Online Data Supplement

Ozone and Survival in Four Cohorts with Potentially Predisposing Diseases

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MATERIALS AND METHODS

Study population

The US Medicare program covers hospitalization for all residents aged 65 and older. Using data for the years 1985 to 2006, we constructed four cohorts of persons with potentially predisposing conditions. These were defined as persons discharged alive after emergency admission for the specific conditions we hypothesized might render subjects at greater risk, defining cases as a primary discharge diagnosis of chronic obstructive pulmonary disease (COPD, International Classification of Disease 9th revision (ICD-9): 490-496, except 493), diabetes (ICD-9: 250), congestive heart failure (CHF, ICD-9: 428), and myocardial infarction (MI, ICD-9: 410).

We obtained date of death for each subject, or whether they were still alive as of the end of 2006, and information on age, gender, race, severity of the index admission expressed by the number of coronary and medical intensive care days, and on medical conditions that might affect the risk of survival. We defined these as previous admissions with diagnoses of atrial fibrillation (ICD-9: 427.3) or MI, and secondary (on the index admission) or previous diagnoses for COPD, diabetes, CHF, and essential hypertension (ICD-9: 401).

Subjects alive the first of May of the year following the index admission entered into the cohort, and follow-up periods were calendar years. We excluded subjects whose death or subsequent admission occurred within the first three months of their index admission, and those who were admitted in 2006.

Environmental data

We obtained ozone (8-hour mean) data from US Environmental Protection Agency's Air Quality System Technology Transfer Network in 105 cities (http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm). For each subject and follow-up period we created yearly averages of the 8-hour mean daily ozone concentrations for the summer (May-September) and transitional season (Spring and Autumn) for that year. Ozone was then treated as a time varying covariate in the survival analysis.

Similarly, Jerrett et al (1) used the daily maximum ozone concentrations during April to September only.

We choose 105 cities with at least 100k inhabitants, monitoring data for ozone, and representing a geographic distribution across the US. The cities and the ozone distributions are in Table 1S in the online supplement. In each city the data was retrieved on a county level; when more than one monitor was available in one county, we computed local daily mean ozone concentrations using an algorithm that accounts for the different monitor-specific means and variances (2,3).

Meteorological data

We obtained temperature data from the National Oceanic and Atmospheric Administration (NOAA) (http://www.ncdc.noaa.gov/oa/ncdc.html), and created the yearly average of summertime (June-August) and wintertime (December- February) temperature in each year in each city.

We examined if the risk differed by prevailing climate by dividing the US into regions based on the Köppen climate classification (4) (http://koeppen-geiger.vu-wien.ac.at/), which is one of the most widely used climate classification systems. We used the following classification: region 1: humid subtropical climates and maritime temperate climates, which includes FL, LA TX, GA, AL, MS, AR, OK, KS, MO, TN, SC, NC, VA, WV, KY; region 2: warm summer continental climates , including ND, MN, WI, MI, PA, NY, CT, RI, MA, VT, NH, ME; region 3: hot summer continental climates with SD, NE, IA, IL, IN, OH; region 4: dry climates (NM, AZ, NV); region 5: dry climates together with continental climate with MT, ID, WY, UT, CO; region 6: Mediterranean climates which includes CA, OR, WA .

Statistical methods

To avoid cross-sectional confounding we fit separate survival analyses in each city. The exposure was warm season (or transitional season) ozone, which was treated as a time varying covariate. To do this, we used the counting process extension of the Proportionate Hazard model pioneered by Andersen and Gill (5). In this formulation, multiple observations are created for each person, where each observation represents a single person-year of mortality follow-up. We analyzed the data with an extended Cox's proportional hazard regression model, which takes the following form:

$$h_i(t) = \lambda_0(t) e^{\beta_1 x_{i1} + \ldots + \beta_k x_{ik} + \delta_1 z_{i1}(t) + \ldots + \delta_j z_{ij}(t)}$$

Where: hi(t) is the hazard for individual i at time t (year), λ_0(t) is the baseline hazard function, $\beta_1 x_{i1} + \ldots + \beta_k x_{ik}$ is a linear function of a set of k fixed time-invariant covariates such as gender, $\delta_1 x_{i1} + \ldots + \delta_j x_{ij}$ is a linear function of time-varying covariates such as air pollution.

