UNIVERSITA' DEGLI STUDI DI PARMA
Dipartimento di Medicina Clinica e Sperimentale
Dottorato di ricerca in Fisiopatologia Respiratoria Sperimentale
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Air pollution and clinical and functional indices in asthma

Inquinamento atmosferico e indici clinico-funzionali nell'asma

Coordinatore:
Chiar.mo Prof. Emilio Marangio

Tutor:
Chiar.mo Prof. Alfredo Chetta

Dottorando: Elisa Mariani

…to Mathias

ABSTRACT

There is growing evidence that air pollution increases the incidence of asthma in both children and adults. The association between air pollution and asthma has been investigated in many studies which have shown this relationship considering respiratory symptoms and hospitalizations. This retrospective study was conducted on a sample of patients resident in the metropolitan area of Parma; 249 patients, with asthma diagnosis according to the international guidelines, were selected among those who have carried out at least two visit at the Asthma outpatient Clinic of Parma University Hospital, from January 2008 to March 2012 . For every day in which an examination took place were registered the concentrations of PM10, NO_2 and benzene. In addition to the general data, for every patient has been collected information about asthma familiarity, atopy, BMI and the possible therapy carried out in the indicated period during the examinations. Regarding the respiratory conditions of patients during every examination, these tests were taken into consideration: Asthma Control test (a test performed by patients to evaluate the pathology grade during the month prior to the test), the fraction of exhaled nitric oxide (FeNO) measurement as an inflammatory index of the airways and some values taken in the spirometric examination. In particular The forced vital capacity (FVC), forced expiratory volume in the first second (FEV 1), FEV 1 /FVC ratio, forced expiratory flow rate over the middle 50% of the FVC (FEF 25–75) and FEF25-75/FVC were recorded. The sample has been studied considering both the changes of the respiratory parameters for every patient in their examinations, and the respiratory parameters of all the examinations took as a whole in relation with the pollutants' variations. Although many confounding factors presence makes difficult to

evaluate atmospheric pollution importance on the breathing functionalities variation, measured by objective test, the results show that FVC and FEV1 decreases are statistically significant in relation to higher PM10 values in non-therapy subjects, similar to the changes observed in NO_2 and benzene high values presence.

Considering consider each subject control of himself, spirometric tests worse in relation to higher pollutant concentration and particularly, reach statistical significance in relation to NO_2 and benzene increases.

Finally, if we only consider steroid therapy, in quartiles analysis, it results more evident the FVC% and FEV% variations both for PM10 and NO_2 and benzene, while the analysis on each individual patient, small airway parameters seem to be more influenced by NO_2 and benzene higher values.

In conclusion, our results provided the evidence that the environmental exposure may be an additional risk factor which should be considered in the assessment of the asthmatic patients.

Numerose evidenze mostrano come l'inquinamento atmosferico aumenti l'incidenza dell'asma sia nei bambini che negli adulti. L'associazione tra inquinamento atmosferico e asma è stata investigata in molti studi i quali hanno messo in evidenza questa relazione considerando i sintomi respiratori e i ricoveri ospedalieri. Questo studio retrospettivo è stato condotto su un campione di pazienti residenti nell'area metropolitana di Parma. Sono stati selezionati 249 pazienti tra quelli che hanno svolto almeno due visite di controllo presso l'Ambulatorio dell'Asma della Clinica Pneumologica dell'Ospedale Universitario di Parma nel periodo che va da Gennaio 2008 a Marzo 2012. Per ogni giorno in cui si è svolta una visita, sono state registrate le concentrazioni degli inquinanti: PM10, NO_2 e Benzene. Oltre ai dati generali per ogni paziente sono state raccolte una serie di informazioni quali la presenza o meno di familiarità per l'asma, l'atopia e l'eventuale terapia svolta nel periodo delle visite considerate. Mentre per quanto riguarda lo stato respiratorio dei pazienti nelle diverse visite sono stati considerati: l'Asma Control Test (un test svolto dal paziente per valutare lo stato della patologia durante il mese precedente il test), la misurazione dell'ossido nitrico esalato (FeNO) quale indice di infiammazione delle vie aeree, e alcuni valori osservati nell'esame spirometrico; in particolare la capacità vitale forzata (FVC), il volume espiratorio forzato nel primo secondo (FEV), l'indice di Tiffeneau (FEV1/FVC), il flusso espiratorio forzato al 50% dell'FVC (FEF25-75) e il rapporto FEF25-75/FVC. Il campione è stato studiato sia considerando i cambiamenti dei parametri respiratori di ogni singolo paziente nelle diverse visite, sia considerando i parametri respiratori nella totalità delle visite come campione messo in relazione con le variazioni degli inquinanti. Sebbene la presenza di numerosi fattori di

confondimento renda difficile stimare il peso dell'inquinamento atmosferico sulle variazioni della funzionalità respiratoria misurata attraverso test oggettivi, i risultati mostrano che sono statisticamente significative le diminuzioni di FVC e FEV1 in relazione a valori più elevati di PM10 in soggetti non in terapia, simili alle variazioni osservate in presenza di valori elevati di NO_2 e di Benzene. Considerando ogni soggetto come controllo di se stesso, i test spirometrici peggiorano in relazione alle concentrazioni più elevate di inquinante, in particolare raggiungono la significatività statistica in relazione all'NO_2 e al Benzene. Infine se si considera esclusivamente la terapia steroidea, risultano, nell'analisi sui quartili, più evidenti le variazioni di FVC e FEV1 sia per il PM10 che per l'NO_2 che per il Benzene mentre nell'analisi su ogni singolo paziente i parametri delle piccole vie sembrano risentire maggiormente dei valori più elevati di NO_2 e di Benzene.

In conclusione i nostri risultati hanno dimostrato che l'esposizione ambientale può essere un fattore di rischio aggiuntivo che dovrebbe essere considerato nella valutazione della popolazione asmatica.

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INTRODUCTION

Air pollution significantly contributes to the global burden of disease [1]. The effects of the air pollution on human health have been known for years, in particular for the huge impact on health of some severe episodes of pollution between 1930-1950. London case in 1952, known as “The Great Smog of London” was emblematic: from the fifth to the eight of December, thanks also to the presence of particular meteorological conditions, London was wrapped up in a smog (= smoke + fog) blanket. It was an hard winter and people have burned huge quantity of coal to heat their homes, causing the emission of many pollutant substances in the atmosphere: the concentrations of sulphur dioxide (SO_2) and total suspended particulate exceeded the daily average of 2000 $\mu g/m^3$, with peaks during the day until 5000 $\mu g/m^3$. In the week affected by the phenomenon it was assessed an excess of nearly 4000 deaths with a case prevalence between children, elderly and subjects with cardio circulatory and respiratory diseases. Deaths were due to respiratory insufficiency, acute bronchitis and pneumonia increased 9.3 times compared with the same period in the year before [12]. It is clear that the urban environment is particularly interested by the air pollution; indeed many human pollutant activities here occur in a confined space and the population is more exposed to mixtures of physical and chemical agents potentially harmful for the human health. The attention should be given mainly to pollutants produced by car traffic, domestic heating and industrial plants. Growing evidences show that it is possible to ascribe to the exposition of environmental pollutant quotes not negligible of the morbidity and mortality for neoplasms [13-15], cardiovascular and respiratory diseases [2-5,11]. Hospital admissions of patients with chronic obstructive pulmonary disease (COPD) [6-10] or asthma are

more frequent during the periods of acute increase in air pollution. In particular asthma higher prevalence in socio-economic developed countries [16] and the difference in prevalence rates between the urban and rural areas [17,18] has led to think that, although genetic predisposition is an essential factor in determining atopy and bronchial hyperactivity [31], for the onset and the course of the disease the environmental factors like cigarette smoking [31], occupational allergens [31] and air pollution [19,20] are determinant. There is growing evidence that air pollution increases the incidence of asthma in both children [21,24] and adults [19,22,23]. The association between air pollution and asthma has been investigated in many studies which have shown this relationship considering respiratory symptoms [25-27] and hospitalizations [27-30]. Epidemiologic studies have importantly contributed to our understanding of the role of air pollution as a risk factor for respiratory disease. In addition, epidemiologic studies, especially those with large populations suitable for population health inference, have become increasingly important as the basis for policies, standards, and regulations.

