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TITLE: Atopic Dermatitis Severity during Exposure to Air Pollutants and Weather Changes with an artificial neural network (ANN) analysis

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ABSTRACT

Background: Epidemiological studies have shown an association between global warming, air pollution and allergic diseases. Several air pollutants, including volatile organic compounds, formaldehyde, toluene, nitrogen dioxide (NO_2) and particulate matter, act as risk factors for the development or aggravation of atopic dermatitis (AD). We evaluated the impact of air pollutants and weather changes on AD patients.

Materials and Methods: Sixty AD patients ≥5 years of age (mean age: 23.5 ± 12.5 years), living in the Campania Region (Southern Italy), were followed for 18 months. The primary outcome was the effect of atmospheric and climatic factors on signs and symptoms of AD, assessed using the SCORAD (SCORing Atopic Dermatitis) index. We measured mean daily temperature (TOD), outdoor relative humidity (RH), diurnal temperature range (DTR), precipitation, particulate with aerodynamic diameter ≤10 μm (PM_{10}), NO_2, tropospheric ozone (O_3), and total pollen count (TPC). A multivariate logistic regression analysis was used to examine the associations of AD signs and symptoms with these factors. An artificial neural network (ANN) analysis investigated the relationships between weather changes, environmental pollutants and AD severity.

Results: The severity of AD symptoms was positively correlated with outdoor temperatures (TOD, DTR), RH, precipitation, PM_{10}, NO_2, O_3 and TPC. The ANN analysis also showed a good discrimination performance (75.46%) in predicting disease severity based on environmental pollution data, but weather-related factors were less predictive.

Conclusion: The results of the present study provide evidence that weather changes and air pollutions have a significant impact on skin reactivity and symptoms in AD patients, increasing the severity of the dermatitis. The knowledge of the single variables proportion on AD severity symptoms is important to propose alerts for exacerbations in patients with AD of each age. This finding represents a good starting point for further future research in an area of increasingly growing interest.

Key words: air pollution, atopic dermatitis, climate change, weather.

Abbreviations: atopic dermatitis (AD); artificial neural network (ANN); outdoor temperatures (TOD); total pollen count (TPC); polycyclic aromatic hydrocarbon (PAHs), and nitrogen oxides (NO_x); secondary pollutants include ozone, nitrates, and secondary organic aerosols (SOAs); diesel exhaust particles (DEP); solid particulate matter (PM); outdoor relative humidity (RH), diurnal temperature range (DTR), precipitation, particulate with aerodynamic diameter ≤10 µm (PM10), nitrogen dioxide (NO2), tropospheric ozone (O3)

INTRODUCTION

Air pollution – especially diesel exhaust particles (DEP); solid particulate matter (PM), ozone, nitrogen dioxide, and sulfur dioxide – results into an inflammatory effect on the airways of susceptible individuals, causing increased mucosal permeability, facilitating the penetration and access of inhaled allergens to the cells of the immune system [1-6]. Environmental PM consists of particles of various sizes, generally ranging from 2.5 to 10 µm; there may also be a fraction of "ultrafine" particulate composed of particles with size <0.1 µm, whose chemical composition is variable [2-4].

Epidemiological studies have shown a close association between global warming, air pollution and allergic diseases, particularly respiratory diseases such as asthma and rhinitis [5].

There is growing interest regarding the impact of exposure to indoor and outdoor air pollutants on the development of allergic diseases such as allergic rhinitis and atopic dermatitis (AD) [2]. Environmental changes are among the main factors involved in the rapid increase and worsening of various allergic diseases [7,8]. Outdoor air pollution is associated with exacerbations of pre-existing asthma, even the development of atopic diseases or allergic sensitization.

An increase in the prevalence of AD has occurred worldwide, arousing interest in the identification of potential risk or protective environmental factors [9-10]. A variety of atmospheric pollutants are associated with development or worsening of AD, due to the oxidative stress induced in the skin [11]. Genetic predisposition, environmental agents, and their interactions contribute to the pathophysiology of AD [11].

