280	0.9148, 1.1551	0.570
	NO2	**1.0083**	**1.0000, 1.0178**	0.001
	SO2	0.9961	0.9928, 0.9995	0.0201
	PM10	**1.0027**	**1.0010, 1.0040**	0.0001
	PM2.5	**1.0049**	**1.0010, 1.0089**	0.013
Male	O3	0.9950	0.9864, 1.0037	0.141
	CO	1.0052	0.8471, 1.1927	0.580
	NO2	1.0080	0.9959, 1.0203	0.713
	SO2	0.9958	0.9913, 1.0003	0.998
	PM10	**1.0033**	**1.0016, 1.0050**	0.026
	PM2.5	1.0052	0.9999, 1.0106	0.717
Female	O3	0.9854	0.9759, 0.9951	0.001
	CO	1.0130	0.8486, 1.2093	0.245

Lag 0				
	NO2	1.0068	0.9927, 1.0211	0.107
	SO2	0.9959	0.9909, 1.0010	0.309
	PM10	**1.0022**	**1.0002, 1.0042**	0.020
	PM2.5	1.0050	0.9990, 1.0111	0.362
< 18 years	O3	0.9955	0.9807, 1.0105	0.650
	CO	0.9933	0.7675, 1.2856	0.591
	NO2	1.0138	0.9953, 1.0326	0.256
	SO2	0.9940	0.9960, 1.0021	0.250
	PM10	**1.0047**	**1.0013, 1.0080**	0.0002
	PM2.5	1.0012	0.9915, 1.0110	0.550
18–59 years	O3	0.9936	0.9857, 1.0015	0.315
	CO	0.9894	0.8504, 1.1512	0.510
	NO2	1.0063	0.9944, 1.0182	0.123
	SO2	0.9954	0.9912, 0.9996	0.013
	PM10	**1.0024**	**1.0008, 1.0041**	0.003
	PM2.5	1.0046	0.9999, 1.0095	0.050
> 59 years	O3	0.9707	0.9542, 0.9875	0.0008
	CO	**1.2834**	**1.0073, 1.6351**	0.006
	NO2	1.1013	0.9868, 1.0405	0.112
	SO2	1.0015	0.9931, 1.0100	0.051
	PM10	1.0022	0.9992, 1.0053	0.255
	PM2.5	**1.0131**	**1.0003, 1.0231**	0.0006
Lag 2				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9882	0.9819, 0.9947	0.0001
	CO	1.1044	0.9748, 1.2511	0.195
	NO2	**1.0099**	**1.0008, 1.0192**	0.012
	SO2	0.9964	0.9931, 0.9998	0.009

Lag 0				
	PM10	**1.0028**	**1.0014, 1.0042**	0.0001
	PM2.5	**1.0066**	**1.0028, 1.0104**	0.0001
Male	O3	0.9919	0.9833, 1.0006	0.61**0**
	CO	1.1010	0.9261, 1.3088	0.133
	NO2	**1.0119**	**1.0001, 1.0239**	0.006
	SO2	0.9960	0.9915, 1.0051	0.112
	PM10	**1.0029**	**1.0011, 1.0048**	0.018
	PM2.5	**1.0066**	**1.0014, 1.0118**	0.009
Female	O3	0.9834	0.9739, 0.9930	0.0001
	CO	1.1324	0.9459, 1.3557	0.209
	NO2	1.0066	0.9926, 1.0207	0.103
	SO2	0.9963	0.9913, 1.0014	0.224
	PM10	**1.0027**	**1.0008, 1.0047**	0.0003
	PM2.5	**1.0071**	**1.0015, 1.0128**	0.009
< 18 years	O3	0.9996	0.9848, 1.0146	0.58**0**
	CO	0.9128	0.6928, 1.2026	0.710
	NO2	1.0144	0.9962, 1.0329	0.308
	SO2	0.9958	0.9880, 1.0036	0.126
	PM10	**1.0064**	**1.0029, 1.0098**	0.003
	PM2.5	1.0038	0.9945, 1.0132	0.187
18–59 years	O3	0.9891	0.9813, 0.9970	0.0001
	CO	1.1089	0.9513, 1.2925	0.197
	NO2	1.0083	0.9971, 1.0197	0.253
	SO2	0.9955	0.9913, 0.9997	0.009
	PM10	**1.0020**	**1.0003, 1.0036**	0.005
	PM2.5	**1.0049**	**1.0003, 1.0096**	0.010
> 59 years	O3	0.9653	0.9489, 0.9818	0.0001
	CO	1.0768	0.8739, 1.3267	0.175