ENVIRONMENTAL POLLUTION

DEFINITION

The environmental pollution was defined by the Italian legislation on air quality, with the DPR 203/88, as: “every modification in the composition or physic state of atmospheric air due to the presence of one or more substances in quantity and with certain characteristics such as to alter the normal environmental condition and the air healthiness, to pose a danger or injury directly or indirectly for the human health, compromising recreational activities and the others legitimate uses of the environment, to alter the biological resources, ecosystems and public and private asset.” [32]. These substances, which cause a measurable effect on living organisms or on different materials, are often absent in the normal composition of air or they are present at a lower concentration. The pollution which they create don’t develop only in the external environments (outdoor pollution) but also in confined settings, such as buildings (indoor pollution). The possibilities that pollutants could react lead to discriminate between:

- Primary pollutant: pollutants which are emitted directly in the atmosphere from the sources without any other modifications; the main primary pollutants are those emitted by combustion processes of any kind, e.g. not combusted hydrocarbon, carbon monoxide, nitrogen oxides (mainly monoxides).

- Secondary pollutant: pollutants which are created in the atmosphere following chemical-physical transformations of many substances which can be primary pollutants or not. Among the formation processes of secondary pollutants, the series of reactions between nitrogen oxides and hydrocarbons with solar light are

particularly important. This reaction chain lead for example to the oxidation of nitrogen monoxide (NO) which create nitrogen dioxide (NO_2) and to the production of ozone (O_3). All the products of these reactions are defined as photochemical smog which represent one of the most dangerous forms of pollution for the ecosystem.

Another way to classify the pollutants is to distinguish them by their origin: natural or anthropic. There are many sources of natural air pollutant however they don't represent a serious problem such as those generated by human activities because they often result less dangerous of the compounds produces by human beings. The natural sources of sulfur dioxide include volcanoes, organic decomposition and forest fire. The natural sources of nitrogen oxides include volcanoes, oceans, organic decompositions and lighting action. Ozone is a secondary pollutant that is created close to the ground as a result of chemical reactions catalyzed by the light. Anyway nearly 10-15% of ozone comes from the higher layer of the atmosphere (stratosphere) where it's created from the molecular oxygen with the action of UV rays. The importance of the natural sources of particulate is smaller than the anthropogenic sources because they originate particles with dimensions not dangerous for the breathing apparatus. In this category are included volcanoes and sandstorms. These sources usually don't cause severe episodes of pollution because the pollution takes place in a limited period. Many volatile organic compounds (VOC) are produced by plants, for example isoprene is a common VOC produced by vegetation. Moreover plants produce pollen (which is considered a component of the atmospheric particulate) and everybody knows the allergic effect that they can cause in predisposed

subjects. Other natural pollutants of great importance in confined environments (indoor) are mold spores and dust in general. Since less could be done by humans towards natural pollution, the main concern must be to reduce the pollution emitted by human activities. The major atmospheric pollution is the one that man produce to satisfy his own civil and industrial need. The several combustion processes used to cook food, to heat, to start motor vehicles and machinery, create the most prevailing pollutants. Air pollution of anthropogenic origin is emitted by the great stable sources (industries, plants for the production of electric energy and incinerators); by small stable sources (plants for the domestic heating) and by mobile sources (vehicular traffic). Many of these sources are strictly linked to the production and consume of energy, especially fossil fuel. The use of fossil fuels for the domestic heating, in particular heavy fuel oil, biomass and coal is a significant origin of environmental pollution, particulate and sulfur dioxide. Even traffic contribute to the emissions of these pollutants in cities where there is a great traffic congestion. Combustions generally represent the principal cause for the nitrogen oxide emissions; the engines of the means of transport are the principal cause for the emissions of carbon monoxide. In addition to all these substances produced by the combustion processes there are all the pollutants originated by particular technological cycles. These compounds are released in considerably low quantities and for this reason they are little relevant to a planetary level; nevertheless they have often a high toxicity and their presence is very important at a local level. The impact of the pollutant on human beings depends on the production area and on their dispersion. Great stable sources, localized mainly far away from great urban centers, waste the pollutants in the air

at great height while domestic heating and traffic waste theirs close to the ground in densely inhabited areas. As a result, mobile and small stable sources contribute in a major way to the air pollution in urban areas so they are a greater threat for the human health than what could be expected making a simple quantitative comparison among the different types of emissions.

The concentration of pollutant in the atmosphere is determined not only by the number and the intensity of the pollution sources, by the distance from those sources and by the chemical-physical transformation to which they are subjected but especially by the meteorological conditions which constitute the key parameter for the comprehension of the origin, the entity and the development in time of an event of atmospheric pollution. In general, in the presence of the same emissions of pollutants from the sources, the concentrations in the air are lower with precipitations, with moderate or high wind or when the wind is gentle or absent but there is a strong sunstroke with blue sky and the sun is high in the sky. Vice versa, the concentrations become high with light wind or with persistent fog that provokes accumulation processes. In association with meteorological conditions even the orographic conformation of the territory affects the air quality we breath, i.e. the particular conformation of Po valley, closed to the north by the Alps and to the south by Apennines, creates a climatic condition more stagnant than other European regions. In this area the pollutant substances remain for prolonged periods, for this reason there is an aggravation of the pollutant values.

PRINCIPAL POLLUTANTS AND THEIR EFFECTS

PARTICULATE

Physical-chemical characteristics

With the term PM, particulate matter, is defined a complex mixture of organic and inorganic substances in the solid or liquid state which, due to their small dimensions, remain suspended in the atmosphere for longer or shorter periods of time. The particles have a dimension between 0,005 μm and 50-150 μm; they are made of a mixture of substances like sulphate, niter, ammonia, carbon, organic compounds, soil fragments, sea salts, metals and radical compound. Particulate is generally distinct in four dimensional class:

- **TSP (total suspended particles):** these particles have dimensions above 10 μm;
- **PM 10:** particulate made of particles with a diameter lower than 10 μm (Figure 1);
- **PM 2.5:** thin particulate made of particles with a diameter lower than 2,5 μm (Figure 1);
- **PM 0,1 or ultrathin:** particulate with a diameter lower or equal to 0,1 μm.

Sources

The particulate sources could be natural or anthropic.

Natural sources

- Sea aerosol
- Fire
- Microorganisms
- Pollen and spores
- Rocks erosion
- Volcano eruptions

Anthropic sources

- Engine combustion emissions (trucks, cars, planes, boats)
- Domestic heating emissions (particularly diesel oil, coal and wood)
- Residues of the use of the pavement, brakes and tires
- Emissions of industrial plants
- Incinerators and electric plants
- Farm production (use of fertilizers)

Permanence and removal time

The permanence time varies between few minutes to days depending on the dimensions of the particulate and the atmospheric layer interested. The particulate could be transported for long distances. Its removal could be achieved by the gravitational sedimentation of the particles and the aggregation with other particles (dry mode) or by precipitations (wet mode).

