Research Article

The Cumulative Effects of Ambient Particulate Matter and Humidity on Acute Clinical Outcomes

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Abstract

Background: The mortality outcomes of an emergency medical admission are sensitive to the air pollutant levels on the day of admission; we study whether the prevailing humidity on the day of admission also influences the mortality outcome.

Methods: Between 2002 and 2016, we have studied all emergency medical admissions (96,526 episodes in 50,731 patients) and investigated air pollutant levels (PM10 particulate matter) and humidity levels on the day of admission. We employed a logisitic multiple variable regression model, to identify pollutant and humidity mortality predictors, having adjusted for Acute Illness Severity and Case Co-morbidity / Complexity.

Results: Relative to low or high prevailing humidity, emergency admissions had similar demographics, illness severity and hospital length of stay. The particulate matter on the day of admission (PM10 quintiles) showed worsening outcomes from Q2-OR 1.14 (95% CI: 0.94, 1.39) to Q5-OR 1.25 (95% CI: 1.02, 1.54) with an overall Odd Ratio for PM10 level of 1.07 (95% CI: 1.02, 1.12). Humidity interaction analysis with the level of pollutant was significant - OR 0.93 (95% CI: 0.86, 0.99); higher humidity levels of >=85% < 95% and >=95% having better survival compared with lower humidity levels.

Conclusion: In temperate climates, with unlikely potential for heat stress, the level of humidity interacted with air pollution levels to influence mortality outcomes. More focus and research on humidity influencing healthcare outcomes appears warranted.

Key Words: Air Pollution; Clinical Outcomes; Humidity; Interactions; Mortality

Introduction

The influence of air pollution on population mortality is not in doubt [1-3] individuals with respiratory disease exposed to elevated concentrations of particulate matter may have symptoms exacerbated with consequent increased morbidity [4-6]. Overall, epidemiological evidence also indicates an elevated mortality rate among individuals with Chronic Obstructive Pulmonary Disease (COPD) following exposure to particulate matter [7,8]. Asthma, rhinosinusitis, respiratory tract infection, lung cancer and cardiopulmonary disease also exhibit susceptibility to poor air quality [9]. Concern raised regarding the public health implications of urban air pollution [10] in Dublin resulted in legislation in 1990 control-ling the marketing, sale and distribution of bituminous coals. The average black smoke concentration fell by approximately 35.6μg/m³ [11] with an estimated reduction in respiratory deaths by 15.5% and cardiovascular deaths by 10.3% [11].

The impact of humidity and any interaction with air pollution to influence mortality outcomes has received less attention. The overall impact of humidity on mortality have hence not been clearly established epidemiologically [12]. In part, this may be due to inconsistency as to how the effects of humidity are interpreted in the literature [9]. Humidity most often is evaluated as relative humidity (temperature linked). The temperature-mortality relationship and the humidity-mortality relationship are both U-shaped; the effects, although large in magnitude at the extremes [13], may not be that relevant at temperate climate ranges. The effect of humidity on human health is exerted via heat stress (impaired surface

evaporation rates with high humidity levels) and dehydration, either of which could exacerbate cardiovascular morbidity [9,14]. There are data also data that demonstrate the potential of ambient temperature and relative humidity to alter DNA methylation on genes related to coagulation, inflammation, cortisol, and metabolic pathways [15].

In respiratory disease, cold temperature and low humidity are associated with increased occurrence of respiratory tract infections [16] and low humidity winter conditions have also been linked to increased COPD exacerbations [17]. Controlled climate chamber studies have demonstrated increased bronchial hyper reactivity in asthmatic patients at low humidity levels [18]. Humidity could also indirectly adversely impact respiratory disease, particularly asthma, via the spread of bacteria, fungi, and dust mites [13].

Over the last decade, evidence of interaction between air pollutants and environmental water vapor status is beginning to emerge in the medical and epidemiological literature. In this study, we investigated whether, by examining 96,526 emergency medical admissions to St James' Hospital, Dublin over a 16year period, we could relate air pollution levels and humidity on the day of admission to the 30-day mortality outcomes.

