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EVALUATION OF AIR POLLUTION AND CLIMATE CHANGES ON CHRONIC INFLAMMATORY DISEASES THROUGH ARTIFICIAL NEURAL NETWORKS ANALYSIS: A PROPOSAL FOR A MULTI-OMICS APPROACH IN CHRONIC INFLAMMATORY DISEASES STUDIES

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ABSTRACT. Recent scientific evidence highlight the negative effects that air pollution and climate change have on human health. In the present review contribution, it will be shown how by means of Artificial Intelligence it is possible to correlate climate change, air pollution and chronic inflammatory diseases through cause-effect relationships. From the present study it clearly emerges that the implementation of machine learning algorithms, together with the development of specific models, may constitute a very powerful tool in early diagnosis, monitoring and treatment of chronic inflammatory disease and, hence, in assisting governments in adopting the best practices for pollutants reduction strategies.

1. Introduction

Over the last decade, a growing number of epidemiological and clinical studies have led to a greater concern on the potential effects that air pollution and climate change have on health and on their relationship with chronic inflammatory diseases. The 2018 Climate and Health Assessment Report by the US Global Change Research Program has summarized the available evidence on the health effects of climate change (Crimmins *et al.* 2016; Kim 2016). In particular, the understanding of the pathophysiological mechanisms underlying the effects related to air pollution and to climate change on health, has led to several documents from Europe and from the United States and to the revision, by the World Health Organization (WHO), of the dimensional fractions and of the chemical constituents of the main gaseous air pollutants, as well as to a better characterization of their effect on health (World Health Organization 2006). Air pollution and climate change have a complex and two-way relationship in common. Indeed, greenhouse gas emissions contribute to climate change and have negative health effects and, conversely, climate change leads to an increase in Particulate Matter (PM) ground level and in ozone levels (Seinfeld and Pandis 2006). Over the past 50 years, the Earth's global temperature has significantly increased due to the rise in greenhouse gas emissions, largely due to anthropogenic sources. Increases in extreme events such as heat waves, droughts, floods, thunderstorms and hurricanes are also occurring, as well as changes in the intensity and frequency of rainfall. In particular, heat waves with temperatures above 35 °C are expected to be more frequent and more intense, leading to an increase in the risk of fires and desertification. For this purpose, a climatic model based on the phenomenon of stochastic resonance has been developed and the responses to changes in thermal noise and the value of the planet's temperature has been evaluated. The effects of the temperature increase are related to the 10 5year Milankovitch cycle. The results obtained show that an increase in the Earth's temperature favors a transition towards a chaotic regime in which the effects of the Milankovitch cycle disappear. These results highlight the so-called threshold effect, i.e. the fact that even a small increase in temperature can give rise to large effects above a certain threshold, provide a perspective on a possible future climate scenario and account for the continuous increase in temperature. intensity of extreme weather events (Caccamo *et al.* 2017; Caccamo and Magazù 2019; Colombo, Caccamo, and Magazù 2019; Rizza *et al.* 2020; Caccamo and Magazù 2021). In order to investigate the signal periodicities that are present in climate parameters, as well as their changes in time, Fourier Transform (FT) and the Wavelet Transform (WT) are often applied. In particular, the wavelet transform has proved to be a powerful tool for the analysis and processing of recorded signals; unlike the Fourier transform which analyzes only stationary signals, it also analyzes non-stationary signals. The main difference is that while the Fourier transform goes from a purely temporal representation of the signal to a purely frequency representation, wavelet analysis, on the other hand, is localized both in time and in frequency. For these reasons such mathematical approaches, besides evidencing a systematic increase in the Earth temperature, have found an increasing number of applications (Caccamo *et al.* 2016; Caccamo and Magazù 2018; Colombo, Magazù, and Caccamo 2018; Caccamo and Magazù 2023). Michelozzi et al studied the impact of high temperatures on health in twelve European cities, concluding that extreme heat events increase daily hospital admissions from respiratory causes and mortality from cardiovascular and cerebrovascular causes (Michelozzi *et al.* 2009; Anderson *et al.* 2013; Analitis *et al.* 2014). Of particular interest for the present study are several air pollutants including carbon monoxide, nitrogen oxides, sulfur dioxide, ozone, lead and PM. In particular, the environmental solid PM is composed of small particles, generally sized between 2.5 and 10 μm and by ultrafine particles with dimensions <0.1 μm (De Hartog *et al.* 2005). Air pollution is convincingly associated with many signs of aggravation of chronic inflammatory diseases; in addition to the now declared relationship between respiratory diseases, allergies and climate change (D'Amato *et al.* 2013; De Sario, Katsouyanni, and Michelozzi 2013; D'amato *et al.* 2015), recent evidence supports associations with cardiovascular disease, as evidenced by the American Heart Association's report on air pollution and cardiovascular disease(R. D. Brook *et al.* 2010; Rajagopalan *et al.* 2020), diabetes (Rao *et al.* 2015; Thiering and Heinrich 2015), rheumatic diseases (Sun *et al.* 2016; Di *et al.* 2020), cognitive functioning (Clifford *et al.* 2016; Power *et al.* 2016), neurodegenerative diseases (Xu, Ha, and Basnet 2016) and dermatological diseases, such as atopic dermatitis (Patella *et al.* 2018, 2020). The objective of the present work is to examine, through innovative methodologies, the cause and effect relationships that exist between the data deriving from chronic inflammatory diseases and the data on air pollution and climate change. In particular, in order to characterize the global behavior and to predict the evolution of such systems, which can be classified as complex systems being constituted by a large number of interacting elements, a multivariate logistic regression analysis will be combined with techniques that use Artificial Neural Networks (ANN) (Al-Shayea 2011; Amato *et al.* 2013). It will be shown how Artificial Intelligence (AI) has the potential to greatly improve traditional statistical analyzes and allows to highlight the "hidden" information in highly complex data sets such as those dealt in this article. The results of applying the ANN methodology to the diagnosis of chronic inflammatory diseases show the ability of the network to learn the symptom patterns.

