ACTA CLIMATOLOGICA ET CHOROLOGICA
Universitatis Szegediensis, Tomus 44-45, 2011, 135-153

MULTIVARIATE ANALYSIS OF RESPIRATORY DISORDERS IN RELATION TO ENVIRONMENTAL FACTORS

Z GUBA[1], I MATYASOVSZKY[2], L MAKRA[1] and Z SÜMEGHY[1]

[1]*Department of Climatology and Landscape Ecology, University of Szeged, P.O.Box 653, 6701 Szeged, Hungary*
E-mail: makra@geo.u-szeged.hu
[2]*Department of Meteorology, Eötvös Loránd University, Pázmány Péter st. 1/A. 1117 Budapest, Hungary*

Summary: The aim of the study is to analyse the joint effect of biological and chemical air pollutants, as well as meteorological variables, on the hospital admissions of respiratory problems for Szeged, Southern Hungary. The data set used covers a nine-year period (1999-2007). The analysis was performed using three age categories for the pollen season of *Ambrosia* and the pollen-free season. Two novel procedures are applied here: factor analysis, including a special transformation and a time-varying multivariate linear regression that makes it possible to determine the rank of importance of the influencing variables in respiratory hospital admissions, and also to compute the relative importance of the parameters affecting respiratory disorders. Both techniques revealed that *Ambrosia* pollen, O_3 and wind speed are important variables that influence hospital admissions. The role of chemical and meteorological parameters vary according to the seasons and the methods. Wind speed is a surprisingly important meteorological variable.

Key words: air pollution, respiratory hospital admissions, cluster analysis, factor analysis including a special transformation, time-varying multivariate linear regression

1. INTRODUCTION

Air pollution, as a major and permanently rising hazard for the environment, is associated with large increases in medical expenses, morbidity and is estimated to cause about 800,000 annual premature deaths worldwide (Cohen et al. 2005). The prevalence of allergic respiratory diseases has also increased during the last three decades, especially in industrialized countries. This increase may be explained by changes in environmental factors: urbanization, the ever increasing automobile traffic with its high levels of vehicle emissions, and the changing lifestyle are linked to the rising frequency of respiratory allergic diseases (D'Amato et al. 2005). Weather conditions can also affect both the biological and chemical air pollutants. There are evidences on the effect of air pollution upon allergens, increasing exposure to the latter, their concentration and/or biological allergenic activity (Just et al. 2007). Habitat regions and levels of pollen are changing in Europe, as a result of cultural factors, more international travel and climate change (Kiss and Béres 2006).

Air pollution in Hungary is one of the highest in Europe. Around 16,000 annual premature deaths attributable to exposure to ambient PM_{10} concentrations are estimated in the country (Ågren 2010). Furthermore, airborne pollen levels are also high. The Carpathian basin, including Hungary is considered the most polluted region with airborne ragweed *(Ambrosia)* pollen in Europe. *Ambrosia* in Hungary discharges the most pollen of all taxa; the ratio of its pollen release compared to the total pollen release in the late summer period is around 60-71% (Juhász and Juhász 2002). About 30% of the Hungarian population has some type of allergy, 65% of them have pollen-sensitivity, and at least 60% of this pollen-sensitivity is caused by *Ambrosia* (Járai-Komlódi 1998).

The substantial increase in respiratory diseases in industrialized countries is attributable to a combination of chemical air pollution and the allergens existing in the air of big cities. Several papers have analysed separately the effects of either chemical air pollutants (Alves et al. 2010) or pollen (Diaz et al. 2007) to hospital admissions of respiratory diseases; however, only very few studies have yet examined the effect of these two kinds of variables together (e.g. Andersen et al. 2007). Such papers revealed a significant connection between partly pollen taxa and chemical compounds and partly health for admitted respiratory patients, and this relationship was stronger than that detected separately either for the chemical air pollutants or pollen.

The purpose of this study is to analyse the joint effect of biological (pollen) and chemical air pollutants, as well as meteorological variables on the hospital admissions of respiratory diseases of different age groups during different seasons in Szeged region, Southern Hungary. The data set applied is unique in the sense that it includes all of the above three categories of influencing variables. Meteorological elements and air pollutants are clustered in order to define optimum environmental conditions for high patient numbers. Afterwards, analysis of variance is used to determine whether cluster related mean patient numbers differ significantly. Then a factor analysis including a special transformation is applied, as well as a time-varying multivariate linear regression making it possible to determine the rank of importance of the influencing variables in respiratory hospital admissions and to compute the relative importance of the parameters affecting respiratory disorders. The study examines one of the largest data sets used in the literature on respiratory hospital admissions.

The following meteorological and pollutant variables will be considered in our study. (1) Temperature. Inhalation of cold air in hyper-reactive bronchia induces the inflammation of the mucous membrane. (2) Relative humidity. Repeated exposition to dry air may produce the inflammation, obstruction and hyper-reactivity of the small respiratory tracts. (3) Global solar flux. This parameter develops its effect through influencing the values of temperature and relative humidity. (4) Wind speed. Strong winds make good ventilation conditions resulting in low pollutant levels. Additionally, winds desiccate and cool the air (see: hyper-reactivity occurring by the influence of cold and dry air). (5) Air pressure. In general, air pressure is not a direct reason for respiratory symptoms but is an indicator of certain atmospheric processes influencing the occurrences of respiratory diseases. (6) Air pollution. (6a) Inhalative chemical and physical substances (industrial and cigarette smoke, soot, carcinogenic and oxidizable substances, e.g. nitrogen-monoxide, etc.). For instance, after inhaling NO_x, an inflammation of mucous membrane in the bronchia will develop by the transmission of different mediators. (6b) Pollen. In the respiratory tracts of individuals sensitive to the given pollen, inflammation mediated by IgE will develop (IgE, the Immunoglobulin E plays an important role in allergy) (Parsons and Mastronarde 2005).

2. MATERIALS AND METHODS

2.1. Location and data

Szeged (46.25°N; 20.10°E) is the largest settlement in South-eastern Hungary. The area is characterised by an extensive flat landscape of the Great Hungarian Plain with an elevation of 79 m AMSL. The built-up area covers a region of about 46 km^2. The city is the centre of the Szeged region with 203,000 inhabitants. In the Köppen system the climate of Szeged is the Ca type (warm temperate climate) with relatively mild and short winters and hot summers (Köppen 1931). The pollen content of the air was measured using a 7-day recording “Hirst-type” volumetric trap. The air sampler is located about 20 m above the ground (Makra et al. 2008).

Meteorological variables and chemical air pollutants were collected in a monitoring station located in the downtown of Szeged at a distance of about 10 m from the busiest main road. Daily values of the above-mentioned 5 meteorological variables are: mean temperature (T, °C), mean global solar flux (GSF, Wm^{-2}), mean relative humidity (RH, %), mean sea-level air pressure (P, hPa) and mean wind speed (WS, ms^{-1}).

Chemical air pollutants include the daily average mass concentrations of CO, NO, NO_2, SO_2, O_3 and PM_{10} (μgm^{-3}) (Alves et al. 2010). When selecting biological air pollutants special emphasis is put on *Ambrosia* due to its above-mentioned characteristics in Hungary. Besides ragweed (*Ambrosia)*, further 23 relevant taxa are also taken into account. The taxa with their Latin (English) names are as follows: *Acer* (maple), *Alnus* (alder), *Artemisia* (mugwort), *Betula* (birch), *Cannabis* (hemp), *Carpinus* (hornbeam), Chenopodiaceae (goosefoots), *Corylus* (hazel), *Fraxinus* (ash), *Juglans* (walnut), *Morus* (mulberry), *Pinus* (pine), *Plantago* (plantain), *Platanus* (platan), Poaceae (grasses), *Populus* (poplar), *Quercus* (oak), *Rumex* (dock), *Salix* (willow), *Taxus* (yew), *Tilia* (linden), *Ulmus* (elm) and *Urtica* (nettle). Two pollen variables corresponding to taxa were formed for our analysis: pollen of *Ambrosia* due to its extremely high levels during its short pollination period, and total pollen excluding the pollen of *Ambrosia*. Both pollen variables were considered for the pollen season of *Ambrosia* (July 15 – October 16).