Health effects

The pollution due to PM10 cause damaging effects to the human health both in the short (acute effects) and in the long period (chronic effects). Its dangerousness is strictly linked to its composition because the particles, due to their particular superficial structure, could adsorb acid and chemical carcinogenic substances from the air. The toxic action of PM10 is performed mainly on the breathing apparatus and the relevant factor to study the effects is the particles dimension because the ability to penetrate in the apparatus depends on this characteristic (Figure 2). The greater particles (with a diameter above 10 µm), in this context called *inhalable fraction*, penetrate in the respiratory tract until the nasopharyngeal area where they are filtered and blocked. When the particles reach the nose-laryngeal area they can be eliminated violently by a simple sneeze but in some cases they can reach the posterior zone of the pharynx and then they can be swallowed. The particles with a diameter lower than 10 µm called *thoracic fraction* are able to pass the extra thoracic tract (nasal cavities, pharynx and larynx) reaching easily the tracheal-bronchial area. The particles with a diameter between 2,5 and 3,3 µm stop before reaching the bronchioles. Finally, the

particles with a diameter lower than 2,5 μm reach the alveolar area penetrating in the alveoli if their diameter is lower than 1 μm. Nowadays there is a great interest in the fraction of particulate represented by ultrathin particles because their size is the reason why they can propagate in all the respiratory tract, walk in the cells and by that to pass the epithelial and endothelial walls. The specific contribute of ultrathin particles to the toxicity in humans is under study with toxicological and epidemiological approaches [33].

The most exposed people are elderly and subjects with preexisting cardiovascular pathologies [34], asthmatic [36], people that carry out an intense physical activity outdoor and children [35] for their higher pulmonary ventilation for body weight unit and for the immaturity of their respiratory apparatus.

SULFUR OXIDES (SO_x)

Chemical-physical characteristics

In the atmosphere, both sulfur dioxide (SO_2) and sulfur trioxide (SO_3) are normally found. Sulfur dioxide is a colorless, irritating, not flammable, very soluble in water with a piquancy. It is heavier than air so it stratify in the lower areas. Sulfur dioxide tarnishes with a slow reaction to sulfur trioxide which, reacting with water, creates sulfuric acid responsible for acid rain.

Sources

Sulfur dioxide is created mainly from combustion processes tarnishing sulfur which is present as an impurity in solid and liquid combustibles (carbon, fuel oil and diesel oil). The sources are the heating plants which works without methane, thermoelectric power plant, industrial combusting processes and the emissions coming from vehicles and maritime mean of transportation (Figure 3).

Permanence and removal time

The SO_2 persists for several days. With particular meteorological conditions and in the presence of high value of emissions it can spread in the atmosphere, affecting even far territories. It is removed by rainfalls.

Health effects

The SO_2 is highly soluble in water, for this reason it is easily adsorbed by the mucous of nose and the higher tract of the respiratory apparatus. The effects of low concentrations of sulfur dioxide are linked to pathologies of the respiratory apparatus like bronchitis, asthma and tracheitis but also irritation of skin, eyes and mucous [79]. The pathological effects induced by SO_2 appear when there are high levels of particulate because it can adsorb to the surface of them. Moreover the suspended dust are able to spread the pollutants to the deepest area in the respiratory apparatus. SO_2 act an important role in the worsening of chronic pulmonary pathologies like asthma [37].

NITROGEN OXIDES (NOx)

Chemical-physical characteristics

Nitrogen oxides (NOx) are present in the atmosphere, Nitrogen oxide or Nitrogen monoxide (NO) and Nitrogen dioxide (NO_2) being the most important as atmospheric pollutants.

Nitrogen monoxide is a gas which is colorless, flavorless and odorless; oxygen and ozone, which are present in the atmosphere, oxidize nitrogen monoxide thus creating nitrogen dioxide. The toxicity of nitrogen monoxide is very low contrary to that of nitrogen dioxide which result considerably high. Nitrogen dioxide is a toxic gas with a yellow-red color, a piquancy, and a strong irritating and oxidizing power. The well-known yellowish color of mist which cover the cities with high traffic is due precisely to nitrogen dioxide. Although it is considered a secondary pollutant because it originate from the oxidation of nitrogen monoxide, the Nitrogen dioxide constitutes the intermediate to create other secondary pollutants like ozone, nitric acid, nitrous acid, alkyl nitrate, peroxyacetyl nitrate (PAN) and others which are responsible for the formation of photochemical smog.

Sources

Nitrogen oxides exists in nature in moderate concentrations, independently from the pollution. The natural sources are constituted basically by anaerobic organic decompositions which reduce nitrate to nitrite. The great part of Nitrogen oxides (mostly Nitrogen monoxide) is emitted by high-temperature combustion

processes like those produced in vehicular engines. The high temperatures start a reaction between oxygen and nitrogen contained in the air creating Nitrogen monoxide. The amount of the compound produced is higher the higher is the combusting temperature and the faster is the cooling of these gases. Nitrogen monoxide emitted by exhaust gases is oxidized by the oxygen present in the air with the formation of Nitrogen dioxide. In general diesel engines emit more Nitrogen oxides and particulate than petrol engines but the second one emit more Carbon monoxide and hydrocarbon. Among the sources of Nitrogen oxides are thermal plants and thermoelectric power plants (the amounts emitted however are low because during the combustion the flame temperature is low), the production of nitrogenous fertilizers, the production of nitric acid coming from the oxidation of ammonia, the manufacture of explosives and the chemical processes which implies nitric acid.

Permanence and removal time

Nitrogen oxides remain in the atmosphere nearly for 4-5 day. They are removed as a consequence of chemical reactions which create acids, with aqueous vapor, or organic substances, with hydrocarbons and radicals.

Effects on health

Nitrogen dioxide is a mucous-irritating gas responsible of many alterations of the pulmonary functions, chronic bronchitis [63] and asthma [19]. Prolonged exposition to this compound, even at low concentrations, provokes a severe decrease of pulmonary defenses resulting in an increase of respiratory pathologies [80].

OZONE (O_3)

Chemical-physical characteristics

Ozone is a bluish toxic gas constituted by instable molecules generated by three oxygen atoms (O_3); these molecules splits easily releasing molecular oxygen and an extremely reactive oxygen atom ($O_3 \rightarrow O_2+O$). Given those characteristics, Ozone is a strong oxidizer able to destroy organic and inorganic materials.

Sources

Ozone is present in the higher levels of the atmosphere (stratosphere), it has a natural origin and it is useful to protect from solar UV radiations. As a consequence of atmospheric circulation it is transported in small concentrations even to the lower levels of the atmosphere (troposphere) where it can also be produced by electric discharge during storms. The generation of huge concentration of ozone in the troposphere is mainly a summer phenomenon linked to the interaction between solar radiation and chemical substances (hydrocarbon and NO_2) which, at high temperatures, start the chemical reactions producing O_3, free radicals, peroxides and strong oxidizing substances. The sources of ozone "precursors" could be natural, like woods and forests which emit volatile organic compounds (COV), or anthropic, like vehicular engines, combustion processes, thermoelectric power plants and chemical solvent industries.

Permanence and removal time

The ability to move with air masses far away from the source entails the presence of high concentration of Ozone at large distances; this determine the risk of significant expositions in people who live away from the principal sources of O_3. Removal systems are strictly correlated to solar radiation and to the presence of precursors.