2. Climate and chronic inflammatory diseases

The attention to the effects of climate changes on the health status of the citizenship is continuously growing as are the evidences towards a role for the climate on the development and/or worsening of clinical conditions, notably concerning chronic inflammatory diseases. Among those, one of the most widely studied is Atopic Dermatitis (AD), whose continuous rise in prevalence throughout the decades is not explainable just by an increased awareness and diagnostic accuracy, but also by hypothesizing a significant role for environmental factors and for interactions between them and genetics (Pezzolo and Naldi 2020). As suggested (Pezzolo and Naldi 2020), early life exposures and events are involved in the early AD onset, making the disease largely prevalent during infancy and adolescence, and climate changes are surely engaged in this complex process, as also happens for psoriasis (Pezzolo and Naldi 2020). Indeed, effects of climate change on health both include direct effects of increased (or varied) temperature, and indirect effects such changes have on natural systems, including vector borne disorders (bacterial infections, viruses spread, pandemic, etc.), and on socioeconomic systems, including those consequent to increased impoverishment (Pezzolo and Naldi 2020). As stated, AD was probably the most largely investigated among chronic inflammatory diseases worldwide, and a recent mini-review confirmed that increased temperatures, humidity, pollen, and air pollution are all associated with changes in the epidemiology and severity of AD, with the causes mostly being currently investigated (Nguyen, Andersen, and Davis 2019). Indirectly, climate changes are also related to air pollution, particularly concerning the inhalable fine particulate matter (notably PM2.5). Without going into depth within the argument, PM2.5 has shown the capacity to induce a pro-inflammatory status into cell models, that translated into a larger scale could demonstrated its likely effect on the whole organs and tissues of an individual (G. Wang *et al.* 2016).