The daily number of hospital admissions registered with respiratory diseases comes from the Thorax Surgery Hospital, Deszk, Csongrád County located about 10 km from the monitoring station in Szeged downtown. This is the only hospital in Csongrád County hosting patients exclusively with respiratory symptoms. Most of the patients were treated as out-patients. Age, date of admission and disease type were available for each patient. Three age groups were considered in the research: young patients (0-14 years), adult patients (15-64 years) and elderly patients (equals to or older than 65 years) because some respiratory illnesses, such as the diagnostic category of asthma, may include different syndromes in children, adults and elderly people (Ko et al. 2007). Due to the very small patient number in the younger age group, the categories of adults and elderly people as well as all patients including the younger age group were analyzed. The population consists of 133,464 hospital admissions of subjects’ residents in Szeged.

The analysis was performed for a nine-year term 1999-2007 with two data sets according to the pollen season of *Ambrosia* (July 15 – October 16) and to the pollen-free season (October 17 – January 13). Note that Saturdays, Sundays and holidays as days without hospitalization were excluded from the analysis. Furthermore, there were no remarkable flu epidemics during the periods examined.

The pollen season is defined by its start and end dates. For the start (end) of the season we used the first (last) date on which 1 pollen grain·m^{-3} of air is recorded and at least 5 consecutive (preceding) days also show 1 or more pollen grains·m^{-3} (Galán et al. 2001). Evidently, the pollen season varies from year to year, here the longest observed pollen season during the nine-year period was considered for each year.

2.2. Methods

2.2.1. Cluster analysis

Cluster analysis is a common statistical technique to objectively group elements. The aim is to maximise the homogeneity of elements within the clusters and to maximise the heterogeneity among the clusters. Here a non-hierarchical cluster analysis with k-means algorithm using a Mahalanobis metric (Mahalanobis 1936) was applied. Data to be clustered include daily values of the 13 explanatory variables (5 meteorological elements, 6 chemical pollutants and 2 pollen types). The homogeneity within clusters was measured by RMSD defined as the sum of the root mean square deviations of cluster elements from the corresponding cluster centre over clusters. The RMSD value usually decreases with an increasing number of clusters. Thus, this quantity itself is not very useful for deciding the optimal number of clusters. However, the change of RMSD (CRMSD) or even the change of CMRSD (CCRMSD) versus the change of cluster numbers is much more informative (Makra et al. 2010). Clustering with the k-means algorithm was performed by using MATLAB 7.5.0. The remaining statistical computations were performed with SPSS (version 16.0) software.

2.2.2. Analysis of variance (ANOVA)

The one-way analysis of variance (ANOVA) is used to determine whether the inter-group variance is significantly higher than the intra-group variance of a data set. After performing ANOVA on the averages of the groups in question, a post-hoc Tukey test is applied to establish which groups differed significantly from each other (Tukey 1985). Significant differences between mean hospital admissions corresponding to different cluster pairs may reveal an important influence of the meteorological elements, chemical air pollutants and pollen types considered on daily number of respiratory diseases.

2.2.3. Factor analysis and special transformation

Factor analysis (FA) identifies linear relationships among subsets of examined variables which helps to reduce the dimensionality of the initial database without substantial loss of information. First, a factor analysis was applied to the initial dataset consisting of 14 variables (13 explanatory variables and 1 resultant variable defined by the number of daily hospital admissions with respiratory diseases) in order to transform the original variables to fewer variables. These new variables called factors can be viewed as latent variables explaining the joint behaviour of weather-pollutant-hospital admission variables. The optimum number of retained factors is determined by the criterion of reaching 80% of the total variance (Jolliffe 1993). After performing the factor analysis, a special transformation of the retained factors was performed to discover to what degree the above-mentioned explanatory variables affect the resultant variable, and to give a rank of their influence (Jahn and Vahle 1968).

2.2.4. Time-varying multivariate linear regression with time lags

The task is to establish a relationship between explanatory variables and the resultant variable. As both kinds of variables exhibit annual trends, regression coefficients in the linear relationship have annual courses described by sine and cosine functions with one year and one half year period lengths. This latter cycle was introduced to describe the asymmetries of the annual courses. Coefficients of these periodic functions were estimated using the least square principle.

It is reasonable to allow time lags between pollutants concentrations and number of hospital admissions. Therefore, the univariate version of the above mentioned time-varying linear regression was carried out with every individual explanatory variable with different time lags including the zero lag. The time lags minimising the mean square errors were taken as optimal.

3. RESULTS

3.1. Cluster analysis and ANOVA

Two clusterings were performed according to the two periods excamined (pollen season of *Ambrosia* and pollen-free season). The cluster analysis for the pollen season of *Ambrosia* and for the pollen-free season resulted in five and four clusters, respectively. The cluster-related mean values of the explanatory and resultant variables are shown in Tables 1a-b.

Table 1a Cluster-related mean values of the meteorological and pollutant parameters as well as patient numbers for the pollen season of *Ambrosia* (**bold:** maximum; *italic:* minimum)

Cluster	**1**	**2**	**3**	**4**	**5**
Parameter			**Mean values**		
Total number of days	68	41	*26*	94	**137**
Frequency (%)	18.6	11.2	*7.1*	25.7	**37.4**
Temperature (°C)	23.3	16.9	20.5	**24.9**	*16.4*
Global solar flux (Wm^{-2})	211.1	155.3	176.4	**223.6**	*126.7*
Relative humidity (%)	66.1	72.2	68.6	*59.3*	**75.0**
Air pressure (hPa)	1002.7	**1009.4**	*1001.7*	1005.3	1005.9
Wind speed (ms^{-1})	0.8	*0.5*	0.9	**1.1**	0.9
CO (μgm^{-3})	468.9	**700.5**	*425.1*	444.5	463.8
PM_{10} (μgm^{-3})	*36.3*	**52.8**	40.4	44.0	40.2
NO (μgm^{-3})	10.8	**44.7**	14.1	*9.5*	15.1
NO_2 (μgm^{-3})	32.9	**48.8**	33.2	34.0	*31.8*
O_3 (μgm^{-3})	41.8	*26.2*	36.3	**58.4**	29.2
SO_2 (μgm^{-3})	*4.0*	5.5	4.9	4.9	**6.0**
Ambrosia (pollen·m^{-3}·day^{-1})	91.7	*43.3*	**593.2**	46.2	57.9
Total pollen excluding *Ambrosia* (pollen·m^{-3}·day^{-1})	**111.9**	16.8	48.7	49.9	*14.1*
Adults (15-64 years) (person)	101.6	76.7	**114.3**	*74.5*	78.2
The elderly (≥65 years) (person)	12.8	11.8	**13.3**	*10.5*	12.2
All age groups (person)	114.5	88.7	**127.9**	*85.1*	90.6

The analysis of variance revealed a significant difference at least at a 95% probability level in the mean values of patient numbers among the individual clusters. The Tukey test indicated 6 (60.0%) and 4 (66.7%) significant differences for adults, while 4 (40%) and 5 (83.3%) significant differences for the elderly in the pairwise comparisons among the possible 10 and 6 cluster pairs for the pollen season of *Ambrosia* and pollen-free season, respectively. Similar results for the mean patient numbers of the cluster pairs for all age groups were obtained. Namely, 5 (50.0%) and 5 (83.3%) significant differences were found among the possible 10 and 6 cluster pairs. Only clusters accompanied with significantly different means were then analysed in detail, principally the clusters with extreme patient numbers.

For the pollen season of *Ambrosia*, patient numbers are the highest in cluster 3, of which the most characteristic components are the highest and medium levels of *Ambrosia* and the remaining pollen, respectively (Table 1a). Furthermore, cluster 4 involving a substantial part of summer with the highest temperature (24.9°C), global solar flux (223.6 Wm^{-2}) and O_3 level (58.4 μgm^{-3}), as well as the lowest relative humidity (59.3%) and NO concentration (9.5 μgm^{-3}) provides the lowest patient numbers. Moderate levels of the two pollen types and of the chemical pollutants (except for O_3) contribute to the lowest number of hospital admissions (Table 1a).