We analyzed the data using Proc PHREG in SAS (6). To control for tied observations we used the appropriate likelihood function as given by Kalbfleisch and Prentice (7).

City-specific cohorts were created for each of the four conditions that we wanted to analyze. Separate survival analyses, with failure defined as death, were conducted for each city and each cohort. A subject entered the cohort if he/she survived at least 3 months and was alive on the first January of the year following the index admission. For each subject the follow up periods were 1 year periods (January – December) until the year in which they die or until December 2006 (censoring). This method has been previously described (8, 9).

The focus of our analysis was whether year- to-year variations in ozone concentrations within each city were associated with year-to-year variations in survival. To avoid confounding by long-term time trends, we controlled for such a trend with a linear term for year of follow up. Hence we were examining whether year-to-year variations in survival *around its long-term trend* were associated with year-to-year variations in ozone, *around its long-term trend*. We also included in the model indicator variables for season of index admission, defined as: cold (December through February), hot (June through August), and transitional. To control for weather we included in the model the yearly averages of summertime and wintertime temperature.

We also controlled for individual risk factors such as age, gender, race, number of days of coronary and medical intensive care, previous diagnoses for atrial fibrillation and MI, and secondary or previous diagnoses for COPD, diabetes, CHF, and hypertension. To allow for possible non-proportionality of the survival rates, age (5 year categories), gender, and race (white, black, others) were treated as stratification variables.

In the second stage of the analysis, the results of these city specific analyses (for each predisposing condition) were combined using a random effect meta-analysis (10).

The pooled analysis was done separately for the two choices of exposure index: the average ozone during summer and the average during the transitional period.

We used a meta-regression between the city specific effect estimates for ozone and city average temperature and temperature squared, and we found an inverted U-shaped relationship. Temperature is a proxy measure for ventilation and therefore also of air conditioning use and may play a role in explaining differences among regions.

We then added dummy variables for region to the meta-regression and we obtained the estimated deviation from the overall effect of ozone in each region, as predicted by temperature. In this way we could determine whether there was any remaining regional variation in ozone effect not explained by temperature.

The results are expressed as Hazard ratio (HR) for a 5 ppb increment of ozone.

References

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Table E1: Total population, population 65 and older and average ozone during warm (May-September) and transitional season (Spring + Autumn) in the 105 cities included in the study during the years 1985-2006

City	State	Total	Pop	Regions	Ozone average May-September			Ozone average Spring+Autumn		
		Pop	65 +		mean	5%	95%	mean	5%	95%
Albuquerque	NM	557	65	4	52.2	43.1	60.6	42.9	35.6	47.9
Allentown	PA	579	92	2	47.7	43.0	53.6	36.5	29.8	41.7
Anaheim	CA	2846	284	6	49.7	44.3	55.1	43.6	38.4	48.9
Ann Arbor	MI	323	27	2	45.9	41.4	50.6	40.1	35.7	46.1
Atlanta	GA	2915	217	1	55.2	48.2	64.8	43.3	37.3	52.2
Austin	TX	812	56	1	45.3	38.9	49.0	42.8	37.2	46.3
Bakersfield	CA	662	63	6	71.4	66.7	76.4	55.1	50.2	62.4
Baltimore	MD	1405	199	1	51.1	41.1	57.6	35.4	29.9	41.9
Baton Rouge	LA	434	44	1	47.2	43.7	52.7	43.1	37.9	48.2
Birmingham	AL	805	105	1	49.5	43.3	56.6	41.1	36.1	49.2
Boston	MA	3529	464	2	41.8	37.7	46.9	34.6	30.9	38.2
Boulder	CO	291	23	5	51.3	45.1	58.5	38.0	29.4	45.1
Broward	FL	1623	256	1	28.4	22.9	32.6	35.8	31.3	39.8
Buffalo	NY	1170	188	2	47.1	40.4	55.1	36.0	32.3	40.5
Canton/Akron	OH	921	136	3	51.5	46.0	59.0	40.3	37.6	44.9
Cedar Rapids	IA	192	24	3	40.1	31.9	47.2	34.2	25.8	40.9
Charleston	SC	310	37	1	43.1	37.9	48.7	41.1	35.2	48.4
Charlotte	NC	695	61	1	55.6	49.3	62.4	46.1	41.9	50.0
Chicago	IL	6925	788	3	40.8	35.8	45.9	29.6	26.1	34.6
Cincinnati	OH	845	116	3	49.9	43.2	55.9	38.4	34.6	43.0
Cleveland	OH	1621	252	3	46.4	39.6	51.5	35.9	31.1	38.1
Colorado Springs	CO	517	46	5	48.3	39.6	55.8	38.9	31.9	43.8
Columbia	SC	537	55	1	49.9	43.8	57.7	43.7	39.7	47.0
Columbus	OH	1069	107	3	50.4	43.8	58.4	38.6	34.5	42.3
Dallas	TX	2219	183	1	49.6	41.4	56.9	40.2	34.1	46.8
Davenport	IL	308	42	3	48.1	40.4	53.6	40.2	35.1	44.1
Dayton	OH	559	78	3	50.0	42.1	58.1	39.5	33.0	46.0
Denver	CO	1446	145	5	49.1	44.2	54.1	35.5	32.4	39.0
Des Moines	IA	375	42	3	35.1	21.5	46.2	29.6	15.3	38.1
Detroit	MI	4043	500	2	43.3	38.2	49.6	36.1	30.3	40.5
Durham	NC	223	22	1	53.3	46.6	59.7	45.1	41.6	48.8
El paso	TX	680	68	1	50.0	41.5	54.5	41.7	34.9	44.8
Erie	PA	281	41	2	49.1	44.8	56.9	38.6	33.7	44.9
Eugene	OR	323	43	6	36.1	32.8	40.9	34.6	30.5	39.7
Fresno	CA	799	80	6	69.0	62.1	75.6	52.7	45.9	59.9
Ft. Worth	TX	1446	124	1	54.2	47.1	59.0	44.1	40.9	47.2
Gary	IN	485	0	3	47.1	39.9	53.8	40.4	35.4	49.4