Effects on health

Increasing concentrations of ozone could cause irritation of the eyes, throat and respiratory apparatus. High concentrations cause cough, a chest tightness and dispnea. These concentrations can also lead to a decrease in the resistance to pulmonary bacterial infections, to the onset of respiratory apparatus pathologies and to the worsening of ongoing pathologies of respiratory (COPD, pneumonia, asthma [63] and pulmonary emphysema) and cardiac type (myocardium ischemia)

CARBON MONOXIDE (CO)

Chemical-physical characteristics

Carbon oxide (CO) or carbon monoxide is a colorless, flavorless, inflammable and toxic gas. It creates from all those incomplete combustion processes which derives from an oxygen deficiency. In optimal conditions the carbon present in fuel combines with the oxygen in the air (combustive agent) and it is transformed in CO_2 (carbon dioxide), according to the falling reaction:

$C+O_2 \leftrightharpoons CO_2$ (Combustion reaction with excess of oxygen)

$2C+O_2 \leftrightharpoons 2CO$ (Combustion reaction with deficiency of oxygen)

Sources

The presence of carbon monoxide in the air we breathe is due to the human activity, however it must be considered also the amount due to natural emissions such as fires, volcanoes eruption, ocean and swamp emission and the oxidation of methane and hydrocarbons naturally emitted in the atmosphere. The main sources of anthropic origin is represented by exhaust gases, especially when the engines work at low speed with intense traffic. Other CO sources are the heating plants and some industrial processes like iron and cast iron production or the oil refining.

Permanence and removal time

Carbon monoxide is a primary pollutant for its long permanence in the atmosphere that could reach four-six months. For this reason it could be used as a marker for the temporal trend of primary pollutant at the ground level.

Effects on health

In normal conditions the oxygen breathed in passes blood to alveolar level and it binds to hemoglobin thus guaranteeing the oxygenation of tissues. The peculiar dangerousness of CO is due to the high affinity that this compound has in confront to hemoglobin; this affinity is nearly 220 times higher than oxygen affinity. CO, once breathed in, binds to hemoglobin creating a compound, carboxyhemoglobin, which, contrary to hemoglobin, is physiologically inactive and it isn't able to

guarantee the normal oxygenation of tissues provoking cellular anoxia. The most damaged organs are central nervous system and cardiovascular system, particularly in people with heart conditions.

At low concentration CO causes headache, diffuse weakness, dizziness; at high concentration it causes death by asphyxiation, a problem well known in cases of malfunctioning of gas stoves. Nevertheless at the concentration normally detectable in the urban atmosphere the effects on health are reversible and less acute.

BENZENE (C_6H_6)

Chemical-physical characteristics

Benzene (C_6H_6) is the basic compound in the category of aromatic hydrocarbons and its strong and sweetish smell make it recognizable even at low concentrations. At room temperature it is in a colorless liquid state and it vaporize quickly in the air. Although it is extremely flammable, its dangerousness is mainly due to the fact of being a carcinogen-recognized substance for humans.

Sources

The benzene present in the atmosphere derives both from natural source, like volcano eruption and forest fire, and from anthropic sources and the last one contributes mainly to the emissions. It Is a compound generated in consequence of the incomplete combustion of coal and oil; it is emitted by industries which use it in the production of plastic and polyesters. It is also present in the exhaust gases

of motor vehicles and it is emitted by some products in which it is contained such as glues, paints, furniture wax and detergent and together with cigarette smoke they are responsible for the exposure in closed environments. The traffic emissions are due to the evaporation of gasoline in tanks (5%) and mainly (95%) to the exhaust gases of gasoline vehicles, in fact to the gasoline it is added benzene, together with other aromatic compounds, to give the desired no explosive properties. The personnel of gas stations or of great warehouse is a worker category most exposed to high concentrations of this pollutant while tobacco smoke could be considered the main individual source of benzene for non-exposed population to this pollutant for professional reasons

Permanence and removal time

Given that Benzene is a very volatile compound, once it is released in the environment it splits preferentially in the air and since it is moderately soluble in water it could be removed from the atmosphere through wet depositions. The permanence of Benzene in the air depends from different factors among which the concentration of other pollutants, climatic conditions and its average lifetime which is variable from some hours to few days.

Effects on health

The exposure to Benzene may occur essentially by inhalation (nearly 99% of benzene), by cutaneous contact or by ingestion (consumption of contaminated food or beverage). The toxic effects caused by this organic compound present different characteristics and they damage different organs due to the exposure duration. Breathing air highly contaminated by benzene produce bedevilments,

tachycardia, headache, tremor and unconsciousness; high levels could be lethal. To eat or drink something contaminated by benzene could cause vomit, gastric wall irritation, drowsiness, convulsions, tachycardia and death. The chronic effects can regard respiratory disorders [24,68] but affect especially the blood cells and the organs that produce them like bone marrow. The effects appear in function of the dose of benzene to which a subject was exposed and they can vary from anemia to a simultaneous decrease of white blood cells and platelets. Epidemiological studies on humans, performed on professionally benzene-exposed workers, suggest a myelotoxicity and leukemic activity [69].

LEGISLATIVE INTERVENTIONS

Some pollutants no longer are a problem; for example carbon monoxide concentrations keep now low enough level and the ones of sulfur dioxide have been sensibly decreased thanks to industrial restructuration, technological innovations and use of low sulfur level combustible or of natural gas which has practically lack of it. Any excess is found instead for nitrogen oxides, but the real problem seems to be the one of fine powders. In effect, in large part of Italian cities, particularly during winter season, it's especially the PM10 concentrations that exceed the thresholds set out in the legislation. Then, actions are take as alternative car plates, traffic stop and restricted areas for most pollutant vehicles. These actions have surely the effect to temporally decrease pollutant outputs but not solve the problem. Same analysis should be done regarding ozone, another critical pollutant for our cities, particularly during summer season. That's way air pollution is one of the most important European care. From 70's Europe searched to develop a air quality improvement policy basing on air pollutant vehicles outputs control and decrease; on combustible quality improvement and on integration of atmospherically environment protection in all productive branches and human activities. Environment action European sixth program [72] ("Environment 2010: our future, our choice") includes "Environment and health" subject as one of the most needed sector of urgent action; air pollution is one of the applications of Environment and Health theme and the goal of the 6st program is to reach air quality levels which generate acceptable protection levels for human health and environment. In May 2008, a new 2008/50/EC Directive has been issued dated May the 21 [70], regarding environment air quality and for

a purer air in Europe, which also present new goals concerning air quality and PM 2,5 (thin powders or breathable powders) adding the ones already published regarding PM10 (thoracic fraction powders). In Italy, European Directive have been received through DLGS 155/10 [71]where are been settled new air quality limits, reported under synthetic form in table 1. Dates reporting on this table must be interpreted basing on following instructions:

- The limit value is a fixed level with goal to avoid negative health effects
- Alarm limit is a level over which any exposure, even of short time, could generate health risk for all population so his attainment forces to take immediate measures.
- Information limit is a level beyond which, although with short time exposures, there is health risk only for some sensible population groups and so, his attainment forces to take immediate information measures.
- The target value is a security level to reach, where it's possible, within determinate date.
- Daily averages are hourly concentration averages during all day long
- yearly averages are daily concentrations from January the 1st to December the 31st
- 8 hours average is a mobile average calculated with a interval sliding on an same day 8 running hours

- 3 hours average is a mobile average calculated with a interval sliding on a same day 3 running hours

HEALTH EFFECTS OF AIR POLLUTION

Exposure to air pollution is associated with numerous effects on human health, including pulmonary, cardiac, vascular, and neurological impairments; they can be acute or short- term effects and chronic or long-term effects. Different groups of individuals are affected by air pollution in different ways. Some individuals are much more sensitive to pollutants than are others. The elderly and the people with health problems such as asthma [65] and chronic bronchitis [66] or with cardiopulmonary disease, are the most vulnerable to air pollution exposure. Also the children are at greater risk because their lungs are still growing and they play outside and are active so they breathe more outdoor air pollution than most adults. The extent to which an individual is harmed by air pollution usually depends on the total exposure to the damaging chemicals: the *duration of exposure,* the *concentration and the type of the chemicals* must be taken into account.