In this framework, artificial neural networks (ANN), inspired by both the structure and functioning of biological neural networks, represent a promising approach [12]: the application of ANN in clinical research is well grounded, with several evidence, for example, in cardiovascular medicine (for a review, see [13]). However, to the best of our knowledge, the use of ANN is quite novel in the field of allergology or immunology, as only few studies have applied such techniques [14,15], and it appears that no studies have investigated the ability of ANNs to evaluate the interplay of environmental pollutants and atmospheric conditions in influencing the severity of AD symptoms. Furthermore, considering that the effects of ambient temperature may last for 21 days while the effects of air pollutants may last shorter, this increases the complexity of analysis of data, also for this reason we use an ANN analysis to support the standard statistical analysis.

Within this context, we present here the results of a prospective observational study conducted to assess the impact of air pollution and weather changes on patients with AD.

METHODS

Participants

Sixty patients with AD aged ≥5 years (mean age: 23.5 y +/- 12.5 years) were enrolled and followed for 18 months between July 2017 and December 2018.

All patient visits, examinations and treatments were performed according to the routine clinical care. Therefore, an approval statement has not been required from our ethical committee for this study. AD diagnosis was made clinically based on the typical disease symptoms and signs. AD was diagnosed based on the Hanifin and Rajka criteria [16]. All patient visits, examinations and treatments were released as part of the routine clinical care and the patients released their informed consent on the treatments and diagnostic procedures provided for the medical record. When the patient was underage the request was obtained from Parents; thus, a formal approval by an Ethics Committee was not required.

Aerobiological and air quality outcomes

Pollen levels were monitored from the start of the study and measured in a systematic and standardized manner (Fig. 1). They were collected volumetrically (10 l/min) using a Hirst pollen trap with the pollen types counted microscopically in the Laboratory of Environmental Analysis, Department of Public Health, ASL Salerno. Results were reported as daily average concentrations of pollen grain/m^3 air. Total pollen count (TPC) was calculated by summing the mean pollen counts. The monitoring station was located on the roof of the Agropoli Hospital of ASL Salerno, 12 m above ground level and 28 m above sea level. It was never moved, and all measurements were made using the same method.

Air pollution data was provided by the air monitoring network of ARPAC Campania, Italy. Data was obtained from four central stations of the air pollutants and meteorology monitoring network (Stations A, B, F, and D). Stations measured SO2, NO2, O3, PM10, and PM2.5; Station D measured only O3, PM10, PM2.5. Particulates (PM10 and PM2.5) were measured by dichotomous samplers (Sierra Andersen). Meteorological data (temperature, relative humidity, wind speed, and direction) was provided by the Battipaglia Parco Fiume Station; description ZONE_CODE: IT1508, TOWN: Battipaglia by ARPAC, Campania, Italy. During the study period, the correlations between PM10 and PM2.5 levels measured by dichotomous samplers [17] and TEOM® (Method for Measurement of Ambient Particulate Mass in Urban Areas dichotomous samplers) [18] were 0.97 for PM10 and 0.92 for PM2.5. The correlations of air pollutants levels measured were high: 0.87–0.97 for PM10; 0.91–0.97 for PM2.5 (24-hr average); 0.90–0.94 for SO2 (24-hr average); 0.70–0.88 for NO2 (24-hr average); and 0.86–0.91 for O3 (8-hr mobile average). Weather parameters included: trends in maximum (T_{max}), minimum (T_{min}), and mean (T_{mean}) temperatures; diurnal temperature range ($DTR = T_{max} - T_{min}$); and relative humidity (RH), i.e. the ratio of the partial pressure of water vapor to the equilibrium vapor pressure of water at a given temperature. Outdoor measures were obtained using the reports from the Meteorological Station n. 46 in Battipaglia (Campania Region, Italy).

Primary outcome

The primary outcome was change in the severity of AD symptoms, measured using the SCORAD (SCORing Atopic Dermatitis) score [19]. SCORAD assesses AD severity, expressed as the sum of the individual scores for each symptom (itching, sleep disturbances, erythema, dry skin, exudation, oedema) [19,20].