Table 1b Cluster-related mean values of the meteorological and pollutant parameters as well as patient numbers for the pollen-free season (**bold:** maximum; *italic:* minimum)

Parameter / Cluster	1	2	3	4
	Mean values			
Total number of days	75	**137**	*44*	108
Frequency (%)	20.6	**37.6**	*12.1*	29.7
Temperature (°C)	**10.8**	3.2	*-2.7*	5.7
Global solar flux (Wm^{-2})	**62.1**	38.9	*36.2*	44.8
Relative humidity (%)	*82.1*	87.6	**93.1**	87.1
Air pressure (hPa)	1010.6	*1004.3*	**1020.3**	1008.5
Wind speed (ms^{-1})	0.6	*0.5*	*0.5*	**1.4**
CO (μgm^{-3})	788.2	**812.4**	729.7	*652.2*
PM_{10} (μgm^{-3})	**79.2**	53.2	61.6	*52.6*
NO (μgm^{-3})	35.9	**40.6**	*28.0*	31.9
NO_2 (μgm^{-3})	**40.4**	38.0	*5.2*	36.0
O_3 (μgm^{-3})	**19.6**	15.2	16.8	*11.3*
SO_2 (μgm^{-3})	10.4	*6.6*	**15.2**	7.4
Adults (15-64 years) (person)	61.4	59.2	*50.2*	**64.6**
The elderly (≥65 years) (person)	11.7	11.6	*10.1*	**13.9**
All age groups (person)	73.2	71.0	*60.3*	**78.5**

For the pollen-free season, the highest patient numbers for each age category are associated with cluster 4 characterised by high temperature, the strongest wind speed, as well as low air pressure. These values of the meteorological parameters assume a cyclonic weather situation facilitating the dilution of the pollutants' concentrations (CO, PM_{10} and O_3 take their minimum levels of all four clusters) (Table 1b). Contrary to the low levels of the chemical air pollutants, relatively high temperature favours reproducing bacteria and viruses, while strong winds desiccating the air may produce inflammation in the small respiratory tracts. Both effects substantially contribute to the highest patient numbers for this cluster in this part of the year. Cluster 3 delivers the lowest patient numbers for each age category. This cluster covers a cold part of the winter period (temperature is -2.7°C) involving an anticyclonic ridge weather situation featured by clouds (global solar flux is the lowest: 36.2 Wm^{-2}), while relative humidity (93.1%) and air pressure (1020.3 hPa) are the highest and wind speed (0.5 ms^{-1}) is the lowest. A possible reason of the lowest patient numbers is that very low temperatures in winter time contribute to restrict respiratory infections. Furthermore, in spite of the highest SO_2 level, the lowest NO and NO_2 concentrations, especially the latter one, may substantially contribute to decreasing respiratory admissions (Table 1b).

3.2. Optimal time lags

Time-varying univariate linear regressions of the resultant variable on every individual explanatory variable were performed in order to determine optimal time lags defining the delay of patient number response to explanatory variables based on the two seasons and the three age categories, respectively.

A wide range of candidate time lags are applied in the literature for finding the optimal time delay. Although there are examples for time lags up to 5 days (Ko et al. 2007) and even 8 days (Nascimento et al. 2006), the literature generally shows delays up to 3 days in patient response to pollution exposure (Alves et al. 2010). It is likely that the explanatory variables develop their effects until the formation of the respiratory diseases within 3 days (Knight et al. 1991). For instance, immediate allergic reactions of pollen can occur within 15-20 minutes, in certain cases 8-10 hours, while all immune reactions in cells can occur 48-72 hours following the exposure (Petrányi 2000).

Our optimal time lag varies from zero to three days. There is a tendency with the increasing age for more non-zero lags. The global solar flux has the largest number of positive time shifts from meteorological variables (typically 2-3 days) for elderly, while the relative humidity has the largest number of non-zero delays (2-3 days) for adults. However, the role of relative humidity in positive delays is substantially smaller than the role of the global solar flux. Within the chemical pollutants, positive lags (0-3 days) are mostly associated with CO and SO_2 for both age groups, and then with NO for adults and PM_{10} for elderly, in agreement with other studies (e.g. Schwartz and Dockery 1992). No time shift is typical for the pollen season of *Ambrosia* in any disease groups.

3.3. Factor analysis and special transformation

Factor analysis was performed for adults, elderly and all age groups based on the two seasons considered. Thus, altogether 3x2=6 factor analyses were carried out. After performing factor analysis 7 and 6 factors were retained for the pollen season of *Ambrosia* and the pollen-free season, respectively. In order to calculate the rank of importance of the explanatory variables in determining the resultant variable, the loadings of the retained Factors were projected onto Factor 1 (special transformation) (Table 2a-b) (Jahn and Vahle 1968).

In the pollen season of *Ambrosia*, temperature and global solar flux for adults, as well as global solar flux for all age groups are proportional to the patient numbers (Table 2a). In the pollen-free season only temperature for all three age groups and wind speed for elderly change proportionally to the number of hospital admissions (Table 2b). These results are confirmed by other authors (Freitas et al. 2010). Furthermore, relative humidity tends to be inversely proportional to the patient numbers for both periods. Air pressure is in significant positive association with the patient numbers only for adults and elderly in the pollen-free season, while its role is negligible for the remaining cases (Table 2a-b). Wind speed is inversely proportional to the number of hospital admissions for all three age groups in the pollen season of *Ambrosia*, while it is proportional to the patient numbers for elderly in the pollen-free season. Wind speed involves a dual character; namely, strong winds facilitate decreasing hospital admissions through reducing levels of the pollutants all over the year. On the other hand, they contribute to desiccating the air and hence to an increase of respiratory diseases. The latter effect seems to be higher in the pollen-free season since in this period wind speed changes proportionally to the elderly patient numbers (Table 2b). In the pollen season of *Ambrosia*, the inverse connection of wind speed with the number of hospital admissions suggests that here the pollutant diluting effect of wind is predominant (Table 2a). In the cold pollen-free season, relatively high temperatures and strong wind speeds are associated to typical cyclonic air masses. This kind of weather can raise the number of hospital admissions of elderly since repeated exposition to dry air desiccated by winds may produce the inflammation of the small respiratory tracts (Table 2b) (Strausz 2003). Furthermore, bacteria and viruses causing respiratory diseases have optimal relative humidity and temperature to multiply. While Mycoplasma bacteria generating pneumonia and other respiratory inflammations favour relative humidity below 40%, adenoviruses provoking upper respiratory infections and conjunctivitis are more infectious at higher than 70% relative humidity. Hence, high relative humidity may also be a reason of respiratory hospital admissions (Dilaveris et al. 2006).

Table 2a Special transformation. Effect of the explanatory variables on respiratory diseases as resultant variables and the rank of importance of the explanatory variables on their factor loadings transformed to Factor 1 for determining the resultant variable; pollen season of *Ambrosia* (thresholds of significance: *italic:* $x_{0.05} = 0.056$; **bold:** $x_{0.01} = 0.074$)

Explanatory variables	**Adults (15-64 years)**		**The elderly (≥ 65 years)**		**All age groups**	
	weight	**rank**	**weight**	**rank**	**weight**	**rank**
Patient number	**0.914**	–	**-0.983**	–	**0.918**	–
Temperature (°C)	**0.081**	10	0.021	13	0.067	10
Global solar flux (Wm^{-2})	**0.168**	7	*0.134*	4	**0.146**	8
Relative humidity (%)	-0.163	8	0.057	10	**-0.152**	7
Air pressure (hPa)	-0.042	13	-0.103	7	-0.018	13
Wind speed (ms^{-1})	**-0.220**	5	**0.142**	2	**-0.228**	5
Total weight	0.675	–	0.457	–	0.611	–
CO (μgm^{-3})	**-0.255**	3	0.095	8	**-0.251**	4
PM_{10} (μgm^{-3})	**-0.314**	2	*0.119*	5	**-0.304**	2
NO (μgm^{-3})	-0.058	11	-0.032	12	-0.041	12
NO_2 (μgm^{-3})	0.047	12	*-0.134*	3	0.059	11
O_3 (μgm^{-3})	**-0.230**	4	**0.272**	1	**-0.252**	3
SO_2 (μgm^{-3})	*-0.115*	9	0.070	9	*-0.119*	9
Total weight	1.018	–	0.722	–	1.025	–
Ambrosia ($pollen \cdot m^{-3} \cdot day^{-1}$)	**0.553**	1	*-0.117*	6	**0.520**	1
Total pollen excluding *Ambrosia* ($pollen \cdot m^{-3} \cdot day^{-1}$)	**0.199**	6	-0.041	11	**0.177**	6
Total weight	0.752	–	0.158	–	0.697	–

Both for the pollen season of *Ambrosia* and the pollen-free season, the total weight of the chemical pollutants is the highest for all three age groups considering all variable types and is substantially higher than that of the meteorological variables. This latter result may be due to the fact that anticyclonic weather situations, being the most frequent during the above seasons, favour the enrichment of chemical pollutants and, in this way, high pollutant levels exert a higher effect on respiratory patient numbers (Table 2a-b).