Lag 0				
	NO2	1.0100	0.9849, 1.0358	0.284
	SO2	1.0017	0.9932, 1.0101	0.520
	PM10	1.0030	0.9998, 1.0062	0.30
	PM2.5	**1.0182**	**1.0088, 1.0276**	0.007
Lag 3				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9900	0.9836, 0.9965	0.003
	CO	1.1138	0.9875, 1.2562	0.200
	NO2	**1.0083**	**1.0001, 1.0176**	0.002
	SO2	0.9969	0.9935, 1.0002	0.220
	PM10	**1.0030**	**1.0016, 1.0045**	0.0001
	PM2.5	**1.0042**	**1.0002, 1.0082**	0.0001
Male	O3	0.9899	0.9813, 0.9986	0.025
	CO	1.1553	0.9787, 1.3638	0.110
	NO2	1.0095	0.9973, 1.0220	0.291
	SO2	0.9964	0.9919, 1.0010	0.283
	PM10	**1.0038**	**1.0019, 1.0057**	0.0001
	PM2.5	1.0048	0.9995, 1.0102	0.220
Female	O3	0.9895	0.9800, 0.9992	0.011
	CO	1.0374	0.8942, 1.2036	0.580
	NO2	1.0058	0.9924, 1.0194	0.630
	SO2	0.9970	0.9919, 1.0020	0.149
	PM10	1.0022	0.9999, 1.0044	0.400
	PM2.5	1.0036	0.9976, 1.0097	0.155
< 18 years	O3	1.0039	0.9893, 1.0188	0.61**0**
	CO	0.9110	0.6910, 1.2008	0.172
	NO2	1.0068	0.9881, 1.0259	0.177
	SO2	0.9964	0.9887, 1.0042	0.199

Lag 0				
	PM10	**1.0060**	**1.0027, 1.0093**	0.0002
	PM2.5	1.0010	0.9912, 1.0108	0.343
18–59 years	O3	0.9878	0.9800, 0.9957	0.002
	CO	1.1581	0.9906, 1.3539	0.302
	NO2	1.0077	0.9964, 1.0193	0.203
	SO2	0.9963	0.9921, 1.0004	0.100
	PM10	**1.0034**	**1.0015, 1.0052**	0.0001
	PM2.5	1.0042	0.9994, 1.0090	0.110
> 59 years	O3	0.9817	0.9653, 0.9983	0.014
	CO	1.3500	0.9461, 1.3615	0.213
	NO2	1.0092	0.9862, 1.0328	0.185
	SO2	1.0026	0.9942, 1.0110	0.168
	PM10	1.0022	0.9989, 1.0055	0.202
	PM2.5	**1.0111**	**1.0004, 1.0218**	0.008
Lag 4				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9923	0.9859, 0.9988	0.032
	CO	1.1114	0.9834, 1.2561	0.110
	NO2	**1.0098**	**1.0008, 1.0190**	0.012
	SO2	0.9965	0.9932, 0.9999	0.006
	PM10	**1.0024**	**1.0010, 1.0038**	0.0001
	PM2.5	1.0019	0.9978, 1.0059	0.102
Male	O3	0.9929	0.9844, 1.0016	0.325
	CO	**1.2352**	**1.0298, 1.4815**	0.022
	NO2	1.0111	0.9993, 1.0231	0.300
	SO2	0.9954	0.9909, 1.0000	0.500
	PM10	**1.0027**	**1.0010, 1.0045**	0.001
	PM2.5	1.0015	0.9959, 1.0071	0.610