Study protocol

The patients (or their parents in case of young children) were followed monthly after inclusion for 18 months, instructed to record AD symptoms using the SCORAD app, a free software application developed by the Foundation for Atopic Dermatitis, available at:https://

play.google.com/store/apps/details?id=com.myguard.scorad.plus.pad (for Android phone) and https://apps.apple.com/it/app/scorad-phone/id1051806648 (for iPhone). SCORAD app can take pictures of the significant lesions and export the patient data in order to file the calculated SCORAD in the medical records. Participants were scheduled every 3 months for follow-up visits, during which SCORAD data were collected. Exposures to air pollutants and weather variables were estimated in everyone using time-weighted average concentrations. Monthly SCORAD data of each patient were matched with these variables, measured in their area of residence, to determine the severity of AD symptoms. Because not all patients reported the symptoms in the same date to compare the data obtained for that month, we report for each patient the symptoms registered in that day for that month, and we compared the data obtained daily for that month with environment values for that day. Exclusion criteria: patients who did not live in the area of observation reported from monitoring stations, this area was the province of Salerno, where they permanently live since 2 years. We evaluated the effects of each air pollutant separately while control was for different weather conditions parameters.

Statistical Analysis

Sensitivity analysis included multivariate logistic regression modeling of increasing severity for the different combinations of symptoms and different substances, temperature and humidity expositions and consulting behavior (modeled as an ordered categorical variable divided into four categories) as additional covariates. Weather parameters, age, sex, SCORAD at enrollment, and use of topical corticosteroids were adjusted as confounders in a generalized linear mixed model. PM_{10}, NO_2, O_3, and TPC were treated as fixed effects and each participant as a random effect in the model.

The percent change of symptoms severity and 95% confidence intervals (CI) was calculated using a regression coefficient method. These factors were measured according to 5-unit increases in temperature (°C), relative humidity, RH (%), diurnal temperature range, DTR (°C), rainfall (mm/day), and 10-unit increases in PM_{10} ($\mu g/m^3$), O_3 (ppb), TPC (pollen grain/m^3 air) and NO_2 (ppb). Descriptive statistical analyses of quantitative data were performed by using SPSS.

Artificial Neural Network (ANN) Analysis

The ANN analysis was used to establish the environmental features that better discriminate between AD severity. A Kohonen Self-Organizing Map (KSOM) [21] ANN, composed of 100 neurons (a 10x10 grid) was used to classify the different AD patients based on disease severity (clustered upon 3 severity classes (Mild, Moderate, Severe, corresponding to 1, 2, 3, respectively) according to the SCORAD ranges indicated by Oranje et al. [20]) starting from environmental parameters derived from the local weather station. More specifically, the data included in the model were: DTR; RH; average-rainfalls; NO_2; $PM_{2.5}$; PM_{10}; O_3; benzene; SO_2. The ANN was trained on 1000 epochs for 10 cross validations. The cross validation method was employed since it seems to give a good estimate of the predictive accuracy of the final model trained with all the data. This approach requires multiple fits but appears to make efficient use of all the data, so it is recommended for small data sets. The training and test sets were fixed at 90 and 10% of the entire dataset, respectively. The ANN was implemented with an ad-hoc developed code within the software Matlab (MathWorks, Inc., Natick, MA, USA).

RESULTS

Study Population

Sixty AD patients aged ≥5 years (mean age: 23.5 y +/- 12.5 years) were enrolled in the study and followed for 18 months. Of these, 58 completed the study, while the remaining 2 patients discontinued the study prematurely.

The characteristics of the study population are summarized in Table 1. Baseline demographic and clinical characteristics were comparable between male and female patients. No significant differences were found between males and females except for comorbidities associated with AD, i.e. a greater number of male patients with rhinitis (total number = 50; male = 27; female = 13; p <0.048).

Kohonen Self-Organizing Maps (KSOM) Analysis

The KSOM analysis resulted in large discrimination ability for environmental pollutants, particularly O_3, SO_2, benzene and $PM_{2.5}$ ($p < 0.001$ in all cases among the three classes; and between class 1 and class 2, as well as between class 2 and class 3). These features were used in combination of 2, 3 or 4 to train the ANN. Poorer discriminatory abilities were seen for atmospheric data (air temperature and humidity, average rainfalls), with lack of significance in discriminating between subjects in class 2 from those in class 3. Those features were discarded and not used for the ANN training.