Methods

Background

St James's Hospital, Dublin serves as a secondary care center for emergency admissions in a catchment area with a population of 270,000 adults. All emergency medical admissions were admitted from the emergency department to an Acute Medical Admission Unit (AMAU), the operation and outcome of which have been described elsewhere [19,20]. As a city center hospital, St James's admits persons resident elsewhere but working in the capital in addition to visitors to Dublin who became acutely ill. The number of emergency medical admissions resident in the catchment area was 74.5%; this compares with a figure of 59% for emergency department presentations where the social influences on emergency department visitations on two London hospitals have been examined [21].

Data Collection

An anonymous patient database was employed, collating core information of clinical episodes from the Patient Administration System (PAS), the national hospital in-patient enquiry (HIPE) scheme, the patient electronic record, the emergency room and laboratory systems. HIPE is a national database of coded discharge summaries from acute public hospitals in Ireland [22,23]. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) has been used for both diagnosis and procedure coding from 1990 to 2005 with ICD-10-CM used since then. Data included parameters such as the unique hospital number, admitting consultant, date of birth, gender, area of residence,

principal and up to nine additional secondary diagnoses, principal and up to nine additional secondary procedures, and admission and discharge dates. Additional information cross-linked and automatically uploaded to the database includes physiological, hematological and biochemical parameters.

Our hospital catchment area contains many small areas characterized by a high deprivation status [24]. The Republic of Ireland census (Central Statistical Office) report Small Area Population Statistics (SAPS); the smallest reporting unit is the Electoral Division (ED). Of the total of 3409, 74 Electoral Divisions are in the hospital catchment area. The catchment area population, measured in 2006, was 210,443 persons, with a median population per ED of 2845 (IQR 2020, 3399). Deprivation metrics have been determined by the Small Areas Health Research Unit (SAHRU) of Trinity College Dublin using methodology similar to Townsend [25] and Carstairs [26] to derive a Deprivation Score based on four indicators, relating to unemployment, social class, type of housing tenure and car ownership [27]. The assignment of patients to small area population area used the ArcGIS Geographic Information System software implementation of the well-known Point-in-Polygon algorithm as outlined by Shimrat [28].

This study had no interventional component, used anonymized routinely collected data, complied with data protection legislation and was undertaken with the approval of hospital authorities; hence did not require approval from our institutional ethics committee.

Acute Illness Severity Score

Derangement of biochemical parameters may be utilized to predict clinical outcome. We derived an Acute Illness Score based on laboratory data. This is an age adjusted 30-day inhospital mortality risk estimator, representing an aggregate laboratory score based on the admission serum sodium (Na), serum potassium (K), serum urea, Red Cell Distribution Width (RDW), White Blood Cell Count (WCC), serum albumin and troponin values at admission and applied as an Acute Illness Severity score [29,30]; the score predicts 30-day in-hospital mortality from the biochemical parameters recorded in the Emergency Department [31]. The Illness Severity score can be enhanced with data from the ICD9/10 discharge codes to compute Co-Morbidity (as per the Charlson Index [32]) and chronic disabling disease [33] status. This Risk Score is exponentially related to the 30-day episodes mortality outcome with a range of model adjusted mortality outcomes from 2.5% (2.3%- 2.6%) to 32.1% (30.4% - 33.8%). We have demonstrated using a nomogram that this laboratory model derives most of its predictive power from the values of albumin, urea and haemoglobin recorded at the time of admission [34].

Air Quality

For the current study, data over the last decade (2002-2016) from three stations within our hospital catchment area (Winetavern and Coleraine Street or Rathmines stations) were assessed and daily

measurements for PM_{10} or hourly SO_2 were recorded, according to methods detailed elsewhere [35]. A single average value for each day was calculated for the analyses. We divided the daily levels into equally spaced quintiles - PM_{10} quintile cut-points were 9.9, 13.2, 16.9 and 23.3 µg/m³ respectively.