Grand Rapids	MI	574	61	2	44.8	40.2	49.6	40.0	37.1	45.3
Greensborough	NC	421	50	1	54.5	43.6	62.2	48.0	39.8	52.8
Harrisburg	PA	252	36	2	49.3	43.1	54.6	37.5	33.0	42.9
Hartford	CT	857	126	2	44.7	39.9	48.4	36.0	29.8	42.1
Holland	MI	344	36	2	48.5	44.2	53.7	43.0	39.1	48.6
Honolulu	HI	876	118	1	15.6	9.8	23.9	20.9	14.4	29.3
Houston	TX	3401	258	1	44.2	39.3	51.2	40.9	35.4	49.4
Indianapolis	IN	860	97	3	51.4	44.5	57.8	44.8	39.5	53.8
Jacksonville	FL	920	97	1	43.3	37.9	48.3	43.8	39.9	48.6
Jersy city	NJ	609	71	2	46.7	38.8	56.2	29.8	24.5	33.5
Kansas City	KS	793	85	1	49.7	41.7	55.0	39.1	34.0	42.8
Kansas City	MO	655	83	1	47.0	42.8	53.5	38.3	33.9	43.5
Knoxville	TN	488	65	1	53.4	46.5	64.9	45.0	40.9	55.2
Las Vegas	NV	1376	153	4	55.3	49.9	59.2	44.5	40.4	47.1
Little Rock	AR	361	42	1	50.1	43.8	55.3	40.2	36.3	45.0
Los Angeles	CA	9519	943	6	58.2	49.8	74.0	44.4	37.2	55.3
Louisville	KY	694	95	1	49.5	41.0	58.0	38.2	28.7	46.6
Medford	OR	181	29	6	45.5	40.7	48.6	42.4	37.8	47.5
Memphis	TN	897	91	1	55.1	46.9	63.2	46.2	40.4	54.7
Mercer	PA	120	22	2	50.7	45.6	59.1	39.9	33.2	45.7
Miami	FL	2253	305	1	29.6	26.9	32.5	38.3	34.8	43.5
Milwaukee	WI	1301	167	2	44.1	38.7	49.8	36.9	33.6	41.1
Nashville	TN	570	64	1	46.5	34.7	57.9	35.4	25.7	42.5
New Haven	CT	824	120	2	44.7	40.8	52.3	37.1	29.8	45.1
New Orleans	LA	940	113	1	42.5	36.2	50.1	41.1	35.4	47.8
Norfolk	VA	1354	136	1	52.2	46.1	59.0	43.6	40.4	47.5
New York City	NY	8008	953	2	39.8	34.7	45.5	26.1	23.0	28.5
Oakland	CA	1444	149	6	32.3	28.3	38.4	30.7	27.4	34.9
Oklahoma City	OK	660	83	1	52.5	45.9	60.0	42.6	38.9	45.8
Omaha	NE	586	60	3	37.0	31.8	43.6	31.7	24.5	40.6
Orlando	FL	1262	131	1	42.0	37.0	45.5	44.0	41.1	49.7
Palm beach	FL	1131	258	1	28.7	23.6	32.1	35.1	30.3	40.8
Pensacola	FL	294	40	1	46.9	40.9	52.1	45.7	38.4	49.2
Philadelphia	NJ	4603	642	2	50.7	45.6	58.9	34.9	30.7	37.5
Phoenix	AZ	3072	364	4	56.2	50.6	60.0	48.8	44.5	52.0
Pinellas	FL	921	206	1	38.2	32.7	43.0	41.4	38.1	45.4
Pittsburg	PA	1282	230	2	48.9	37.1	56.2	34.8	27.7	39.9
Port Arthur	TX	252	35	1	42.2	36.1	49.6	41.4	34.7	47.9
Portland	OR	1789	186	6	34.0	30.8	37.0	31.5	27.7	36.1
Providence	RI	789	117	2	44.8	41.8	50.0	38.9	33.7	44.9
Provo/Orem	UT	369	24	5	54.7	51.2	58.0	49.1	47.0	52.1
Raleigh	NC	628	48	1	53.8	46.0	65.1	46.4	39.5	55.1
Reno	NV	339	37	4	49.8	43.4	53.5	39.8	36.6	41.7
Richmond	VA	720	82	1	53.6	46.5	60.6	44.3	40.9	49.5
Riverside	CA	1545	197	6	67.7	60.0	81.3	52.7	49.4	56.3
Sacramento	CA	1223	137	6	55.0	50.6	58.0	43.3	39.6	48.7