Acute effects are usually immediate and often reversible when exposure to the pollutant ends. Examples of short-term effects include irritation to the eyes, nose and throat, and upper respiratory infections such as bronchitis and pneumonia. Other symptoms can include headaches, nausea, and allergic reactions. Short-term air pollution can aggravate the medical conditions of individuals with asthma and emphysema. Chronic effects are usually not immediate and tend not to be reversible when exposure to the pollutant ends. Long-term health effects can include chronic respiratory disease, lung cancer, heart disease, and even damage to the brain, nerves, liver, or kidneys. Continual exposure to air pollution affects

the lungs of growing children and may aggravate or complicate medical conditions in the elderly.

Although in humans pollutants can affect the skin, eyes and other body systems, they affect primarily the cardio-respiratory system (Figure 4) . Air is breathed in through the nose, which acts as the primary filtering system of the body. The small hairs and the warm, humid conditions in the nose effectively remove the larger pollutant particles. Both gaseous and particulate air pollutants can have negative effects on the lungs. Solid particles can settle on the walls of the trachea, bronchi, and bronchioles. Most of these particles are removed from the lungs through the cleansing (sweeping) action of "cilia", small hair like outgrowths of cells, located on the walls of the lungs. This is what occurs when you cough or sneeze.

A cough or sneeze transports the particles to the mouth. The particles are removed subsequently from the body when they are swallowed or expelled. However, extremely small particles may reach the alveoli, where it takes weeks, months, or even years for the body to remove the particles. Gaseous air pollutants may also affect the function of the lungs by slowing the action of the cilia. Continuous breathing of polluted air can slow the normal cleansing action of the lungs and result in more particles reaching the lower portions of the lung. The lungs are the organs responsible for absorbing oxygen from the air and removing carbon dioxide from the blood-stream. Damage to the lungs from air pollution can inhibit this process and contribute to the occurrence of respiratory diseases such as bronchitis, emphysema, and cancer [67]. This can also put an additional burden on the heart and circulatory system [67].

ASTHMA

Asthma is defined by the Global Initiative for Asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment" [38].

The inflammation of the airways makes them swollen, very sensitive and highly reactive to certain inhaled substances. When the airways react, the muscles around them tighten (Figure 5,6). This narrows the airways, causing less air to flow into the lungs and the classic symptoms of wheezing. Cells in the airways might make more mucus than usual (Figure 7). Mucus is a sticky, thick liquid that can further narrow the airways (Figure 7). Also another typical changes in the airway include an increase in eosinophils and thickening of the lamina reticularis.

Symptoms and exarcebation

Asthma is characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing [38]. Symptoms are often worse at night and in the early morning or in response to exercise or cold air [39]. Some people with asthma only rarely experience symptoms, usually in response to triggers, whereas others may have marked and persistent symptoms [38]. Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma with asthma attacks that can last for minutes to days, and can become

dangerous if the airflow is severely restricted. Different individuals react differently to various factors [41]. Most individuals can develop severe exacerbation from a number of triggering agents [41]. Psychological stress may worsen symptoms, it's thought that stress alters the immune system and thus increases the airway inflammatory response to allergens and irritants [42].

Causes

Asthma is caused by a combination of environmental and genetic factors [43]. These factors influence both its severity and how responsive it is to treatment. Many environmental factors have been associated with asthma's development and exacerbation including: allergens, air pollution, and other environmental chemicals. There is a relationship between exposure to air pollutants and the development of asthma [44]. Smoking during pregnancy and after delivery is associated with a greater risk of asthma-like symptoms [38]. Low air quality, from traffic pollution or high ozone levels has been associated with both asthma development and increase asthma severity [21-25,27,28,30]. Exposure to indoor volatile organic compounds may be a trigger for asthma; formaldehyde exposure, for example, has a positive association [46]. Also, phthalates in PVC are associated with asthma in children and adults [47,48] as are high levels of endotoxin exposure. Asthma is also associated with exposure to indoor [49] and outdoor allergens. Common indoor allergens include: dust mites, cockroaches, animal dander, and mold [50,51]. The most common outdoor allergens are pollen. Family history is a risk factor for asthma with many different genes being implicated [52]. By the end of 2005, 25 genes had been associated with asthma in six or more separate populations including: GSTM1, IL10, CTLA-4, SPINK5, LTC4S, IL4R and

ADAM33 among others [53]. Many of these genes are related to the immune system or to modulating inflammation. Even among this list of genes supported by highly replicated studies, results have not been consistent among all populations tested [53], in fact these studies are still in developing. The strongest risk factor for developing asthma is a history of atopic disease; with asthma occurring at a much greater rate in those who have either eczema or hay fever [38]. There is a correlation between obesity and the risk of asthma with both having increased in recent years [55,56]. Several factors may be at play including decreased respiratory function due to a buildup of fat and the fact that adipose tissue leads to a pro-inflammatory state [57].

Diagnosis

A diagnosis of asthma should be suspected if there is a history of: recurrent wheezing, coughing or difficulty breathing and these symptoms occur or worsen due to exercise, viral infections, allergens or air pollution. There are two tests that can confirm the diagnosis: spirometry and methacoline challenge testing. Spirometry assesses lung function through different parameters, one of these is FEV1 (forced expiratory volume in one second) that is the volume of air you can breathe out in one second; if the FEV1 measured by this technique improves more than 12% following administration of a bronchodilator such as salbutamol this is supportive of the diagnosis. The methacoline challenge involves the inhalation of increasing concentrations of a substance that causes airway narrowing in those predisposed. If positive it's possible establish the diagnosis of asthma.

Other supportive evidence includes: a ≥20% difference in peak expiratory flow rate on at least three days in a week for at least two weeks, a ≥20% improvement of peak flow following treatment with either salbutamol, inhaled corticosteroids or prednisone, or a ≥20% decrease in peak flow following exposure to a trigger [58]. Testing peak expiratory flow is more variable than spirometry, however, and thus not recommended for routine diagnosis. It may be useful for daily self-monitoring in those with moderate to severe disease and for checking the effectiveness of new medications. It may also be helpful in guiding treatment in those with acute exacerbations.

Management

While there is no cure for asthma, symptoms can be improved. A specific, customized plan for proactively monitoring and managing symptoms should be created. This plan should include the reduction of exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan should be written down and advise adjustments to treatment according to changes in symptoms.

The most effective treatment for asthma is identifying triggers, such as cigarette smoke, air pollution or pets and eliminating exposure to them. If trigger avoidance is insufficient, the use of medication is recommended. Pharmaceutical drugs are selected based on, among other things, the severity of illness and the frequency of symptoms.