Lag 0				
Female	O3	0.9909	0.9814, 1.0005	0.151
	CO	1.0568	0.9836, 1.2497	0.170
	NO2	1.0068	0.9936, 1.0202	0.118
	SO2	0.9971	0.9921, 1.0022	0.134
	PM10	**1.0030**	**1.0008, 1.0052**	0.0001
	PM2.5	1.0026	0.9965, 1.0087	0.193
< 18 years	O3	1.0008	0.9862, 1.0156	0.155
	CO	1.0455	0.7878, 1.3874	0.151
	NO2	1.0121	0.9938, 1.0309	0.188
	SO2	0.9969	0.9895, 1.0043	0.188
	PM10	**1.0047**	**1.0015, 1.0080**	0.0008
	PM2.5	1.0007	0.9910, 1.0104	0.141
18–59 years	O3	0.9917	0.9839, 0.9996	0.007
	CO	1.0844	0.9349, 1.2579	0.129
	NO2	**1.0103**	**1.0001, 1.0219**	0.002
	SO2	0.9956	0.9914, 0.9998	0.007
	PM10	**1.0021**	**1.0004, 1.0038**	0.009
	PM2.5	1.0009	0.9959, 1.0058	0.151
> 59 years	O3	0.9826	0.9664, 0.9991	0.008
	CO	1.1031	0.8878, 1.3705	0.197
	NO2	1.0045	0.9829, 1.0265	0.153
	SO2	1.0015	0.9931, 1.0099	0.151
	PM10	1.0004	0.9999, 1.0038	0.155
	PM2.5	1.0090	0.9988, 1.0193	0.200
Lag 5				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9925	0.9861, 0.9989	0.025
	CO	1.0090	0.8982, 1.1336	0.878

Lag 0				
	NO2	**1.0123**	**1.0023, 1.0225**	0.015
	SO2	0.9953	0.9918, 0.9987	0.007
	PM10	**1.0026**	**1.0011, 1.0042**	0.0001
	PM2.5	1.0024	0.9983, 1.0065	0.235
Male	O3	0.9956	0.9868, 1.0044	0.349
	CO	1.0078	0.8475, 1.1984	0.932
	NO2	**1.0155**	**1.0022, 1.0290**	0.027
	SO2	0.9937	0.9891, 0.9983	0.012
	PM10	**1.0029**	**1.0011, 1.0047**	0.001
	PM2.5	1.0007	0.9949, 1.0065	0.849
Female	O3	0.9885	0.9793, 0.9978	0.015
	CO	1.1199	0.9404, 1.3337	0.180
	NO2	1.0037	0.9891, 1.0184	0.616
	SO2	0.9972	0.9480, 1.0489	0.285
	PM10	**1.0021**	**1.0000, 1.0042**	0.045
	PM2.5	1.0046	0.9986, 1.0107	0.291
< 18 years	O3	1.0119	0.9972, 1.0267	0.331
	CO	0.7856	0.5749, 1.0737	0.282
	NO2	1.0058	0.9860, 1.0260	0.563
	SO2	0.9927	0.9849, 1.0000	0.072
	PM10	**1.0060**	**1.0028, 1.0093**	0.0002
	PM2.5	0.9990	0.9890, 1.0092	0.855
18–59 years	O3	0.9920	0.9841, 0.9998	0.053
	CO	1.0189	0.8838, 1.1747	0.795
	NO2	1.0110	0.9988, 1.0234	0.072
	SO2	0.9955	0.9913, 0.9997	0.036
	PM10	**1.0019**	**1.0002, 1.0036**	0.018
	PM2.5	0.9993	0.9942, 1.0045	0.808