Table 2b Special transformation. Effect of the explanatory variables on respiratory diseases as resultant variables and the rank of importance of the explanatory variables on their factor loadings transformed to Factor 1 for determining the resultant variable; pollen-free season (thresholds of significance: *italic:* $x_{0.05} = 0.105$; **bold:** $x_{0.01} = 0.138$)

Explanatory variables	Adults (15-64 years)		The elderly (≥ 65 years)		All age groups	
	weight	rank	weight	rank	weight	rank
Patient number	**0.993**	–	**0.943**	–	**0.992**	–
Temperature (°C)	**0.168**	2	**0.165**	4	**0.188**	2
Global solar flux (Wm^{-2})	0.048	8	-0.004	11	0.047	9
Relative humidity (%)	0.009	10	-0.083	9	-0.020	11
Air pressure (hPa)	*0.110*	7	*0.124*	7	0.055	7
Wind speed (ms^{-1})	0.035	9	**0.273**	2	0.022	10
Total weight	0.370	–	0.649	–	0.331	–
CO (μgm^{-3})	-0.009	11	*-0.126*	6	-0.049	8
PM_{10} (μgm^{-3})	**0.147**	3	0.092	8	**0.138**	4
NO (μgm^{-3})	*0.120*	6	**0.148**	5	0.104	5
NO_2 (μgm^{-3})	**0.175**	1	**0.186**	3	**0.197**	1
O_3 (μgm^{-3})	*-0.121*	5	**-0.351**	1	**-0.158**	3
SO_2 (μgm^{-3})	*-0.124*	4	-0.073	10	-0.091	6
Total weight	0.696	–	0.977	–	0.737	–

For the pollen season of *Ambrosia*, pollen variables indicate the second highest weight for adults and all age groups, basically due to the very high *Ambrosia* pollen levels (Table 2a). For adults, the first three explanatory variables influencing most the patient numbers in decreasing order are *Ambrosia*, PM_{10} and CO, while for all age groups *Ambrosia*, PM_{10} and O_3, respectively. For the elderly, there are much less significant associations between the explanatory variables and the number of respiratory diseases; furthermore, pollen variables show the smallest total weight in this case. Here, influencing variables ranked highest in decreasing order are O_3, wind speed and NO_2. *Ambrosia* pollen is yet in significant connection with the number of respiratory diseases, however it is ranked only 6 (Table 2a).

For the pollen-free season, the chemical variables are ranked highest (Table 2b). The sequence of the most important influencing variables in decreasing order for adults is NO_2, temperature and PM_{10}, for the elderly O_3, wind speed and NO_2, while for all age groups NO_2, temperature and O_3 (Table 2b).

CO and photochemical pollutants (NO_2, O_3) can be considered as determinants of acute respiratory conditions. Since CO and NO_2 are good indicators of combustion products from traffic-related sources the detected effect may be due to unmeasured fine and ultrafine particles (Fusco et al. 2001). We received a statistically significant negative association between daily hospital admissions for respiratory causes and CO levels for adults and all age groups in the pollen season of *Ambrosia*, as well as for elderly in the pollen-free season. CO has been associated to respiratory conditions in several investigations. Freitas et al. (2010) did not find any statistically significant relationship between respiratory hospital admissions and CO, while Kassomenos et al. (2008), Fusco et al. (2001), Migliaretti et al. (2007) and Chiu et al. (2009) confirmed the role of CO on respiratory health effects. The impacts of long-lasting but low level exposure to CO on the respiratory system are thus still uncertain (Table 2a-b).

For the pollen season of *Ambrosia*, we found significant negative associations between the number of respiratory admissions and PM_{10} levels for all three age groups, while for the pollen-free season significant positive associations were detected between these variables for adults and all age groups (Table 2a-b). Time-series analysis conducted in the scope of the "Air Pollution and Health, European Approach" (APHEA) project involving 15 European cities, 10 different countries and 25 million people (Katsouyanni et al. 1996), as well as other epidemiological studies in Europe (Fusco et al. 2001) have suggested that gaseous air pollutants, in particular CO and NO_2, are more important predictors of acute hospitalisation for respiratory conditions than particulate matter. On the contrary, in Athens (Kassomenos et al. 2008) elevated PM_{10} levels seem to play a dominant role among the main air pollutants. Furthermore, some studies (Tenías et al. 1998, Fusco et al. 2001) showed the association between particulate matter and health conditions not to be significant, while others (Andersen et al. 2007, Ko et al. 2007, Chiu et al. 2009) found that the number of admissions for respiratory causes rose significantly with increased exposure to particulate matter. Additionally, Freitas et al. (2010) detected but Alves et al. (2010) did not detect associations between the number of respiratory diseases and PM_{10} levels in Lisbon. It should be noted that the impact of particulates on health is complex, since their biological effect can be influenced by the particle size and composition. It is also possible that PM_{10} itself is a by-product of some chemical reactions involving other pollutants and that these precursors are the real cause of hospital admissions (Alves et al. 2010).

For the pollen season of *Ambrosia*, we received a significant positive association between respiratory causes and NO_2 levels for the elderly, while for the pollen-free season significant positive associations were found between NO concentrations and respiratory admissions for adults and elderly, as well as between NO_2 levels and admissions for all three age groups, respectively (Table 2a-b). Although NO and NO_2 are considered to increase predisposition to respiratory diseases, results of different studies concerning the association between NO_x and respiratory causes still show discrepancies. For example, both Alves et al. (2010) and Freitas et al. (2010) found no significant association between respiratory diseases and NO levels. Spix et al. (1998) observed no significant relationship between NO_2 and respiratory admissions for adults and elderly from five West-European cities. Atkinson et al. (1999) reported no significant associations between NO_2 and respiratory admissions in London for each three age groups (children, adults and elderly) and for all ages. Similarly, no significant association between NO_2 and hospital admissions for respiratory morbidity was found in Dab et al. (1996). On the contrary, Luginaah et al. (2005) found a significant association between NO_2 levels and respiratory admissions only for females, 0-14 years of age. Further examples for significant impact of NO_2 levels on respiratory causes are in Fusco et al. (2001), Wong et al. (2006), Nidhi and Jayaraman (2007), Kassomenos et al. (2008), Cadum et al. (2009). In Lisbon, due to the dual role of NO_2, its high levels partly indicate no significant association with respiratory admissions (Alves et al. 2010), and partly increase the susceptibility for respiratory disorders (Freitas et al. 2010).

Several studies suggest that high concentrations of O_3 are harmful to human health and have indicated a positive association between O_3 and respiratory hospital admissions (Kassomenos et al. 2008). In particular, individuals exposed to higher than common ambient O_3 levels develop reversible reductions in lung function often associated with symptoms such as airway hyper-reactivity and lung inflammation (Uysal and Schapira 2003). In contrast, we observed a statistically significant negative effect of ozone for all three age categories in both seasons (Table 2a-b). This was the most characteristic connection between the number of respiratory disorders and levels of chemical pollutants. The aforementioned role of O_3 is confirmed in Lisbon for children and elderly people (Alves et al. 2010), as well as for all ages (Freitas et al. 2010). Some further studies (Karr et al. 2007) found that, sometimes low levels of ozone appear to be more harmful to health than moderate values. As there is no evidence that low levels of ozone are really harmful, this association seems paradoxical. The phenomenon called Paradoxical Ozone Association, i.e. POA (Joseph 2007) could be due to methyl nitrite from combustion of methyl ethers or esters in engine fuels. Methyl nitrite is known to be highly toxic, and closely related alkyl nitrites are known to induce respiratory sensitivity in humans (Joseph and Weiner 2002). Since sunlight is essential for ozone formation by photochemical oxidation a probable explanation for POA would be the existence of this nitrite pollutant that is rapidly destroyed by solar radiation. Hence, methyl nitrite is negatively correlated with O_3. Days with low solar radiation are likely to be days with both low ozone and high methyl nitrite, so that low ozone would be a marker for low solar radiation and high methyl nitrite. Since sunlight has opposing effect on ozone and methyl nitrite, one would expect the most acute methyl nitrite effect in winter (Joseph 2007). Negative association between O_3 levels and respiratory disorders in the summer period (pollen season of *Ambrosia*) can be explained by the fact that our monitoring station is found at a junction with heavy traffic (Table 2a-b).