Statistical Method

Descriptive statistics were calculated for demographic data, including means/Standard Deviations (SD), medians/Interquartile Ranges (IQR), or percentages. We examined 30-day in-hospital mortality as the primary outcome. We performed comparisons between categorical variables and 30-day in hospital mortality using chi-square tests; multiple comparisons were adjusted for multiplicity using Scheffe's comparison statistic. Logistic regression analysis was employed to examine significant outcome predictors ($p<0.10$ by Wald test from the univariate analysis) of 30-day in hospital mortality to ensure that the model included all variables with predictive power. Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated for those significant model predictors. A stepwise logistic regression analysis examined the association between 30-day mortality and the following predictor variables: Acute Illness Severity [36-38], Charlson Co-Morbidity Index [32], and Chronic Disabling Disease [33], sepsis status [39] and Deprivation Index according to the Quintiles of the SAHRU deprivation number.

We used the margins command in Stata to estimate and interpret adjusted predictions for sub-groups, while controlling for other variables such as time, using computations of average marginal effects. Margins are statistics calculated from predictions of a previously fitted model at fixed values of some covariates and averaging or otherwise over the remaining covariates. In the multiple variable logistic model, we adjusted univariate estimates of effect, using the previously described outcome predictor variables. The model parameters were stored; post-estimation intra-model and cross-model hypotheses could thereby be tested.

Statistical significance at P<0.05 was assumed throughout. Stata v.15 (Stata Corporation, College Station, Texas) statistical software was used for analysis.

Result

Patient Demographics

A total of 96,526 episodes in 50,731 unique patients were admitted as medical emergencies from the hospital catchment area over the 15-year study period (2002-2016). These episodes represented all emergency medical admissions, including patients admitted directly into the Intensive Care Unit or High Dependency Unit, respectively. The proportion of males was 48.6%. The median (IQR) length of stay (LOS) was 4.4 (1.8, 8.9) days. The median (IQR) age was 58.7 (38.0, 76.2) years, with the upper 10% boundary at 84.9 years.

The demographic characteristics (Table 1) are outlined with a division of Humidity levels at the time of admission (lower/higher cut at Quintile 3). Humidity cut-points per quintile were at 77%, 82%, 86% and 91% values; high humidity was taken to be at Q3 or above (>= 83%). The patient group characteristics at time of presentation are tabulated by our Co-morbidity and Chronic Disabling Score, Charlson Index [32] and Sepsis status [39]. There were no major differences between the groups in age at admission 64.9 yr. (IQR: 44.3, 78.7), hospital length of stay-6.0 days (IQR: 2.5, 13.1) or total hospital episode mortality - 5.6% (95% CI: 5.5%, 5.8%) outcomes. From an overall clinical perspective, one therefore could regard the groups, relating to admission on days of low or of high humidity, as essentially equivalent in risk profile and complexity / co-morbidity status.

	Low	High	
	• (N = 38651)	(N = 51604)	p-value
Age (yr.)			
Mean (SD)	60.75 (20.73)	61.37 (20.68)	<0.001
Median (Q1, Q3)	64.4 (43.9, 78.4)	65.2 (44.7, 79.0)	
Length Stay (day)			
Mean (SD)	14.63 (35.64)	15.40 (37.23)	0.002
Median (Q1, Q3)	5.9 (2.4, 12.9)	6.0 (2.5, 13.3)	
Gender			
Male	18831 (48.7%)	25068 (48.6%)	0.673
Female	19820 (51.3%)	26535 (51.4%)	
30-day Hospital Mortality			
Alive	36498 (94.4%)	48699 (94.4%)	0.711
Dead	2153 (5.6%)	2904 (5.6%)	
Illness Severity Score			
1	1022 (2.9%)	1386 (2.9%)	0.017