Results suggested an optimal correct discrimination, when using a combination of all the 4 features above mentioned, between the three severity classes of 75.46%, with the relative confusion matrix displayed in Figure 2.

In our study, the confusion matrix displayed that 77.4% of patients with mild AD were correctly placed in class 1, 82.4% of individuals with moderate AD were correctly classified as class 2, and 66.7% of patients with severe AD were labeled as belonging to class 3 Figure 3. The main mismatch resulted to be between class 2 (actual class) and class 1 (predicted class), occurring in 17.6% of class 2 patients, as well as between class 3 (actual) and class 1 (predicted), occurring in 25% of class 3 patients. Risk overestimation was only seen in class 1 patients, classified into class 2 and class 3 in 9.4% and 13.2% of cases, respectively. No risk overestimation was highlighted in class 2 patients.

Multivariate model

By using a multivariate model, temperatures (°C), RH (%), DTR (°C), rainfall (mm/day), PM_{10} ($\mu g/m^3$), O_3 (ppb), TPC (granules/mm3), and NO_2 (ppb) were positively associated with increased symptoms severity. The AD symptoms increased by 222.7% (95% CI: 68.4-782.4) following a 5 °C increase in DTR (when >14 °C). Increases of 1 log10 in environmental pollutants PM_{10}, NO_2, O_3 and TPC resulted in increases in the severity of AD symptoms by 3.0% (95% CI: 0.3-4.2), 5.0%(95% CI: 1.4-8.8), 5.9% (95% CI: 2.4-9.3), and 4.5% (95% CI: 3.2-7.0), respectively. A 5 °C increase in outdoor temperature and a 5% increase in outdoor relative humidity (RH) were associated, respectively, with reductions of 14% (95% CI: 3.2-29.0) and 4.0% (95% CI: 2.2-7.0) in AD symptoms, recorded on the same day. For days with precipitation <40 mm, a 5 mm increase in rainfall was associated with a 9% (95% CI: 4.5-14.2) increase in the SCORAD score. Table 2 summarizes the results of the study.

DISCUSSION

This longitudinal study points out that severity of AD symptoms, as evaluated by SCORAD (a validated tool for assessing extent and intensity of AD signs and symptoms) was associated with synchronous changes in different atmospheric parameters, including outdoor temperature and humidity, and a range of different pollutants.

The severity of symptoms increased proportionally with increasing concentrations of PM_{10}, NO_2, O_3 in the atmosphere, as well as with the increase of the total pollen count.

Despite the data reported here are not sufficient for final conclusions, the severity of AD symptoms was found to be positively correlated with outdoor temperatures, PM_{10}, NO_2, O_3, and TPC. However, the effects of outdoor temperature were apparently more complex: an increased range of diurnal thermal excursions (when outdoor temperature was > 14°C) was associated with a considerable increase in AD symptom severity, whereas an absolute increase in outdoor temperature seemed to reduce symptoms intensity. This apparently contradictory effect can be explained by a possible susceptibility of the skin to temperature fluctuations, in contrast to the apparently favorable effect of absolute increases in outdoor temperature.

In other words, outdoor temperature excursions – and not the absolute increases in temperature – would be the real trigger for the skin reactions. However, the simplest explanation could be the favorable effect of increased humidity, given the fact that environmental humidification would attenuate skin dryness, which may increase eczema symptoms.

Based on the results of the KSOM analysis, a good discrimination performance was obtained, reaching a correct selection between 3 severity classes based on only environmental data in more than 75% of cases. Unfortunately, based on the analysis of false positive and false negative data, the ANN underestimated the severity grade of patients in most cases, highlighting the need for acquiring more data, especially about more severe patients, to reach a satisfying dataset to correctly train the network also with severe AD patients.

It is worth noting that environmental pollutants were more predictive in classifying disease severity than weather data, suggesting that AD severity is probably more affected by pollutants than by weather-related factors. On the other hand, we could not find striking evidence about the effect of weather-related factors on AD severity, in contrast to the findings of Engebretsen et al. [22], who reported the negative effects of low humidity, low temperatures and different seasons on the risk of flares in AD patients.