SO_2 reacts with other chemicals in the air to form tiny sulphate particles. When these are breathed in, they gather in the lungs and are associated with increased respiratory symptoms together with decreased lung functions (Alves and Alvim-Ferraz 2005). We received a significant negative association between SO_2 levels and respiratory admissions for adults in both seasons and all age groups in the pollen season of *Ambrosia* (Table 2a-b, Matyasovszky et al. 2011). For the remaining cases the connection is not characteristic. Previous findings regarding the association between SO_2 levels and the number of respiratory causes have been inconsistent, since in some studies the pollutant was not significantly associated with respiratory diseases but other papers have reported positive relationships. Atkinson et al. (1999), Martins et al. (2002), Sunyer et al. (2003) or Alves et al. (2010) associated SO_2 levels with visits to the emergency departments. Contrarily, studies performed by the APHEA project (Katsouyanni et al. 1996), Tenías et al. (1998), Fusco et al. (2001), Galán et al. (2003), Ko et al. (2007) or Chiu et al. (2009) found no relationship between SO_2 concentrations and the hospital admissions for respiratory diseases.

Ambrosia pollen levels are in significant positive association with the number of hospital admissions for all three age categories (Table 2a). Furthermore, the remaining pollen is positively associated with respiratory disorders only for adults and all age groups. Similar results can be found e.g. in Carracedo-Martinez et al. (2008). However, factor loadings belonging to the remaining pollen are much smaller indicating their substantially weaker connection with hospital admissions (Table 2a).

Results received for elderly differ substantially from the remaining age categories for both periods (Table 2a-b). Though the sign of the associations betwen elderly patient number and the explanatory variables is the same for the most variables, the explanatory variables indicate generally smaller (higher) factor loadings, and the total weight of the variable types is also smaller (higher) than that for the remaining age categories in the pollen season of *Ambrosia* (pollen-free season). Furthermore, the sensitivity of the elderly to pollen seems to be definitely smaller than that of the remaining age groups. Accordingly, respiratory diseases for elderly people depend less on the explanatory variables in the pollen season of *Ambrosia*. Some of elderly habits, as social factors, contribute to this result as they tend to underestimate chronic diseases and consider them as natural attendant of age. Hence, the elderly do not turn to physician and do not partake in medical attendance in time (Johnson 2005), which may result in a weaker connection of the number of respiratory admissions with the explanatory variables in the pollen season of *Ambrosia*. At the same time, in the pollen-free season inhalation of generally colder air induces inflammation of the respiratory tracts especially for the elderly (Strausz 2003), who may be more sensitive to inflammation due to colder air. This may be the reason of the fact that the respiratory hospitalization of the elderly peaks in the winter months (Table 2a-b) (McCoy et al. 2005).

3.4. Time-varying multivariate linear regression

In order to measure the role of the explanatory variables in the number of hospital admissions the relative variances explained by these variables are used. Three questions can be addressed here. What is the order of explanatory variables with regard to the strength of the influence on patient number? What is the relative contribution of these variables to the variance explained by all of the variables? How do the patient numbers answer to a unit change in the explanatory variables? Concerning the first question, the selection of the importance of explanatory variables in the formation of patient numbers was performed by the well-known stepwise regression (Draper and Smith 1981).

The ratio of the variance of patient numbers explained by explanatory variables to the variance of patient numbers is considerably larger for adults than for elderly people. Also, the annual cycle of adult patient numbers is substantially larger (Table 3) suggesting that hospital visit of elderly people depends on pollutants and meteorological conditions to a lesser degree. This might be due to the social factor mentioned before (Table 3).

Table 3 Relative variance (%) of patient numbers accounted for by explanatory variables including and omitting (in parentheses) the annual cycle of patient numbers

Patients	**Pollen season of *Ambrosia***	**Pollen-free season**
Adults	26.8 (50.0)	17.8 (21.2)
The elderly	19.9 (23.9)	9.9 (13.9)
All age groups	26.5 (48.1)	13.8 (17.7)

The answer to the second question is more difficult due to the multicollinearity among the explanatory variables. Namely, the sum of variances explained by individual variables is larger than the variance explained by all of the variables. Therefore, neither univariate regressions with individual explanatory variables nor the multivariate regression performed with all of the variables is appropriate to quantify the individual explained variances. However, elementary consideration shows that the variance percentage explained by the *i*th variable is between V-V_i and v_i, where V is the total explained variance, and v_i and V_i are the variances explained by the *i*th variable and all of the variables excluding the *i*th variable, respectively. Therefore, only the ranges of variances explained by the explanatory variables corresponding to V-V_i and v_i can be shown in Table 4. The most important explanatory variables influencing patient numbers in the pollen season of *Ambrosia* are O_3

and temperature for every age category. The order of the remaining variables is the same for adults and all of ages: global solar flux, NO, wind speed, PM_{10}, air pressure, and *Ambrosia*. Almost the same variables are considered to be most substantial for the elderly group, but with a slightly different order. It is remarkable that *Ambrosia* is only the sixth-eighth most important explanatory variable influencing patient numbers. For the pollen-free season, O_3 is the second main factor for adults and all age groups, but is just the fifth for the elderly. The order is rather variable under different age groups. For instance, the most significant variable is PM_{10}, NO and global solar flux for adults, elderly and all age category, respectively.

Table 4 Ratio (%) of variances accounted for by explanatory variables to variance accounted for by all of the explanatory variables. Variables are indicated in an order of importance obtained via a stepwise regression. Only variables with a joint contribution just exceeding 90% of the total explained variance are shown. (in *X:* significant for $p < 0.1$, in **X**: significant for $p < 0.05$, in ***X***: significant for $p < 0.01$)

Pollen season of *Ambrosia*			**Pollen-free season**		
Adults	**The elderly**	**All ages**	**Adults**	**The elderly**	**All ages**
O_3: 15.8-31.7	**O_3: 20.1-36.7**	***O_3: 16.8-46.6***	**PM_{10}: 14.6-18.5**	*NO: 10.0-17.1*	**GSF: 8.0-12.3**
T: 1.5-10.9	T: 1.0- 5.0	*T: 1.5-10.4*	*O_3: 7.9- 9.0*	CO: 8.0-18.1	*O_3: 10.9-12.3*
GSF: 2.3- 6.4	NO_2: 5.0-10.0	GSF: 2.2- 6.0	*RH: 3.4-19.1*	SO_2: 8.0-14.1	*RH: 4.3-20.3*
NO: 3.8- 6.4	WS: 5.0- 6.0	NO: 3.7- 6.3	T: 7.9- 8.4	RH: 3.0-16.1	*CO: 4.3-11.6*
WS: 6.8-10.2	PM_{10}: 3.5-10.1	*WS: 7.1-10.1*	P: 0.2- 9.6	*O_3: 13.1-16.1*	*NO_2: 12.3-13.8*
PM_{10}: 6.0- 7.9	A: 2.5- 4.0	PM_{10}: 6.0- 8.2	*GSF: 8.4-10.7*	WS: 5.0- 9.0	P: 0.1- 9.4
P: 0.1- 5.3	GSF: 4.5- 5.0	P: 0.1- 5.0	SO_2: 5.6- 6.2	NO_2: 8.0-13.1	*NO: 8.0-16.7*
A: 5.7- 6.4	P: 0.0- 3.5	A: 4.9- 6.3	*NO: 7.3-12.9*	PM_{10}: 5.0- 5.1	T: 5.1- 9.4
RH: 1.1- 4.2	CO: 2.0- 4.0	RH: 0.7- 3.7			

T = Temperature (°C); GSF = Global Solar Flux (Wm^{-2}); RH = Relative humidity (%); P = Air pressure (hPa); WS = Wind speed ($m{\cdot}s^{-1}$); CO = Carbon-monoxide (μgm^{-3}); PM_{10} = Particulate matter smaller size than 10 μm (μgm^{-3}); NO = Nitrogen-monoxide (μgm^{-3}); NO_2 = Nitrogen-dioxide (μgm^{-3}); O_3 = Ozone (μgm^{-3}); SO_2 = Sulphur-dioxide (μgm^{-3}); *A* = *Ambrosia* ($pollen{\cdot}m^{-3}{\cdot}day^{-1}$)

Additionally, the order of importance of explaining variables identified by the stepwise regression is not the same as the order of level of the statistical significance (Table 4). The significance depends not only on the strength of the relationship but also on data length and autocorrelations of the different variables. Significance levels were determined by a Monte-Carlo simulation experiment. Approximating the autocorrelations of an explaining variable by a first order autoregressive model fitted to observed values of this variable, a time series independent of patient numbers was generated according to the time-varying empirical probability distribution function of the underlying explaining variable. The observed values were then substituted by this simulated data and the time-varying multivariate linear regression was performed. Finally, the mean squared error for patient numbers obtained from this regression was calculated. These steps were repeated 1,000 times, and the appropriate quantiles of the empirical probability distribution function of these 1,000 simulated mean squared errors delivered the critical value for checking the null-hypothesis of this explaining variable being uncorrelated with patient numbers. The procedure was applied to every explaining variable separately.