Lag 0				
> 59 years	O3	0.9726	0.9577, 0.9877	0.001
	CO	1.2800	0.9305, 1.3672	0.167
	NO2	1.0073	0.9821, 1.0332	0.569
	SO2	0.9994	0.9908, 1.0081	0.908
	PM10	1.0007	0.9971, 1.0044	0.671
	PM2.5	**1.0157**	**1.0062, 1.0252**	0.001
Lag 6				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9936	0.9871, 1.0000	0.054
	CO	1.0437	0.9369, 1.1628	0.436
	NO2	1.0096	0.9999, 1.0195	0.051
	SO2	0.9959	0.9925, 0.9993	0.018
	PM10	**1.0027**	**1.0013, 1.0040**	0.0001
	PM2.5	1.0022	0.9981, 1.0064	0.278
Male	O3	0.9973	0.9886, 1.0062	0.560
	CO	1.0608	0.8948, 1.2575	0.496
	NO2	**1.0143**	**1.0011, 1.0277**	0.033
	SO2	0.9955	0.9909, 1.0001	0.053
	PM10	**1.0021**	**1.0003, 1.0039**	0.019
	PM2.5	0.9995	0.9937, 1.0053	0.807
Female	O3	0.9879	0.9787, 0.9972	0.011
	CO	1.0555	0.9220, 1.2083	0.433
	NO2	1.0099	0.9956, 1.0244	0.211
	SO2	0.9966	0.9915, 1.0017	0.186
	PM10	**1.0031**	**1.0011, 1.0050**	0.001
	PM2.5	1.0055	0.9994, 1.0116	0.072
< 18 years	O3	1.0100	0.9952, 1.0250	0.201
	CO	0.9225	0.9090, 0.9361	0.586

Lag 0				
	NO2	1.0005	0.9803, 1.0211	0.958
	SO2	0.9923	0.9842, 1.0005	0.068
	PM10	**1.0053**	**1.0023, 1.0082**	0.0001
	PM2.5	1.0036	0.9940, 1.0132	0.461
18–59 years	O3	0.9939	0.9860, 1.0019	0.137
	CO	1.0478	0.9168, 1.1976	0.492
	NO2	**1.0123**	**1.0005, 1.0242**	0.039
	SO2	0.9961	0.9920, 1.0003	0.071
	PM10	**1.0018**	**1.0001, 1.0036**	0.037
	PM2.5	0.9985	0.9932, 1.0037	0.577
> 59 years	O3	0.9728	0.9560, 0.9898	0.001
	CO	1.1216	0.9217, 1.3648	0.251
	NO2	1.0021	0.9770, 1.0278	0.866
	SO2	1.0011	0.9926, 1.0098	0.784
	PM10	1.0020	0.9988, 1.0052	0.182
	PM2.5	**1.0148**	**1.0051, 1.0245**	0.003
Lag 7				
	Pollutant	**RR**	**95% CI**	**P-value**
Total	O3	0.9911	0.9848, 0.9975	0.006
	CO	1.0272	0.9233, 1.1427	0.621
	NO2	**1.0102**	**1.0002, 1.0203**	0.043
	SO2	0.9947	0.9913, 0.9982	0.001
	PM10	**1.0031**	**1.0017, 1.0045**	0.0001
	PM2.5	1.0026	0.9638, 1.0429	0.190
Male	O3	0.9967	0.9879, 1.0056	0.494
	CO	1.1097	0.9176, 1.3420	0.272
	NO2	**1.0148**	**1.0015, 1.0283**	0.016
	SO2	0.9950	0.9905, 0.9996	0.045

Lag 0				
	PM10	**1.0031**	**1.0012, 1.0050**	0.001
	PM2.5	0.9998	0.9943, 1.0054	0.951
Female	O3	0.9874	0.9779, 0.9971	0.011
	CO	1.0615	0.9289, 1.2129	0.377
	NO2	1.0041	0.9890, 1.0193	0.838
	SO2	0.9952	0.9901, 1.0003	0.062
	PM10	**1.0030**	**1.0010, 1.0049**	0.002
	PM2.5	1.0049	0.9990, 1.0109	0.096
< 18 years	O3	1.0074	0.9925, 1.0225	0.112
	CO	0.8833	0.6405, 1.2179	0.449
	NO2	0.9990	0.9786, 1.0197	0.925
	SO2	0.9925	0.9843, 1.0007	0.075
	PM10	**1.0055**	**1.0023, 1.0087**	0.0001
	PM2.5	**1.0102**	**1.0017, 1.0187**	0.018
18–59 years	O3	0.9914	0.9836, 0.9993	0.035
	CO	1.0565	0.9242, 1.2079	0.420
	NO2	1.0109	0.9998, 1.0229	0.067
	SO2	0.9942	0.9900, 0.9984	0.007
	PM10	**1.0025**	**1.0009, 1.0041**	0.001
	PM2.5	0.9980	0.9928, 1.0032	0.453
> 59 years	O3	0.9707	0.9540, 0.9877	0.0001
	CO	1.0964	0.8781, 1.3690	0.416
	NO2	1.0074	0.9792, 1.0364	0.790
	SO2	1.0025	0.9938, 1.0114	0.560
	PM10	1.0014	0.9981, 1.0046	0.396
	PM2.5	**1.0110**	**1.0009, 1.0212**	0.030