2	2394 (6.8%)	3188 (6.7%)	
3	4047 (11.5%)	5448 (11.4%)	
4	5606 (15.9%)	7405 (15.6%)	
5	6901 (19.6%)	9016 (18.9%)	
6	15219 (43.2%)	21170 (44.5%)	
Charlson Index			
0	17026 (44.2%)	22835 (44.3%)	0.003
1	10436 (27.1%)	14359 (27.9%)	
2	11067 (28.7%)	14326 (27.8%)	
Sepsis Group			
1	28637 (74.1%)	37860 (73.4%)	0.001
2	8211 (21.2%)	11472 (22.2%)	
3	1803 (4.7%)	2271 (4.4%)	
Humidity cut-points per quintile were at 77%, 82%, 86% and 91%; high Humidity was taken at Q3 or above (>= 83%).			

Table1: Characteristics of Emergency Medical Admission Episodes by Humidity *.

Temperature and Humidity Variation with Season

The median temperature in our temperate climate was 11.1°C (IQR: 7.2, 12.8) with respective 10 and 90 cent values at 4.4°C and 15.2 °C. The variation by season range from a maximum of 17.3°C (IQR: 15.2, 19.5) in summer to a minimum of 3.7°C (IQR: 1.8, 5.7) in winter. The corresponding Humidity levels were 84 % (IQR: 78%, 91%) with respective 10 and 90 cent values at 54 % and 91%. The variation by season range from a maximum of 88% (IQR: 83%, 91%) in winter to a minimum of 80% (IQR: 74%, 87%) in summer (Figure 1).
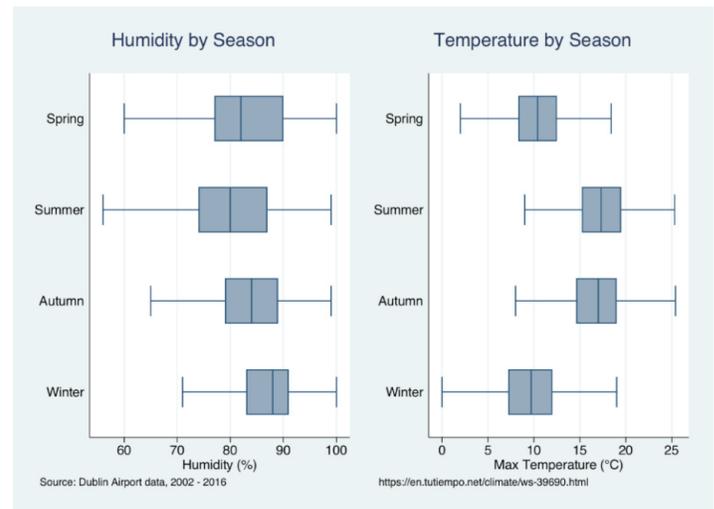

Figure 1: Humidity and maximal daily Temperature from the daily Dublin Airport records between 2012 and 2016. The box & whisker plots indicate the median (line subdividing the box) and the interquartile range (IQR). The upper and lower extremes (fence) are the smallest and largest values that are not outliers.

Logistic multiple variable predictor model including temperature, humidity and air pollutant level of 30-day mortality outcome

Both the level of humidity and the air pollutant level on the day of admission predicted the 30-day hospital mortality; higher levels of pollutant or drier air (lower humidity predicted worse outcomes). The particulate matter on the day of admissions (PM_{10} quintiles) showed worsening outcomes as one increased from Q2 (comparisons with base QI level) - OR 1.14 (95% CI: 0.94, 1.39) to Q5 -OR 1.25 (95% CI: 1.02, 1.54) with an overall Odds Ratio for PM_{10} level of 1.07 (95% CI: 1.02, 1.12). Humidity was a weaker trend to predict worse outcomes overall. As per other data previously published from our group, Acute Illness Severity [36-38], Charlson Co-Morbidity Index [32], and Chronic Disabling Disease [33], sepsis status [39] and Deprivation index were all predictive of worse outcome. The average temperature on the day of admission was predictive with a higher temperature predicting a lower mortality.