A series of environmental factors, such as air pollutants, have been considered potential risk factors for the development and aggravation of AD. Several studies have shown that air pollution influences the prevalence of AD. Pollutants probably act by inducing oxidative stress in the skin cells, leading to skin barrier dysfunction or immune response dysregulation [23].

Genetic predisposition and environmental triggers contribute to the pathophysiology of AD. Therefore, the identification and control of environmental risk factors in susceptible individuals is very important to provide effective treatment and prevention strategy [23].

Epidemiological studies and meta-analyses have shown that respiratory allergies and AD are associated with exposure to traffic-related air pollution (TRAP) [24-27]. TRAP is a complex mixture, including in varying proportions particulate and gaseous pollutants derived from primary emissions associated with vehicle traffic, as well as secondary pollutants formed by chemical reactions in the atmosphere [28]. Pollutants from primary emissions (combustion and non-combustion sources) include road dust, tyre wear, soot, metals, polycyclic aromatic hydrocarbon (PAHs), and nitrogen oxides (NO_x); secondary pollutants include ozone, nitrates, and secondary organic aerosols (SOAs) [23, 29]. Ozone also reacts with skin lipids (e.g. squalene) generating organic compounds (monocarbonyls and dicarbonyls), which can act as skin irritants [30].

Few studies have evaluated the relationship between PM and AD symptoms. Using linear regression analysis, a significant association was found between the concentration of ambient ultrafine particles (< 0.1 μm in diameter) and itching, but not with larger particles, after adjustment for confounding factors such as age, sex, height, SCORAD index, commuting time and temperature [31]. Finally, a recent study evaluated the role of weather in the association between air pollution and AD. In this study, including a total of 125 young children under 6 years of age with AD living in Seoul, Korea, a significant harmful effect of PM on AD symptoms was found particularly on dry and moderate days [32]. Different confounding factors need to be reported, in particular although the summer sunlight UVAB and to some extent UVB lights are effective treatments for atopic dermatitis [33], the addition of steroids reduces the total UVB dose and duration of treatment without influencing the duration of remissions and frequency of side effects [34]. These factors have been very difficult to discriminate in this observational study.

We underline that the study population was relatively large including both children and adults with a history of allergic disease, which supports the validity of our findings and suggests the importance of further research on this topic. In conclusion, the results of the present study provide evidence that weather conditions and air pollutants have a significant impact on skin reactivity and symptoms in AD patients, increasing the severity of the dermatitis. The knowledge of the single variables proportion on AD severity symptoms is important to propose alerts for exacerbations in patients with AD of each age.

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Table 1 *Demographic and clinical data of the study population*

	Total	**Male**	**Female**	**P-value***
No. of subjects	60	32	28	-
Age	23.5 y +/- 12.5 y	5-62 y	6-51 y	0.876
Total IgE (kU/L)	373.2 ± 834.2	337.3 ± 665.6	388.5 ± 550.4	0.810
SCORAD^{+}	28.3 ± 14.2	28.1 ± 11.4	29.9 ± 12.7	0.967
Asthma	32	16	16	-
Rhinitis	50	27	13	0.048
Polyposis	19	10	9	-
Conjunctivitis	41	22	19	-

Table 2. *Correlation between the variation of atmospheric parameters and the symptoms of atopic dermatitis (AD).*

	Atmospheric parameters			
	Variation	*Severity of AD symptoms (assess by SCORAD**)*	95% CI:	*P-value****
DTR*	+ 5°C	+222.7%	68.4-782.4	0.001
PM_{10}	+1 Log 10	+3.0%	0.3, 4.2	0.03
NO_2	+1 Log 10	+5.0%	1.4, 8.8	0.04
O_3	+1 Log 10	+5.9%	2.4, 9.3	0.05
TPC	+1 Log 10	+4.5%	3.2, 7.0	0.05
TOD	+ 5°C	-14.0%	3.2, 29.0	0.08
RH	+5.0%	-4.0%	2.2, 7.0	0.03
P	+5mm	+9%	4.5, 14.2	0.04

*DTR, diurnal temperature range according to a 5°C, when it was >14°C; PM10, particulate matter with diameter ≤10 µm; NO2, nitrogen dioxide; O3, trophospheric ozone; TPC, total pollen count; TOD, outdoor temperature; RH, outdoor relative humidity; P, precipitation <40 mm.