Two types of asthma medications include short-acting, quick relief, medications and long-acting, controller, medications. Quick relief medications are used to treat

asthma symptoms when they occur. They relieve symptoms rapidly and are usually taken only when needed. Long-acting medications are preventative and are taken daily to help a patient achieve and maintain control of asthma symptoms.

Bronchodilators are recommended for short-term relief of symptoms. In those with occasional attacks, no other medication is needed. If mild persistent disease is present (more than two attacks a week), low-dose inhaled glucocorticoids or alternatively, an oral leukotriene antagonist or a mast cell stabilizer is recommended. For those who have daily attacks, a higher dose of inhaled glucocorticoid is used. In a moderate or severe exacerbation, oral glucocorticoids are added to these treatments [59].

Epidemiology

As of 2011, ~235 million people worldwide are affected by asthma, and approximately 250,000 people die per year from the disease [38]. Rates vary between countries with prevalence between 1 and 18% [38]. It is more common in developed than developing countries [38]. One thus sees lower rates in Asia, Eastern Europe and Africa [40]. Within developed countries it is more common in those who are economically disadvantage while in contrast in developing countries it is more common in the affluent [38]. The reason for these differences is not well know [38]. Low and middle income countries make up more than 80% of the mortality [45].

While asthma is twice as common in boys than girls [38], severe asthma occurs at equal rates [54]. In contrast adult women have a higher rate of asthma than men [38] and it is more common in the young than the old [40].

Global rates of asthma have increased significantly between the 1960s and 2008 [60] with it being recognized as a major public health problem since the 1970s [40]. Rates of asthma have stabilized in the developed world since the mid 1990s with recent increases primarily in the developing world. Asthma affects approximately 7% of the population of the United States [61] and 5% of people in the United Kingdom [62]. In Italy 11% of the population suffers from Bronchial Asthma. The figure emerged in the 110th Congress of the Italian Society of Internal Medicine.

AIM OF THE STUDY

The aim of the present study was to assess the effects of the changes of atmospheric pollutants on lung function parameters in a large cohort of asthmatic patients.

MATERIALS AND METHODS

Subjects

The retrospective study was conducted on a sample of patients resident in the metropolitan area of Parma; 249 patients, with asthma diagnosis according to the international guidelines [31], were selected among those who have carried out at least two visits at the Asthma outpatient Clinic of Parma University Hospital, in a period from January 2008 to March 2012.

In addition to the general data, for every patient has been collected information about asthma familiarity, smoking habit, atopy, BMI and the possible therapy carried out in the indicated period during the examinations.

BMI was defined as the weight in kilograms divided by the square of the height in meters; in each subject it was calculated from patients' self-reported height and weight. Atopy was assessed by skin prick tests with a battery of 10 common inhalant allergens. Therapies normally taken by patients are bronchodilators and steroids. Regarding the respiratory conditions of patients during every examination, these tests were taken into consideration: Asthma Control test (a test performed by patients to evaluate the pathology grade during the month prior to the test), the fraction of exhaled nitric oxide (FeNO) measurement as an inflammatory index of the airways and some values taken in the spirometric examination.

FeNO MEASUREMENT

We ensured that the patients were not affected by any acute respiratory infection and had followed the pretest instructions, i.e. no nitrate-rich foods or beverages, including alcoholic ones, no tobacco smoking, and no exercise within 1 h preceding the test, as these factors can affect the test results. Moreover, all patients underwent FeNO measurement before the lung function test. Only patients able to perform at least two acceptable FeNO measurements were included in the analysis. FeNO was measured according to American Thoracic Society/European Respiration Society (ATS/ERS) guidelines [74] using an FeNO stationary chemiluminescence analyzer (NIOX; Aerocrine AB, Solna, Sweden). All FeNO measurements were performed at the same time of day (±2 h) to allow a possible circadian rhythm effect. Patients were seated in the upright position without a nose clip and were asked to inhale nitric oxide-free air through a filter connected to the device deeply to total lung capacity and then to exhale for 10s at a constant pressure guided by a visual cue to stabilize the flow rate. All tests were performed at an exhalation pressure of 10–20 cm H 2 O to maintain a fixed flow rate of 50 ml/s. Measurements were repeated after a brief rest period until two acceptable values (±2.5 ppb for measurements <50 ppb and ±5% for measurements ≥50 ppb) were obtained (maximum six attempts). The mean of two adequate values for each subject was recorded for analysis. The system calibration was performed every 14 days.

Asthma Control Assessment

Asthma control was assessed using the Italian version of the ACT [75] . Patients subjectively evaluated the degree of impairment caused by their disease during the preceding 4 weeks by responding to five questions using a five-point scale. The ACT is reliable, valid, and responsive to changes in asthma control over time [75,76] . The sum of the scores of the five questions gave the total ACT score (range 0–25). A cut-off score of 19 or less identifies patients with poorly controlled asthma.

Lung Function Testing

Lung function was measured by a flow-sensing spirometer connected to a computer for data analysis (CPFS/D Spirometer; MedGraphics, St. Paul, Minn., USA) which met the ATS standards.

The forced vital capacity (FVC), forced expiratory volume in the first second (FEV 1), FEV 1 /FVC ratio, forced expiratory flow rate over the middle 50% of the FVC (FEF 25–75) and FEF25-75/FVC [73] were recorded. FVC, FEV 1 and FEF 25–75 are expressed as percents of predicted values [77], FEV 1 /FVC is expressed as a percent and FEF25-75/FVC is expressed as absolute values.

Air quality measurement

For every day in which an examination took place were registered the concentrations of PM10, NO2 and benzene; were taken into account only those three pollutants because they are the once that, in the city of Parma, most exceed the limits allowed by law. These data were collected by the air monitoring station

ARPA (Regional Agency for Environmental Protection) in Montebello and made public , according to the Legislative Decree 195-2005 [78], on the site Service.arpa.emr.it/qualita-aria/bollettino.aspx?prov=pr.

Statistical analysis

For descriptive analysis data were summarized in terms of frequencies, of means, standard deviations, minimum and maximum value.

It 'was preliminarily assessed the possible association between the dependent variables (spirometry tests etc.) and personal characteristics, medical history and clinical characteristics of the study subjects through two models, simple linear regression and analysis of variance.

After dividing the concentrations of pollutants into quartiles (Q1 to Q4), was conducted an analysis of variance followed by a post hoc test (LSD) to identify the possible different distribution of average values of the dependent variables in quartiles of pollution. It 'was subsequently identified the fourth quartile of pollution (maximum values) for each pollutant considered and spirometric values associated with it have been tested compared to those found in the first three quartiles through a Student's t test for unpaired data.

For each subject in the study were selected 2 visits corresponding to the minimum and maximum concentrations of pollutant considered individually. The results of the comparisons performed by a Student's t test for paired data were stratified by whether or not taking medications.

Through a multiple regression model, we evaluated the possible association between pollution and spirometric outcome adjusting for BMI and treatment. All statistical tests were considered significant at 0.05%. The analysis was performed with SPSS 20.0 statistical software.

RESULTS

Patient's personal data were collected together with other information concerning BMI, atopy, smoke tendency, familiarity to asthmatic pathology and the therapy followed in the period of the medical examination (Table 2). It was evident a greater amount of female patients in regard to male patients (162 vs 87). There was also a clear prevalence of atopic subjects: 178 compared to 71 non-atopic subjects. Furthermore the 89% of patients are non-smokers and only the 17% of them was never treated with a therapy for asthma.