We used margins statistics to estimate and interpret adjusted predictions for sub-groups, while controlling for other variables, using computations of average marginal effects. These statistical predictions were computed using the fitted model at fixed values of some covariates and averaging or otherwise over the remaining

covariates. The risk of a death by the 30-day of a hospital episode increased essentially as a linear function of to the underlying PM_{10} Quintile at the time of hospital admission. Interaction analysis with the level of pollutant showed it to be predictive of worse outcome with both the >=85% < 95% and the >=95% showing better survival compared with lower humidity values (Table 2, Figure 2).
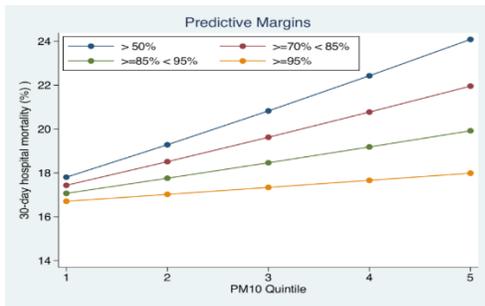
Figure 2: The risk of a death by the 30-day of a hospital episode increased essentially as a linear function of to the underlying PM_{10} Quintile at the time of hospital admission. The mortality outcome, plotted against deciles of Humidity levels was adjusted in the model for Acute Illness Severity, Charlson Co-Morbidity Score, Chronic Disabling and Sepsis Status. Lower humidity levels, on the day of admission, independently predicted worse outcomes.

Predictor Variable	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
PM_{10} Quintile						
QII	0.85	0.09	-1.6	0.12	0.7	1.04
QIII	1.14	0.11	1.3	0.19	0.94	1.39
QIV	1.14	0.12	1.3	0.2	0.93	1.39
QV	1.25	0.13	2.2	0.03	1.02	1.54
Humidity Group						
>=70% < 85%	1.04	0.8	0.1	0.95	0.23	4.69
>=85% < 95%	0.81	1.22	-0.1	0.89	0.04	15.3
>=95%	0.61	1.37	-0.2	0.83	0.01	50
Illness Severity	4.31	0.88	7.2	0	2.89	6.42
Charlson Index	1.36	0.06	6.9	0	1.25	1.49
Disabling Group	1.35	0.05	8.6	0	1.26	1.44
Sepsis	2.11	0.11	14.8	0	1.91	2.32
Deprivation	1.07	0.03	2.4	0.02	1.01	1.14
Average Temp	0.98	0.01	-2.4	0.02	0.96	1
PM_{10} # Humidity	0.93	0.03	-2.1	0.04	0.86	0.99

Table 2: Multivariable Logistic Regression Model of Mortality Outcome.

Discussion

These data demonstrate that the level of humidity interacted with the prevailing level of air pollution to influence the outcome of an emergency medical admission. The amount of water vapor within a given mass of air is temperature sensitive. The absolute humidity is the mass of water vapor divided by the mass of dry air in a volume of air at a given temperature (expressed as grams of moisture per cubic meter of air (g/m^3)). The relative humidity is the ratio of the current to the maximal absolute humidity that a given volume of air could hold (at that temperature).

The optimum environmental relative humidity has been estimated to lie between 45% and 55% [40]. According to our local stations the prevailing humidity is typically at a median of 84% (IQR: 78%, 91%) with the lower 10% limit at 73%. A minimum value of 54% was recorded over the monitored time period. However, the bronchi and alveoli require a relative humidity of 95% [40] as a lower degree would result in excessive evaporation from mucosal surfaces, and one nearer 100% would risk precipitation of droplets at dew point, if the temperature of the air in the bronchi dropped for any reason [41]. A 95% saturation requires that the air be warmed to bring its potential absolute humidity to a high level, so that the inspired gases can be charged to the appropriate saturation level [41].

Much of the research relates to infective agents and the correlation between temperature, humidity and risk of viral infection or other respiratory tract illness. Absolute humidity has been found to be a critical determinant of human influenza mortality, even after controlling for temperature; humidity below approximately 6 g/kg of air increased influenza mortality with approximately half of the average seasonal differences in US influenza mortality ascribable to differences in absolute humidity alone [42]. Cold temperature and low humidity have also been reported to precede the onset of a variety of respiratory tract infections [16].