3. Use of Artificial Intelligence with Cronic Inflammatory Diseases

Artificial Intelligence (AI), mainly Machine Learning (ML), is actually used in a variety of fields, including for dealing with healthcare purposes and, more specifically, with chronic inflammatory diseases and related issues. Indeed, among the positive sides of ML relies the possibility to perform data analysis and variable selection, leading to precision medicine, both in terms of diagnosis and prognosis. Variable selection represents one of the most useful features in precision medicine, as it help to screen out and combine variables that are significant for decision-making at the clinicians' side. This process could be particularly tricky when in presence of multifactorial conditions, like chronic inflammatory diseases, where both genetics and environmental determinants are present (Peng *et al.* 2021). Within the universe of chronic inflammatory diseases, AI is predominantly used for diagnosis, notably to identify diagnostic biomarkers, as happens with immune mediated inflammatory diseases (Tabib *et al.* 2020) (Stafford *et al.* 2020). In this specific domain, one of the most significant works was published by Glazyrin and colleagues, successfully applying ML techniques, including Principal Component Analysis (PCA) and K-Nearest Neighbours (KNN) to proteomics to distinguish between immune-mediated Chronic Kidney Disease and the same disorder brought by other causes (Glazyrin *et al.* 2020). Juvenile Idiopathic Arthritis (JIA) was predicted thanks to immune-based Random Forest (RF) approach in a cohort of 72 patients and 43 matched controls by Van Nieuwenhove and colleagues (Van Nieuwenhove *et al.* 2019), highlighting the usefulness of this powerful, albeit difficult to interpret ML technique. Imaging data are also successfully processed by ML approaches, as demonstrated by Simos and colleagues on fMRI images obtained by patients with Systemic Lupus Erythematosus (SLE) classified by various techniques, among which Support Vector Machine (SVM) displayed the best results (Simos *et al.* 2019). However, AI is also used for purposes of predicting disease prognosis. Taking SLE as the target disease, the SLEDAI score for the outcome has been attempted to be predicted by Kegerreis and colleagues (Kegerreis *et al.* 2019) from gene expression, with various fortunes related to the fine tuning of the ML techniques applied, including RF. Disease activity was also successfully predicted without the use of the SLEDAI score through a multinomial logistic regression model trained over a high number of possible parameter combinations (Hoi *et al.* 2021). Supervised recurrent neural network (RNN) was otherwise employed to classify SLE patients without chronic damage who developed damage in the 2 years following a disease-free baseline with respect to those who did not develop chronic damage with fairly good and stable performances (Ceccarelli *et al.* 2017). Similar approaches were also used with different diseases, including Multiple Sclerosis (MS) (Seccia *et al.* 2020) or atherosclerosis (Sánchez-Cabo *et al.* 2020; Coelewij *et al.* 2021). Even in the case of Systemic Sclerosis, ML could help predicting early lung involvement through spirometry and pH impedentiometry, as described (Murdaca *et al.* 2021b). Finally, also in completely different disorders, like in Alzheimer's Disease, a quick, not computationally burdensome ML approach could identify reliable biomarkers predicting the clinical outcome (Murdaca *et al.* 2021a). To wrap up a complete outlook on the usefulness of AI within chronic inflammatory diseases, it is worth mentioning that such approach can be used also for therapy selection, as well as for drug development and repurposing, which are beyond the scope of the present paper.

4. Use of Artificial Intelligence in predicting climate changes effects on Human Health

As reported, the effects of human activities are more and more visible in terms of fast climate changes, with significant effects on the human health. To eventually control the spreading of infectious conditions, AI is used for disease prediction and forecasting, strictly related to the interactions of environmental variables in the etiopathology of a given disorder. However, further disorders, even within the category of chronic inflammatory diseases, can follow a similar approach in terms of disease onset prediction also taking into account environmental variables, for example temperature and humidity, in the model (McMichael, Woodruff, and Hales 2006). For example, Leishmaniasis is endemic in nearly 100 countries worldwide, and its diffusion appears to be related to climate changes enabling new habitats for vectors and reservoirs. Ecological niches models, whose maximum entropy algorithms were applied, were used to predict the relocation of vectors within different climate change scenarios up to 2080, predicting how further climate changes can boost the disease spread even northbound (González *et al.* 2010). A non-necessarily chronic disease, but potentially modifying into chronic, is infectious diarrhoea, which was studied by Wang and colleagues (Y. Wang *et al.* 2015) through AI. There, feed-forward Back-Propagation Artificial Neural Networks (BPNN), Support Vector Regressions (SVR), and Random Forest Regressions (RFR) were applied, with temperature-related variables reportedly being the most effective predictors, whereas weekly average rainfall was seen as the least effective one.