The answers of the patient numbers to unit changes in the explanatory variables exhibit annual cycles as the regression coefficients depend on dates within the year. There are evidences that confirm different effects of the explanatory variables in different periods of the year. For instance, wind speed is inversely proportional to the patient numbers in the pollen season of *Ambrosia* since this period is characterized by pollutant diluting effect of wind due to an intense vertical exchange in the boundary layer. In the pollen-free season, however, wind speed is mainly in positive association with respiratory diseases, especially for the elderly, since repeated exposition to strong winds may produce an inflammation of the small respiratory tracts (Strausz 2003). Furthermore, the role of bacteria and viruses affecting respiratory hospital admissions may be different under given meteorological conditions. While, for example, Mycoplasma bacteria generating pneumonia and other respiratory inflammations favour low relative humidity (pollen season of *Ambrosia*), adenoviruses provoking upper respiratory infections and conjunctivitis are more infectious at higher relative humidity (pollen-free season). Hence, not only low but also high relative humidity may contribute to an incraese in respiratory hospital admissions (Dilaveris et al. 2006).

Minima and maxima of regression coefficients during the year are shown in Table 5.

Table 5 Minima and maxima of regression coefficients during the year

Variable	Pollen season of Ambrosia						Pollen-free season					
	Minimum			Maximum			Minimum			Maximum		
	Adults	The elderly	All	Adult	The elderly	All	Adults	The elderly	All	Adults	The elderly	All
T	-3.61	-0.27	-3.96	5.28	0.01	5.83	-0.52	-0.55	-0.59	2.26	0.08	1.58
GSF	-0.03	-0.02	-0.03	0.38	0.01	0.40	-0.20	-0.02	-0.13	0.13	0.00	0.13
RH	-0.54	-0.06	-0.56	0.17	0.01	0.18	-0.77	-0.21	-0.82	0.29	0.05	0.35
P	-0.04	-0.01	-0.05	0.01	0.01	0.07	-0.03	0.00	-0.03	0.06	0.02	0.08
WS	-35.1	-2.61	-37.7	0.26	0.33	0.17	-4.11	0.00	-3.50	4.49	3.72	6.06
CO	-0.04	-0.01	-0.04	0.00	0.01	0.00	-0.01	-0.01	-0.02	0.01	0.01	0.00
PM_{10}	-0.50	-0.03	-0.55	0.14	0.03	0.18	0.00	-0.04	-0.05	0.24	0.04	0.13
NO	-1.00	-0.11	-1.07	0.25	0.01	0.23	-0.15	-0.03	-0.18	0.27	0.09	0.38
NO_2	-0.26	-0.07	-0.31	0.13	0.09	0.16	-0.42	-0.14	-0.68	0.21	0.08	0.47
O_3	-1.20	-0.16	-1.37	0.60	0.03	0.10	-0.47	-0.20	-0.70	0.24	0.02	0.00
SO_2	-1.54	-0.20	-1.75	0.63	0.18	0.99	-1.24	-0.09	-0.54	0.00	0.21	0.47
A	-0.08	-0.03	-0.11	2.78	0.24	3.05						
TP	-0.02	-0.13	0.00	0.34	0.02	0.59						

T = Temperature (°C); GSF = Global Solar Flux (Wm^{-2}); RH = Relative humidity (%); P = Air pressure (hPa); WS = Wind speed (ms^{-1}); CO = Carbon-monoxide (μgm^{-3}); PM_{10} = Particulate matter smaller size than 10 μm (μgm^{-3}); NO = Nitrogen-monoxide (μgm^{-3}); NO_2 = Nitrogen-dioxide (μgm^{-3}); O_3 = Ozone (μgm^{-3}); SO_2 = Sulphur-dioxide (μgm^{-3}); *A* = *Ambrosia* ($pollen \cdot m^{-3} \cdot day^{-1}$); TP = Total pollen ($pollen \cdot m^{-3} \cdot day^{-1}$)

These values mean boundaries of how the patient number changes with a unit change in different explanatory variables. The comparison of the main results of the factor analysis including special transformation (Table 2a-b) with stepwise regression (Table 4) and with the regression coefficients (Table 5) clearly indicates the difficulty of quantifying the importance of the explanatory variables due to multicollinearity among variables. The most evident example is *Ambrosia* in the pollen season of *Ambrosia*. It is considered to be the most important variable influencing patient numbers by the factor analysis for adults and all age groups, while stepwise regression takes it as only the sixth-eigth most significant parameter. However, Table 5 shows that a rise of 10 pollen grains·m^{-3} in the *Ambrosia* level may imply an increase of 28-30 patient numbers (24%) except for elderly people. This is because temperature, global solar flux, relative humidity and wind speed being important meteorological variables influencing the patient numbers well correlate with *Ambrosia* levels and so the stepwise regression prefers the aforementioned variables instead of *Ambrosia*. Another essential circumstance is that when using factor analysis, the relationship between two variables is due partly to the similarity of their annual cycles and partly to the correlation between centralized (difference between data and their annual cycle) data. Additionally, this relationship is constant in time for factor analysis, while time-varying linear regression allows different types of relationships during the year. Finally, a time lag between actual explanatory variables and patient numbers not introduced in the factor analysis is allowed for the regression approach. To sum up, time-varying regression produces a refinement of the overall picture provided by the factor analysis not discriminating between annual cycles and variations around these cycles. Considering O_3 (the most significant variable during the pollination season of *Ambrosia*), a 10 μgm^{-3} rise results in a relative patient number change from -17% (beginning of the season) to +11% (end of the season). Temperature and wind speed, weakly significant explaining variables, may imply a 7-8% increase at the beginning and 5% decrease at the end of the pollination season against a 1°C temperature rise and up to a 42-45% decrease of patient numbers under a 1 ms^{-1} wind speed growth (except for elderly people). The number of significant explaining variables is larger for the pollen-free season. The relative contribution of the influencing variables to all patient number varies during the year between the following ratios: -1.5% - +1.5% for global solar flux, 0% - +8% for O_3, -10% - +5% for relative humidity, -9% - +6% for NO_2 and -3% - +6% for NO under a rise of 10 Wm^{-2}, 10 μgm^{-3}, 10%, and 10 μgm^{-3} of the aforementioned variables, respectively.

Note that regression results coincide with the findings of factor analysis including special transformation according to which the connection of the number of respiratory admissions for the elderly age group with the explanatory variables is substantially weaker than for adults.

4. DISCUSSION AND CONCLUSIONS

The analysis of hospital admissions due to respiratory disorders originating in meteorological conditions and air pollutant levels is a very important issue of public health. The present study analyzes one of the largest databases in the field. Our study can be considered unique in the sense that it concurrently includes three categories of influencing variables with 5 meteorological, 6 chemical and 2 biological (pollen) parameters. We know of only one study (Kassomenos et al. 2008) that made an attempt to quantify the impact of different chemical pollutants together with meteorological elements on the incidence of respiratory diseases. However, pollen has not been studied from this point of view.