Our data is not seasonally focused nor attempting to relate humidity to infective emergency medical admissions; but addressing a more general question as to how seemingly unrelated factors, such as humidity and air pollution, influence the mortality outcomes of an emergency medical admission, irrespective of the primary condition. We have in previous work related outcomes of unselected admissions to factors such as Illness Severity [43], Age and Co-morbidity / Case Complexity [44] and have sought to develop predictive models that might focus limited resources on those who could be identified at most risk [44].

We have previously reported that high levels of particulate matter on the day of a hospital admission were associated with worse outcomes with higher 30-day mortality rates [13]. This component of air pollution that is made up of extremely small particles and liquid droplets containing acids, organic chemicals, metals, and soil or dust particles leads to increased mortality particularly from respiratory and cardiovascular disease [11,15,19,20]. The World Health Organization estimates that PM air pollution contributes to approximately 800,000 premature deaths each year, ranking it the 13th leading cause of mortality worldwide [12]. It may be that in the context of an acute emergency medical admis-

sion that oxidative stress may influence the progression and prognosis of the acute disease state [16]. Now these data extend these observations to how the prevailing level of humidity on the day of the emergency admission interacted with the level of pollutant to alter the overall risk outcome. We made no arbitrary assumptions about what level of air pollutant or humidity that might be detrimental to human health. The particulate matter (PM_{10}) cut-points were distribution determined with cut-points at 9.9, 13.2, 16.9 and 23.3 $\mu g/m^3$ respectively; for humidity with a range of 50%-100%, we used mathematical cut-points of 50, 70, 85, and 95. But, as clearly demonstrated in (Figure 2), increasing levels of particulate matter at time of admission were associated with worse outcomes but the underlying level of humidity worsened such outcomes. For example, at the third and fifth quantile of PM_{10}, the predicted 30-day per patient mortality at a humidity level of > 95% was predicted at 17.3% and 18.0% but with lower humidity values between 50% and 70% would have risen to an estimated 20.9% and 24.1% respectively.

The results of this study are consistent with scarce but convincing reports in the literature regarding interactions between humidity and air pollution impacting human health. For example, a study conducted in Hong Kong showed that the effects of PM_{10}, Nitrogen Dioxide (NO_2) and Sulfur Dioxide (SO_2) on emergency COPD admissions were higher on the low humidity days than on the high humidity days [45]. Another study demonstrated that the adverse effect of total suspended particles (TSP) on chronic bronchitis was reduced with higher absolute humidity [46]. Two studies identified relative humidity as a modifier to the effects of ambient particles on total mortality in 29 European cities; a higher effect of particulate matter on mortality was found in drier countries [47,48].

This emerging complex interaction between humidity and air particulate matter and health is difficult to entangle. While TSP's are a trigger for respiratory diseases, the airways of individuals suffering from respiratory diseases seem to be protected by water vapor in the air. The protective effect could be due to a reduction in the number of inorganic salt molecules in ambient aerosols when humidity exceeds the level of deliquescence [46]. Soluble gases such as SO_2, NO_2 may also dissolve in humid air, thus reducing ambient pollutant concentrations [45]. The fact that this study was conducted in a single inner-city center may limit generalizability. The pollutant profiles might vary from one area to another. Indeed, regional differences in volatile organic compounds (VOC's) concentrations may also be of significance in quantifying the humidity effect on health outcomes given that water vapor interacts in a complex manner with VOC's to form deleterious organic aerosols. This potential variability is worthy of further study.

Conclusion

Our data demonstrated an interaction between humidity and prevailing levels of air pollution to favorably influence the out-come of emergency medical admissions to St James's Hospital in Dublin. The study was based on a large database of clinical data spanning a 16 year period. These results are supported by sparse but emerging epidemiological and clinical literature linking humidity to reduction in pollution driven morbidity in respiratory disease.

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