5. Conclusions and future perspectives

the integration of air pollution data, the use of increasingly powerful computing devices, and the application of Artificial Intelligence are winning components for the diagnosis of chronic inflammatory diseases. This approach is crucial for retrieving the cause and effect relationship between these diseases and changes in climatic conditions resulting from atmospheric pollution (see Figure 1). Our results suggest that the implementation of machine learning algorithms and the creation of models that relate climate change and chronic inflammatory diseases are a powerful and promising tool for providing more adequate health services and improving specialist decision-making. In fact, the accurate analysis of medical data, through innovative methodologies, benefits the early diagnosis of diseases, patient care and, in this specific case, can support governments to introduce good practices for reducing air pollution. The key point that should be emphasized is that, the use of AI techniques in medicine is less developed than in other knowledge fields, yet. However, researchers and clinicians are increasingly attracted from the use of AI-based predictive and diagnostic models that turn out to be one of the turning points of the current knowledge advancement in healthcare. In the future, AI techniques, such as machine learning, deep learning and others could play a pivotal role in the diagnosis and treatment of chronic diseases as well as in the quality of patient care and in reducing medical costs resulting from prevention. Among those, as displayed, Artificial Neural Networks are a powerful tool for simulating the impact of climate change on chronic inflammatory diseases, capable of estimating their future relevance for the adoption of protective measures in areas with the highest incidence of such conditions. However, great accuracy is required in the selection of Artificial Intelligence techniques to be adopted based on the data to be analyzed, the output foreseen, and the understanding of which input variables have the most significant influence in the analysis. Employing these techniques in the medical setting requires a rigorous approach and clinical validation in a real-world setting, prior to launch and implementation in patient care, but ultimately their use will lay the foundation for high-performance and “p4” (predictive, preventative, personalized, participatory) medicine. The future perspectives of the study on the use of Artificial Intelligence and Machine Learning for the diagnosis of chronic inflammatory diseases and their link to climate variations due to air pollution are wide-ranging and involve several areas; In particular, with the advancement of AI and ML techniques, greater accuracy is expected in predicting the effects of climate variations on the incidence and severity of chronic inflammatory diseases, thanks to the development of more sophisticated models that take into account a wide range of variables, capable of linking air pollution data to individual biological and behavioural data. With a deeper understanding of the relationship between environmental factors and health, new opportunities could emerge to tailor disease prevention and management strategies. This could include targeted interventions based on specific environmental conditions and the individual risk profile of patients. Furthermore, the integration of data from different sources, such as genomes, microbiomes, proteomes and transcriptomics, with environmental, and clinical data could allow a more comprehensive understanding of the mechanisms underlying the relationship between environment, genetics and disease. This could lead to deeper insights into pathogenic pathways, the identification of new therapeutic targets, and the development of more sophisticated personalised medicine approaches that could include the prediction of a patient's response to certain therapies based on their genetic, environmental and clinical profile. Finally, study results could influence public policies to mitigate air pollution and take preventive measures for public health. This could include the implementation of stricter regulations on the emission of air pollutants and the adoption of urban planning strategies aimed at reducing population exposure to pollutants.

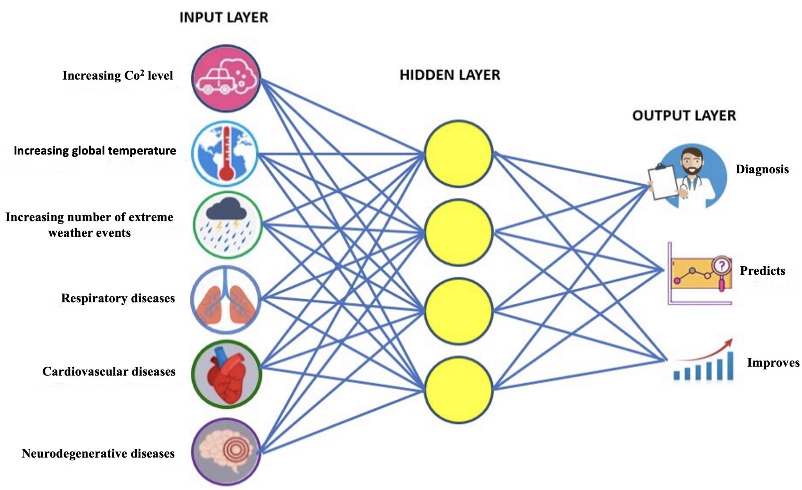

FIGURE 1. Details of inputs and outputs related to the use of an artificial neural network for climate change data analysis and chronic inflammatory disease management. In input, the correlation between climate change, air pollution and chronic inflammatory diseases; development of specific models and use of artificial intelligence provide, in output, powerful tools for early diagnosis, monitoring and treatment of chronic inflammatory diseases..

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