The mean daily concentrations of pollutants, present the examinations days, were divided into quartiles (Table3). This allowed to distribute the values of the observations in four groups (from Q1= minimum concentration to Q4= maximum concentration). Depending on these concentrations the trend of the respiratory parameters was observed for all the examinations (n=1095). Although there aren't differences statistically significant (except for FEV1/FVC in relation to NO_2 with *p*=0,038) it's of note that there was a general trend towards the decreasing of respiratory parameters in relation to the fourth concentration quartile (Figures 8-13).

Factors like atopy, sex, familiarity and the use of drugs (Table 2) could be considered as risk factors for the asthmatic pathology or as factors able to influence the respiratory functionality of patients. We have stratified the respiratory parameters according to these factors (Table 4-6) to evaluate their influence on the patient's status. There was a statistically significant association of the respiratory parameters with the considered factors (Table 4-6).

Among all the risk factors considered, those which could be changed are therapy and BMI; we have evaluated the association of the respiratory parameters depending on the pollutants, taking also in consideration whether the patients were under therapy at the time of the examination or not. The evaluation was done with three type of analysis:

1. Whole sample analysis in relation to the quartiles of concentration of the pollutants (Table 7-9); in this case the totality of the medical examinations were considered independently from the patients. There was a significant inverse association of FEV1 and FVC without therapy in relation to the increasing of the three pollutants considered. In the presence of a therapy there's a significant negative relationship of FVC, FEV1/FVC and FEF25-75/FVC in the presence of the increase of NO_2.

2. Analysis of the whole patients considered as a single sample. In this case each patient is also control of himself because they are compared for the respiratory parameters recorded in two examinations in which the concentrations of the pollutants assume a maximum and minimum value (Table 10-12). It is observed a significant inverse association in the absence of the therapy for FVC both in relation to the maximum concentrations of NO_2 and Benzene and for FEV1 in relation to Benzene. On the other hand the presence of the therapy reveals a significant negative relationship for the small airways (FEF25 and FEF25-75) and for FEV1 with the maximum concentrations of Benzene but only for the small airways (FEF25 and FEF25-75 respectively) in relation to NO_2 and PM10.

3. Evaluation of which respiratory parameters change, in relation to the variation of the pollutants, with the same BMI and the presence of a therapy (Table 13). This analysis have underlined only a significance in relation to FeNO values.

Finally, we have investigated, with the same three types of analysis, the variation of the respiratory parameters according to the various pollutants, but we have considered the use of or less of the steroid as therapy at the time of the examination:

1. Whole sample analysis in relation to the quartiles of concentration of the pollutants (Table 14-16); in this case the totality of the medical examinations were considered independently from the patients. There was a significant negative association of FEV1 and FVC without steroids in relation to the increasing of the three pollutants considered. In the presence of the therapy there's a significant inverse relationship of FEV1/FVC and FEF25-75/FVC in the presence of the increase of NO_2.

2. Analysis of the whole patients considered as a single sample. In this case each patient is also control of himself because they are compared for the respiratory parameters recorded in two examinations in which the concentrations of the pollutants assume a maximum and minimum value (Table 17-19). It is observed a significant negative association in the absence of the therapy for FVC both in relation to the maximum concentrations of NO_2 and Benzene and for FEV1 in relation to Benzene. On the other hand the presence of the therapy reveals a significant inverse relationship for the small airways (FEF25) and for FEV1 with the

maximum concentrations of Benzene but only for the small airways (FEF25) in relation to NO_2.

3. Evaluation of which respiratory parameters change, in relation to the variation of the pollutants, with the same BMI and the presence of a therapy (Table 20). Also in this case the analysis have underlined only a significance in relation to FeNO values.

DISCUSSION

The study sample, consisting of 65.1% of female subjects, is representative of the series of patients with asthma related to the Asthma outpatient Clinic of Parma University Hospital relative to average age and individual characteristics such as BMI, family history, atopy and frequency of recruitment of drugs (Table 2). In fact, the selection was based on the actual residence or domicile in the metropolitan area of Parma and the availability of the results of spirometric tests performed in at least two separate occasions during the period from January 2008 and March 2012. The average concentrations of the pollutant (PM10, NO_2 and benzene), but decreasing in the last 10 years, amounted on average levels quite high (Table 3) often above the level of attention especially in winter.

The spirometric values observed over 1095 total visits are good overall, with statistically significant differences between the sexes, related on familiarity and atopy, age and BMI. Notably females, elderly and non-atopic patients, the subject with familiarity and a high BMI, had spirometric values lower than males, young and atopic patients, subject with no familiarity and a low BMI. The subjects at the time of the tests are in therapy (steroids and / bronchodilators) showed worse spirometric indices, particularly evident at the level of small airways.

Analyzes for quartiles of average concentrations of pollutants showed a general deterioration in performance and respiratory visits that fall in the 4th quartile (Figures 8-13), and in particular, there was statistically significant decreases in FVC and FEV1 (Tables 7-9) in relation to higher values of PM10 in subjects not in therapy (from 103 to 98 and from 94 to 90 respectively), similar to variations observed in the presence of high values of NO_2 (from 103 to 99 and from 94 to 90) and Benzene (from 103 to 98 and from 94 to 90).

Deepening the investigation, analysis "min-max" allowed to consider each individual control of himself, allowing for a more accurate estimate. Also in this case the data were stratified for therapy (Tables 10-12). Although not reaching statistical significance (except in a few cases, in particular for NO_2 and Benzene), the spirometric tests deteriorated with respect to higher concentrations of the pollutant. However, if that treatment in a generic sense (any) shall be considered exclusively steroid therapy, are, in the analysis on quartiles, the most obvious changes in FVC and FEV%% for both PM10 and NO_2 to that for benzene (Tables 14-16). Analysis min-max instead, tests on small streets seem to suffer most from higher values of NO_2 and Benzene (Tables 17-19).

Finally, multivariate analysis, carried out to adjust the association between pollution and spirometric values taking into account BMI and treatment shows that the NO_2 values, regardless of BMI and treatment is positively correlated with an increase in exhaled nitric oxide (Tables 13 and 20).

The growing interest towards the influence of environmental pollution on asthma led to the development of many clinical and epidemiological trials which are able to connect the hospital admittance due to asthma to the increase in environmental pollutants [28,29] and the worsening of the pathology of people living near high traffic areas [21]. Another interesting approach of investigation, although it was rarely explored in literature, was the observation of possible changes in respiratory parameters in relation to the variation of pollutants in a given period of time. This analysis was carried out also by P.C.Martins et al [24] on a population of asthmatic children; this allowed to set an objective association between the risk factor and the pathology. However the population under study

often didn't present a real asthma diagnosis because the costs and the technical personnel required to do the diagnosis have limited widely the use of asthma in epidemiological trials. In this study we have taken into consideration 249 adult patients with an asthma diagnosis determined by the test of bronchial provocation with methacholine and we have also evaluated the changes in respiratory parameters recorded during many medical examinations. The analysis of their variation in relation to the increase of environmental pollutants was evaluated not only for the sample as a whole, which it was made in other studies, but also in regard to the single patient. This is the most important aspect faced in our research inasmuch it allowed to have a more precise assessment of the spirometric parameters, although the presence of many confounding factors made difficult to assess the weight that the environmental pollutants have on the variation of the respiratory functionality measured with objective trials.

In conclusion, our results have provided the evidence that the environmental pollution may be an additional risk factor for the asthmatic patients. Therefore, in the evaluation of the asthmatic population, it is relevant to consider the environmental exposure of patients together with the other factors, such as sex, familiarity, age, BMI and atopy.