A large variety of statistical methods has been used to quantify the relationship of meteorological and air pollutant variables on the one hand and respiratory disorders on the other. The most frequently used procedures include stepwise regression (Kassomenos et al. 2008), artificial neural networks (Kassomenos et al. 2008), generalized additive Poisson regression (e.g. Alves et al. 2010), logistic regression (Heinrich et al. 2005), or case-crossover analysis as an alternative to Poisson regression (Yang et al. 2004). In our study, cluster analysis and factor analysis including special transformation, as well as a time-varying multivariate linear regression were applied in order to explore the role of influencing variables in respiratory hospital admissions and to determine the rank of importance of these variables as well as to quantify their effects. The aforementioned two methods are novel procedures in the subject.

The clustering of the pollen season of *Ambrosia* produced five clusters. It was found that for each age category, patient numbers were the highest in cluster 3, most probably due to the highest and medium levels of *Ambrosia* and the remaining pollen, respectively (Table 2a). Furthermore, cluster 4 involving a substantial part of summer provides the lowest patient numbers. It can be explained by moderate levels of both the two pollen types and the chemical pollutants (except for O_3) (Table 2a). Concerning the pollen-free season, four clusters were retained. The highest patient numbers for each age category are associated with cluster 4; that can be explained by the relatively high temperature facilitating the reproduction of bacteria and viruses, as well as by strong winds promoting inflammation in the small respiratory tracts by desiccating the air. On the other hand, cluster 3 having an anticyclonic character exhibits the lowest patient numbers for each age category, probably due to the very low temperatures in winter time that contribute to restricting respiratory infections (Table 2b).

In the pollen season of *Ambrosia*, factor analysis including special transformation revealed that the most important factors influencing respiratory diseases in decreasing order include *Ambrosia*, PM_{10}, CO, O_3 and wind speed for adults; furthermore, O_3, wind speed, NO_2, global solar flux and PM_{10} for the elderly, as well as *Ambrosia*, PM_{10}, O_3, CO and wind speed for all age groups. The sign of the relationship between patient numbers and the above variables is negative except for *Ambrosia* in every age group and NO_2 for elderly group (Table 2a). The most significant variables for this season obtained with time-varying linear regression are O_3 for every age group with its negative effect on patient numbers, furthermore temperature, global solar flux, NO and wind speed for both the adults and all age groups, while temperature, NO_2, wind speed and PM_{10} for elderly people. The sign of their effects are variable during the season (Table 4). Regression coefficients of the wind speed are rather large indicating the importance of this variable (Table 5). In the pollen-free season, factor analysis including special transformation showed the following explanatory variables to be most important: NO_2, temperature, PM_{10}, SO_2 and O_3 for adults; O_3, wind speed, NO_2, temperature and NO for elderly people; while NO_2, temperature, O_3, PM_{10} and NO for all age groups (Table 2b). The sign of these relationships is now positive except for O_3 and SO_2. The order of importance of explanatory variables obtained by time-varying linear regression is highly variable among age groups, but O_3 is again a main explaining variable. The role of wind speed is essentially smaller, while relative humidity is more important compared to the pollen season of *Ambrosia*.

Note that rank of the importance of the explanatory variables is different when using factor analyses and time-varying linear regressions due to three reasons. Specifically, factor analysis explores relationships among variables coming from two sources. Namely, the relationship between two variables is partly due to the similarity (or dissimilarity) of their annual cycles but partly due to the correlation between variations around these annual cycles. Additionally, this relationship is constant in time for factor analysis, while time-varying linear regression allows different types of the relationships between the explanatory variables and patient numbers during the year. Finally, a time lag between the actual explanatory variables and patient numbers not introduced for factor analysis is allowed for the regression approach. Hence, factor analysis shows an overall picture, while time-varying linear regression characterises the relationship between daily variations of explaining variables and number of daily hospital admissions.

Additional reasons make further difficulties in determining direct association between the explanatory variables and the number of respiratory diseases. A major concern is a dual character, namely different effects of specific explanatory variables on the respiratory admissions in the two periods examined or even during the same period. A typical example is the inverse role of O_3; see section 3.3 discussing the Paradoxical Ozone Association. Another case is temperature that is proportional to the patient numbers in both seasons. In the pollen season of *Ambrosia*, it affects patient numbers possibly purely. Namely, higher temperature contributes to the intense reproduction of bacteria and viruses that raises the number of hospital admissions. On the other hand, in the pollen-free season the effect of temperature increase occurs jointly with wind speed during a cyclonic activity. Concerning wind speed in the pollen season of *Ambrosia* it is in inverse connection with the number of hospital admissions as here the pollutant diluting effect of wind is predominant (Table 2a). In the cold pollen-free season, however, wind speed together with temperature is proportional to the number of hospital admissions, especially for elderly, since repeated exposition to dry air desiccated by winds may produce an inflammation of the small respiratory tracts (Table 2b) (Strausz 2003). Bacteria and viruses indicate also a dual effect. While, for example, Mycoplasma bacteria generating pneumonia and other respiratory inflammations favour relative humidity below 40%, adenoviruses provoking upper respiratory infections and conjunctivitis are more infectious at higher than 70% relative humidity. Hence, not only low but also high relative humidity may contribute to an incraese in respiratory hospital admissions (Dilaveris et al. 2006).

In the knowledge of the weight of the explanatory variables determined in developing respiratory diseases, age categories of high risk, as well as vulnerable groups with specific activity patterns can be warned by authorities, especially before and during given weather situations that favour extreme values of meteorological and pollutant variables.

Acknowledgements: The authors would like to thank Gábor Motika (Environmental and Natural Protection and Water Conservancy Inspectorate of Lower-Tisza Region, Szeged, Hungary) for handling meteorological data of Szeged and Miklós Juhász (University of Szeged, Department of Botany) for providing pollen data for Szeged. The European Union and the European Social Fund have provided financial support to the project under the grant agreement no. TÁMOP 4.2.1/B-09/1/KMR-2010-0003 and TÁMOP-4.2.1/B-09/1/KONV-2010-0005.

REFERENCES

Ågren C (2010) Particles killing half a million. Acid News 2:1-5 http://www.airclim.org/acidnews/2010/AN2-10.php#1

Alves CA, Alvim-Ferraz MCM (2005) Effects of Air Pollution on Emergency Admissions for Chronic Obstructive Pulmonary Diseases in Oporto, Portugal. Int J Environ Pollut 23:42-64

Alves CA, Scotto MG, Freitas MC (2010) Air Pollution and Emergency Admissions For Cardiorespiratory Diseases in Lisbon (Portugal). Quim Nova 33(2):337-344

Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Scheike T, Loft S (2007) Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. J Exposure Sci Environ Epidemiology 17(7):625-636

Atkinson RW, Anderson HR, Strachan DP, Bland JM, Bremner SA, Ponce de Leon A (1999) Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur Respir J 13(2):257-265

Cadum E, Berti G, Biggeri A, Bisanti L, Faustini A, Forastiere F (2009) The results of EpiAir and the national and international literature. Epidemiologia & Prevenzione 33(6):113-119 Suppl 1

Carracedo-Martinez E, Sanchez C, Taracido M, Saez M, Jato V, Figueiras A (2008) Effect of short-term exposure to air pollution and pollen on medical emergency calls: a case-crossover study in Spain. Allergy, 63(3):347-353

Chiu HF, Cheng MH, Yang CY (2009) Air Pollution and Hospital Admissions for Pneumonia in a Subtropical City: Taipei, Taiwan. Inhal Toxicol 21(1):32-37