** SCORAD (SCORing Atopic Dermatitis) index, a score used worldwide to assess AD severity in patients. SCORAD index consists of six items: erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness. Each item can be graded on a scale 0-3.

***A *P-value* ≤ *0.05* is statistically significant. All results were from the whole range of air pollution.

LEGEND OF FIGURES

Figure 1. Airborne particles were collected volumetrically (10 l/min) using a Hirst pollen trap and the pollen types identified and counted microscopically, the results were reported as daily average concentrations (pollen grain/m3 air). The total pollen count (TPC) is the sum of pollens average values reported from 01/07/2017 to 31/12/2018.

Figure 2. Confusion matrix. Correctly classified items (concordance between actual class and predicted class items) are displayed in the matrix diagonal. The confusion matrix plots the agreement between the "actual" class of an individual (i.e., the real class of a given patient) and the "predicted" class of the same subject (i.e., the class assigned by ANN). The ideal classifier would put all the individuals on the diagonal of the confusion matrix (i.e., all subjects are correctly classified in their respective classes; e.g., a subject whose actual class is "1" should be classified into the predicted class "1" by the ANN and so forth). With the ANN, a correct discrimination between the three severity classes of 75.46% was achieved.

Figure 3. Principal Component Analysis (PCA) performed after training the ANN. The different colors indicate the three clusters based on disease severity. Patients with mild AD were correctly labeled as belonging in class 1 (green dots), moderate AD as class 2 (blue dots), and severe AD as to class 3 (red dots).