CO, NO_2, PM_{10} and $PM_{2.5}$ had a direct association with epilepsy admission in males. The strongest relations were in lag 4 for CO (RR = 1.2352, 95% CI: 1.0298–1.4815), lag 0 for NO_2 (RR = 1.0409, 95% CI:

1.0282–1.0537), lag 2 for $PM_{2.5}$ (RR = 1.0066, 95% CI: 1.0014–1.0118) and lag 0 for PM_{10} (RR = 1.0057, 95% CI: 1.0039–1.0075).

PM_{10} and $PM_{2.5}$ also had a direct association with epilepsy admission in females. The strongest relations were in lag 2 for $PM_{2.5}$ (RR = 1.0071, 95% CI: 1.0015–1.0128) and lag 6 for PM_{10} (RR = 1.0031, 95% CI: 1.0011–1.0050).

In all age groups CO, NO_2, PM_{10} and $PM_{2.5}$ showed direct relations with epilepsy admission. The strongest relation between CO with epilepsy admission was seen in the over 59 year group in lag 0 (RR = 2.1455, 95% CI: 1.5823–2.9091), for NO_2 in the over 59 year group in lag 0 (RR = 1.0407, 95% CI: 1.0139–1.0681), for $PM_{2.5}$ in the over 59 year group in lag 5 (RR = 1.0157, 95% CI: 1.0062–1.0252) and for PM_{10} in the under 18 year's group in lag 2 (RR = 1.0064, 95% CI: 1.0029–1.0098).

Discussion

This study showed significant relations between short-term exposure to air pollutants CO, NO_2, PM_{10}, $PM_{2.5}$ and epilepsy admissions in Kerman, Iran.

In this study CO increased epilepsy admissions. Consistent with this study, Bao et al's study in China showed an association between CO and increased epilepsy hospitalization 1.1% (95% CI: 0.1%, 2.1%) (16). Also in Mexico, there was an association between ambient CO and epilepsy admissions RR = 1.098 (95% CI: 1.045–1.155) (17).

In this study, NO_2 had a significant relation with epilepsy admission in total and several different age groups, and the strongest relation was observed in males. Automobile exhaust is one of the most important sources of nitrogen dioxide. Wang et al's study in China found a significant association between the NO_2 of automobile exhaust and neurobehavioral function in school age children. In this study two primary schools were chosen. One school was located in a clear area and the other in a traffic dense and polluted area. NO_2 had been monitored for traffic related air pollution on the school campuses and classrooms. Children participated in assisted neurobehavioral testing to assess neurobehavioral performance (18). A systematic review, in 2017 concluded that high concentrations of NO_2 in polluted air significantly affects the central nervous system in children and adults, and represent a significant risk factor for human health (19). A study from China showed a significant relation between increasing concentration of NO_2 with epilepsy attacks 2% (95% CI: 0.5% – 3.6%) (16). Also in Mexico, an ecological study showed a significant relation between nitrogen dioxide with epilepsy attacks RR = 1.083 (95% CI: 1.038–1.13) (17). In a cohort study in Denmark, the authors found that residential exposure to road traffic and air pollution is associated with a higher risk for febrile seizures IRR = 1.05, (95% CI: 1.02–1.07) (20). A study in southern Spain showed that even low level NO_2 exposure and traffic related air pollution had adverse effects on children’s neurodevelopment (21). Xu et.al's study in China showed that the RR for epilepsy attacks was 3.17 (95% CI: 1.41–4.93) per 10 $\mu g/m^3$ increase of NO_2 (11). However, in the US, the

authors showed a protective effect for N_2O in epilepsy IRR = 0.85 (95% CI: 0.74–0.97) (9). N_2O is a different compound and is derived mainly from agricultural fertilizers and natural sources, but NO_2 is mainly produced by vehicles.