Cohen AJ, Anderson HR, Ostro B, Pandey KD, Krzyzanowski M, Künzli N, Gutschmidt K, Pope A, Romieu I, Samet JM, Smith K (2005) The global burden of disease due to outdoor air pollution. J Toxicol Environ Health A 68(13-14):1301-1307
D'Amato G, Liccardi G, D'Amato M, Holgate S (2005) Environmental risk factors and allergic bronchial asthma. Clin Exp Allergy 35(9):1113-1124
Dab W, Medina S, Quénel P, Le Moullec Y, Le Tertre A, Thelot B, Monteil C, Lameloise P, Pirard P, Momas I, Ferry R, Festy B (1996) Short term respiratory health effects of ambient air pollution: results of the APHEA project in Paris. J Epidemiol Commun H 50 Suppl 1 S42-S46
Diaz J, Linares C, Tobias A (2007) Short-term effects of pollen species on hospital admissions in the city of Madrid in terms of specific causes and age. Aerobiologia 23(4):231-238
Dilaveris P, Synetos A, Giannopoulos G, Gialafos E, Pantazis A, Stefanadis C (2006) Climate impacts on myocardial infarction deaths in the Athens territory: the climate study. Heart 92:1747-1751
Draper N, Smith H (1981) Applied Regression Analysis. 2nd edition. John Wiley & Sons, New York
Freitas MC, Pacheco AMG, Verburg TG, Wolterbeek HT (2010) Effect of particulate matter, atmospheric gases, temperature, and humidity on respiratory and circulatory diseases' trends in Lisbon, Portugal. Environ Monit Assess 162(1-4):113-121
Fusco D, Forastiere F, Michelozzi P, Spadea T, Ostro B, Arca M, Perucci CA (2001) Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur Respir J 17:1143-1150
Galán C, Cariňanos P, Garcia-Mozo H, Alcázar P, Domínguez-Vilches E (2001) Model for forecasting Olea europaea L. airborne pollen in South-West Andalusia, Spain. Int J Biometeorol 45(2):59-63
Galán I, Tobias A, Banegas JR, Aranguez E (2003) Short-term effects of air pollution on daily asthma emergency room admissions. Eur Respir J 22(5):802-808
Heinrich J, Topp R, Gehring U, Thefeld W (2005) Traffic at residential address, respiratory health, and atopy in adults: the National German Health Survey 1998. Environ Res 98(2):240-249
Jahn W, Vahle H (1968) Die Faktoranalyse und ihre Anwendung. Verlag die Wirtschaft, Berlin. 231
Járai-Komlódi M (1998) Ragweed in Hungary. In: Spieksma FThM (ed) Ragweed in Europe. Satellite Symposium Proceedings of 6th International Congress on Aerobiology. Perugia, Italy. Alk-Abelló A/S, Horsholm, Denmark. 33-38
Johnson ML (ed) (2005) The Cambridge Handbook of Age and Ageing. Cambridge University Press, Cambridge. 770 ISBN 9780521826327
Jolliffe IT (1993) Principal component analysis: A beginner's guide – II. Pitfalls, myths and extensions. Weather 48:246-253
Joseph PM (2007) Paradoxical ozone associations could be due to methyl nitrite from combustion of methyl ethers or esters in engine fuels. Environ Int 33(8):1090-106
Joseph PM, Weiner MG (2002) Visits to physicians after the oxygenation of gasoline in Philadelphia. Arch
Juhász M, Juhász IE (2002) A hazai gyomnövények aeropollinológiai jelentősége. [Aeropollinological importance of domestic weeds. (in Hungarian)] In Szabó T, Bártfai I, Somlai J (ed) Környezeti ártalmak és a légzőrendszer. Vol 12. F & G Press, Zalaegerszeg. 149-160
Just J, Nikasinovic L, Laoudi Y, Grimfeld A (2007) Air pollution and asthma in children. Rev Fr Allergol 47(3):207-213
Karr C, Lumley T, Schreuder A, Davis R, Larson T, Ritz B, Kaufman J (2007) Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am J Epidemiol 165:553-560
Kassomenos P, Papaloukas C, Petrakis M, Karakitsios S (2008) Assessment and prediction of short term hospital admissions: the case of Athens, Greece. Atmos Environ 42(30):7078-7086
Katsouyanni K, Zmirou D, Spix C (1996) Short-term effects of urban air pollution on health: a European approach using epidemiologic time series data. The Aphea protocol. J Epidemiol Commun H 5 Suppl 1 S12-S18.
Kiss L, Béres I (2006) Anthropogenic factors behind the recent population expansion of common ragweed (Ambrosia artemisiifolia L.) in Eastern Europe: is there a correlation with political transitions? J Biogeogr 33:2156-2157
Knight A, Drouin MA, Yang WH, Alexander M, Delcarpio J, Arnott WS (1991) Clinical-evaluation of the efficacy and safety of noberastine, a new H1 antagonist, in seasonal allergic rhinitis - a placebo-controlled, dose-response study. J Allergy Clin Immun 88(6):926-934
Ko FWS, Tam W, Wong TW, Lai CKW, Wong GWK, Leung TF, Ng SSS, Hui DSC (2007) Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. Clin Exp Allergy 37(9):1312-1319
Köppen W (1931) Grundriss Der Klimakunde. Walter De Gruyter & Co., Berlin
Luginaah IN, Fung KY, Gorey KM, Webster G, Wills C (2005) Association of ambient air pollution with respiratory hospitalization in a government-designated "Area of concern": The case of Windsor, Ontario. Environ Health Perspectives 113(3):290-296

Mahalanobis PC (1936) On the generalized distance in statistics. Proceedings of the National Institute of Sciences of India 12:49-55

Makra L, Tombácz Sz, Bálint B, Sümeghy Z, Sánta T, Hirsch T (2008) Influences of meteorological parameters and biological and chemical air pollutants to the incidence of asthma and rhinitis. Climate Res 37(1):99-119

Makra L, Sánta T, Matyasovszky I, Damialis A, Karatzas K, Bergmann KC, Vokou D (2010) Airborne pollen in three European cities: Detection of atmospheric circulation pathways by applying three-dimensional clustering of backward trajectories. J Geophys Res 115, D24220, doi:10.1029/2010JD014743

Martins LC, Latorre MDDD, Saldiva PHD, Braga ALF (2002) Air pollution and emergency room visits due to chronic lower respiratory diseases in the elderly: An ecological time-series study in Sao Paulo, Brazil. J Occup Environ Med 44(7):622-627

McCoy L, Redelings M, Sorvillo F, Simon P (2005) A Multiple Cause-of-Death Analysis of Asthma Mortality in the United States, 1990-2001. J Asthma 42:757-763

Migliaretti G, Dalmasso P, Gregori D (2007) Air pollution effects on the respiratory health of the resident adult population in Turin, Italy. Int J Environ Heal R 17(5):369-379

Nascimento LFC, Pereira LAA, Braga ALF, Modolo MCC, Carvalho JA (2006) Effects of air pollution on children's health in a city in Southeastern Brazil. Revista de Saude Publica 40(1):77-82

Nidhi and Jayaraman G (2007) Air quality and respiratory health in Delhi. Environ Mon Assess 135(1-3):313-325

Parsons JP, Mastronarde JG (2005) Exercise-Induced Bronchoconstriction in Athletes. Chest 128:3966-3974

Petrányi Gy (ed) (2000) Klinikai Immunológia. [Clinical Immunology. (in Hungarian)]. Medicina Könyvkiadó, Budapest. ISBN: 9789632425610

Schwartz J, Dockery DW (1992) Particulate air pollution and daily mortality in Steubenville, Ohio. Am J Epidemiol 135:12-19

Spix C, Anderson HR, Schwartz J, Vigotti MA, LeTertre A, Vonk JM, Touloumi G, Balducci F, Piekarski T, Bacharova L, Tobias A, Ponka A, Katsouyanni K (1998) Short-term effects of air pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study results. Arch Environ Health 53(1):54-64

Strausz J (ed) (2003) Asthma bronchiale. Mediszter GlaxoSmithKline, Budapest

Sunyer J, Atkinson R, Balleste, F, Le Tertre A, Ayres JG, Forastiere F, Forsberg B, Vonk JM, Bisanti L, Anderson RH, Schwartz J, Katsouyanni K (2003) Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. Occup Environ Med 60(8) e2-e2

Tenías JM, Ballester F, Rivera ML (1998) Association between asthma emergency room visits and air pollution in Valencia, Spain. Occup Environ Med 1998:55:541-547

Tukey JW (1985) The problem of multiple comparisons (1953) (unpublished manuscript). In The Collected Works of John W. Tukey. Vol 2. Wadsworth Advanced Books & Software, Monterey, CA. 1965-1984

Uysal N, Schapira RM (2003) Effects of ozone on lung function and lung diseases. Curr Opin Pulm Med 9(2):144-150

Wong TW, Tam W, Yu ITS, Wun YT, Wong AHS, Wong CM (2006) Association between air pollution and general practitioner visits for respiratory diseases in Hong Kong. Thorax 61(7):585-591

Yang CY, Chang CC, Chuang HY, Tsai SS, Wu TN, Ho CK (2004) Relationship between air pollution and daily mortality in a subtropical city: Taipei, Taiwan. Environ Int 30(4):519-523