Figure 1

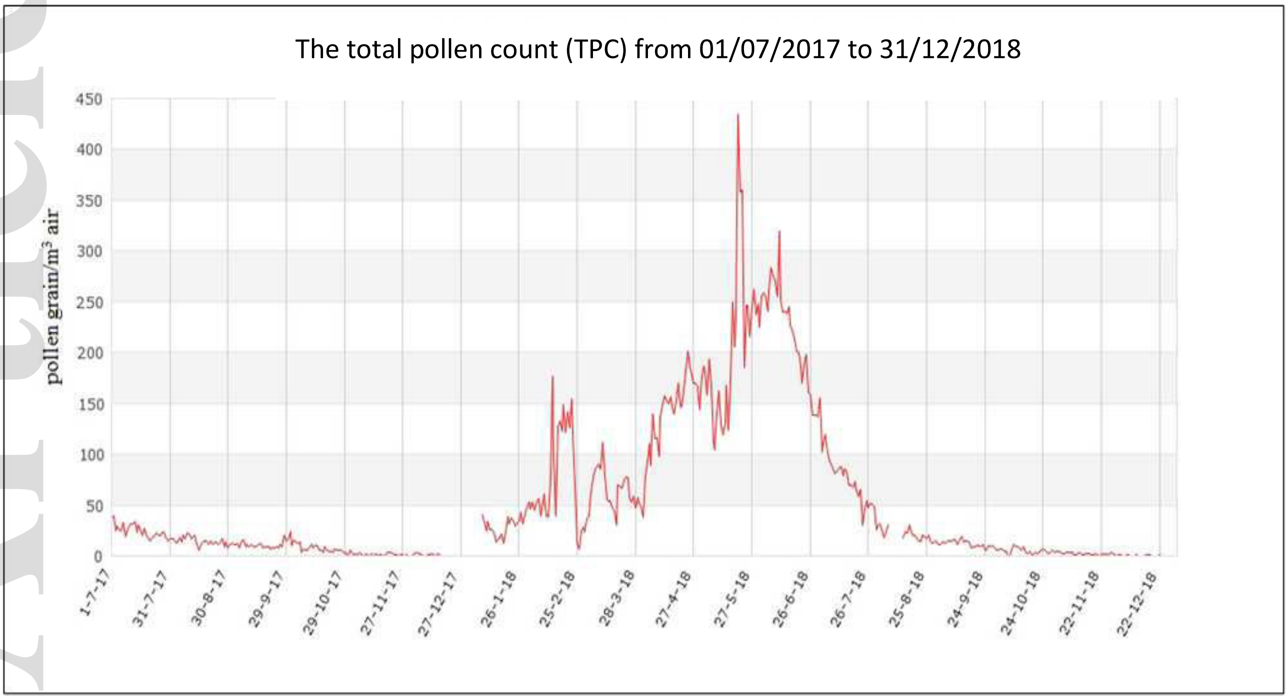
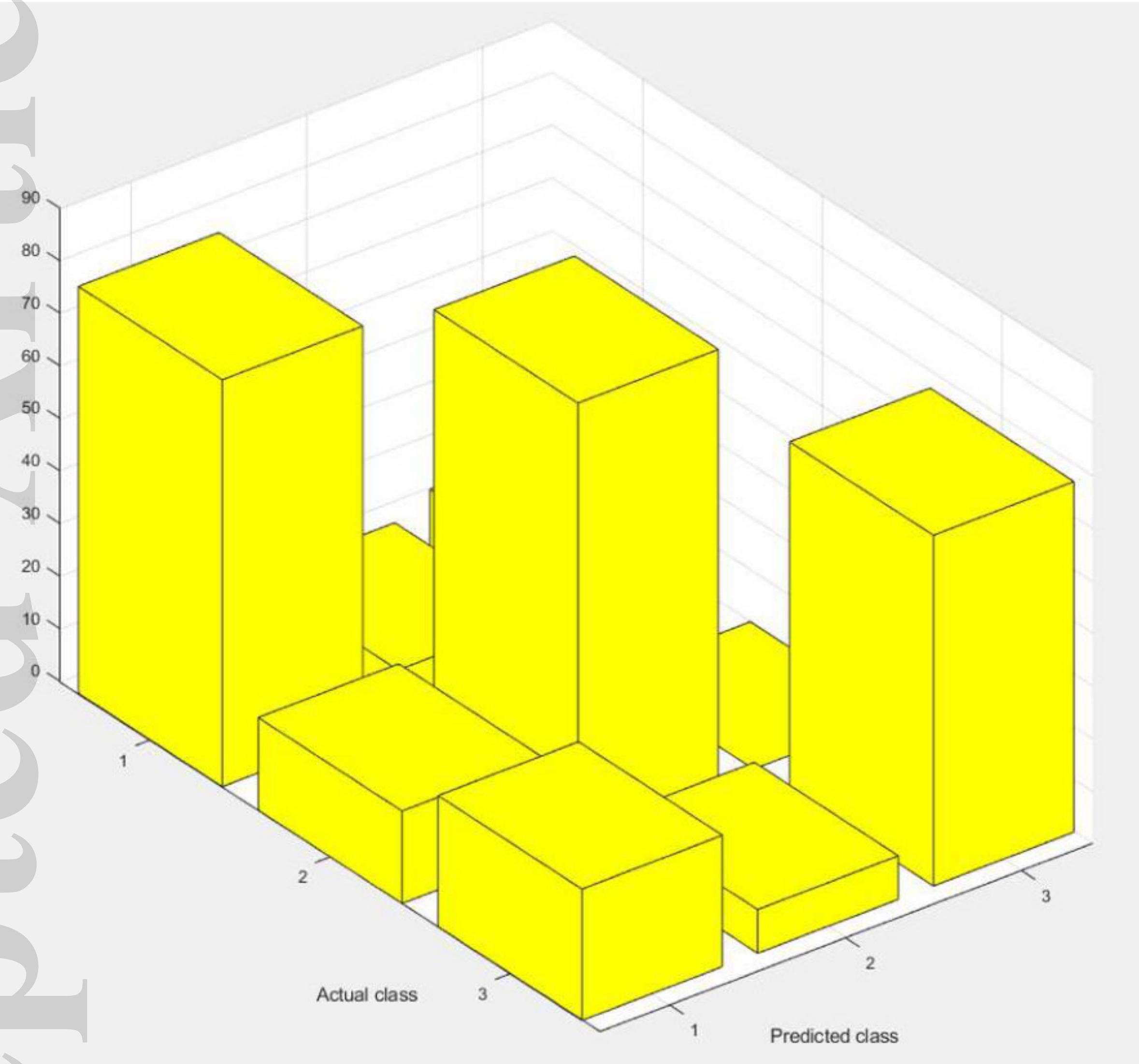
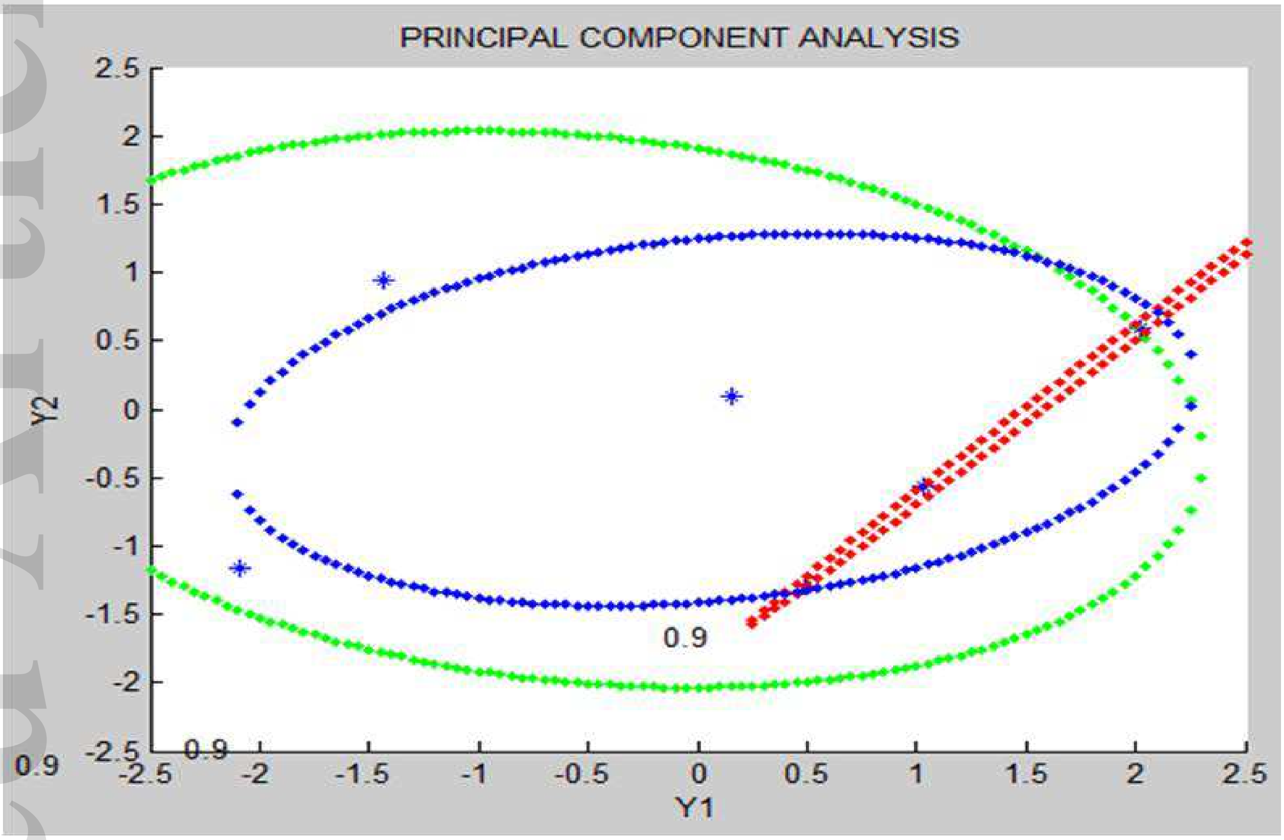

The total pollen count (TPC) from 01/07/2017 to 31/12/2018
pollen grain/m³ air
450
400
350
300
250
200
150
100
50
0
1-7-17
31-7-17
30-8-17
29-9-17
29-10-17
27-11-17
27-12-17
26-1-18
25-2-18
28-3-18
27-4-18
27-5-18
26-6-18
26-7-18
25-8-18
24-9-18
24-10-18
22-11-18
22-12-18

Figure 2



90
80
70
60
50
40
30
20
10
0
1
2
3
Actual class
1
2
3
Predicted class

Figure 3



PRINCIPAL COMPONENT ANALYSIS
Y2
Y1
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-2.5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
0.9
0.9
0.9