Another pollutant evaluated in this study was PM_{10}, which had a significant relation with epilepsy admission in total and several subgroups, and the strongest relation was found in the under 18 year's subgroup. Several studies have shown relations between ambient PM_{10} and epilepsy attacks (17, 22, 23). Consistent with this study, Cakmak et al. in Mexico showed an association between PM_{10} and hospital admission for epilepsy RR = 1.083 (95% CI: 1.038–1.13) (17). A study in six cities in Italy found positive associations between PM_{10} exposure and total emergency calls from 2002 to 2006 (24). Also, increased emergency calls for epilepsy attacks were observed with exposure to PM_{10} in China, RR = 1.5 (95% CI: 1.1–2.0) (22). Radmanesh et al's study in Iran, showed that hospital admissions for patients with cerebral ischemic attack, epilepsy, and different types of headaches on dusty days increased significantly compared to clean days. Also hospital admissions of these patients significantly increased with increased concentrations of ambient PM_{10} (23). Another study from Iran showed that exposure to PM_{10} increased oxidative stress and the expression of inducible nitric oxide synthase (iNOS) messenger RNA levels and reduced the concentrations of antioxidant enzymes (25).

In this study $PM_{2.5}$ had a significant relation with epilepsy admission in total and several subgroups, and the strongest relation was found in the above 59 years subgroup. Consistent with this study, a significant association observed between $PM_{2.5}$ and epilepsy attacks in Mexico RR = 1.065 (95% CI: 1.002–1.132) (17). Prenatal exposure to pollutants may cause permanent changes in neurotransmitters and altered brain development resulting in long term deficits in one or more memory systems (26). Other studies have shown that oxidative stress, neuro inflammation, glial activation, and cerebrovascular damage are the primary pathways for inducing brain pathology by air pollution (27). Oxidative stress, changes in autonomous function and progression of atherosclerosis can be exacerbated by exposure to ambient PM (28).

In this study O_3 and SO_2 were inversely related with epilepsy admission. In an ecological study in China, Xu et al. also reported negative associations between ambient O_3 and epilepsy attacks − 0.84% (95%CI: -1.58%, 0.09%) (11). An interventional study showed that ozone can be protective against pentylenetetrazole (PTZ) induced epilepsy attacks (29). But in another study conducted in Mexico, a significant direct association was observed between O_3 and hospital admission for epilepsy attacks RR = 1.100 (95% CI: 1.025–1.181) (17). In Fluegge et al's study in the USA, no significant relation was observed between O_3 and epilepsy attacks (9). In the current study the average concentration of O_3 was 30.21 ± 11.19ppb, which is less that Xu et al's study (mean = 100 ppb ± 63) (11) which showed a negative association, and Cakmak et al's study (mean = 93.26 ppb) (17). More research is needed to clarify the effect of ozone exposure on epilepsy.

Some of the strengths of this study was including about 12 years air pollution and epilepsy admission data, and using Generalized Additive Models (GAM) to adjust for nonlinear confounder variables. However, given the ecological nature of this study, results cannot be easily inferred to the individual level.

Conclusion

The findings of this study showed that ambient CO, NO_2, PM_{10} and $PM_{2.5}$ might be related with epilepsy admissions in Kerman. This study further emphasizes the necessity to control and reduce ambient air pollutants.

Declarations

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Data availability statement

Data can be inquired from the first author by reasonable request.

Authors' Contribution

NK conceptualized the idea, helped in writing and editing the manuscript. MAF acquired the data, cleaned the data, analyzed the data and wrote initially manuscript. HAE reviewed the manuscript, provided scientific advice for neurological diseases. MM supervised data analysis, provided statistical consultation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics in Research Committee of Kerman University of Medical Sciences approved the study protocol under code IR.KMU.REC.1398.582. All methods were performed in accordance with the relevant guidelines and regulations. Individual consent was not needed and was waived by the ethics committee, because the information inquired was only in counts and without any identifiable information.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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