Salt Lake City	UT	898	74	5	54.6	49.0	57.8	47.7	37.6	51.9
San Antonio	TX	1393	147	1	44.1	36.7	49.2	42.4	36.6	48.0
San Diego	CA	2814	317	6	48.6	45.1	55.4	47.8	43.3	56.3
San Francisco	CA	1484	197	6	26.6	21.2	30.9	27.5	22.5	31.5
San Jose	CA	1683	163	6	38.7	35.3	42.4	34.2	30.7	36.8
Scranton	PA	213	42	2	47.5	42.2	54.4	38.9	34.4	43.4
Seattle	WA	3044	312	6	34.3	30.6	39.3	32.1	28.3	35.5
Spokane	WA	418	53	6	45.4	40.4	50.9	42.7	37.2	48.7
Springfield	MA	456	67	2	45.2	39.9	48.5	36.4	32.2	44.6
Steubenville	OH	132	25	3	47.7	38.9	56.6	36.8	28.7	42.4
St. Louis	MO	1563	213	1	48.8	43.6	55.0	37.6	33.1	44.2
Tallahassee	FL	239	20	1	41.2	34.3	45.4	43.2	38.1	50.5
Tampa	FL	999	121	1	41.0	34.9	45.6	43.9	39.4	48.7
Terra Haute	IN	106	15	3	48.9	41.7	58.2	42.7	34.5	50.6
Toledo	OH	455	61	3	45.6	41.0	49.3	35.9	31.4	40.2
Tucson	AZ	844	121	4	50.5	46.7	53.0	45.6	43.1	47.7
Tulsa	OK	563	68	1	52.8	46.3	58.0	42.7	39.1	46.2
Washington	DC	762	88	1	49.8	43.4	56.9	32.3	27.0	36.9
Wilmington	DE	500	59	1	49.7	41.8	55.2	35.1	28.9	38.8
Winston	NC	306	40	1	52.8	46.9	59.4	45.6	41.8	49.3
Worcester	MA	751	99	2	45.3	40.3	50.2	39.7	32.5	45.8
Youngstown	OH	483	82	3	49.7	40.4	56.2	39.6	33.2	43.4