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FIGURES

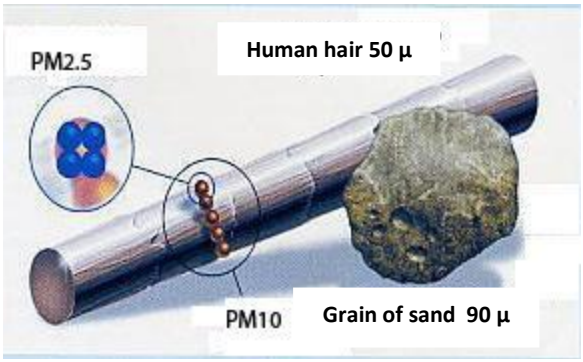

Figure 1: Example of particulate dimension

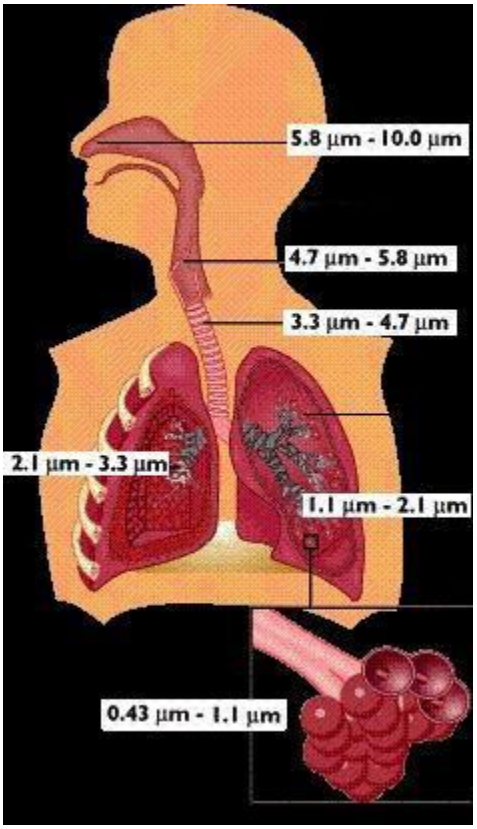

Figure 2: Penetration capacity of the particulate in the respiratory tract.

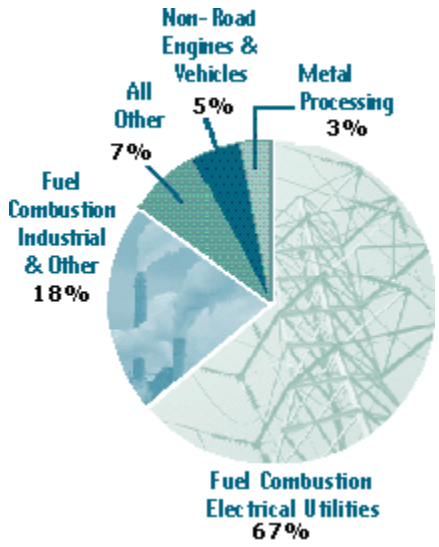

Figure 3: Sources of Sulfur dioxide

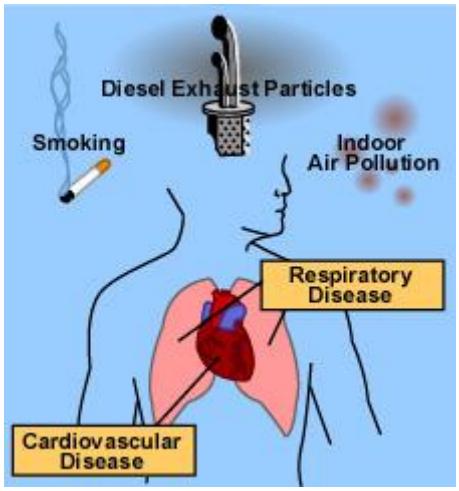

Figure 4: Air pollutants that affect cardio-respiratory system

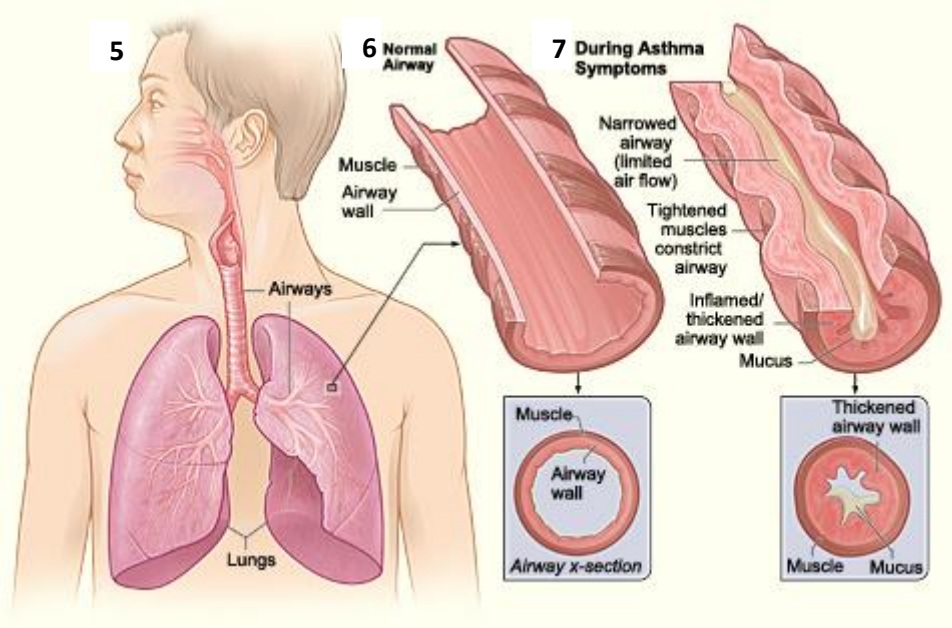

Figure 5: the location of the lungs and airways in the body. Figure 6: a cross-section of a normal airway. Figure 7: a cross-section of an airway during asthma symptoms.

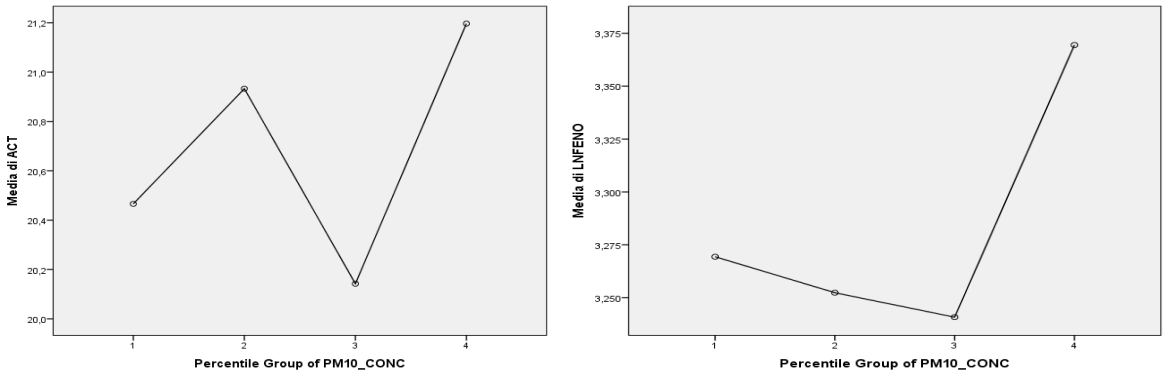

Figure 8: Changes of the ACT and FeNO in relation to quartiles of PM10 concentrations. The analysis has been made on the entire sample of visits.

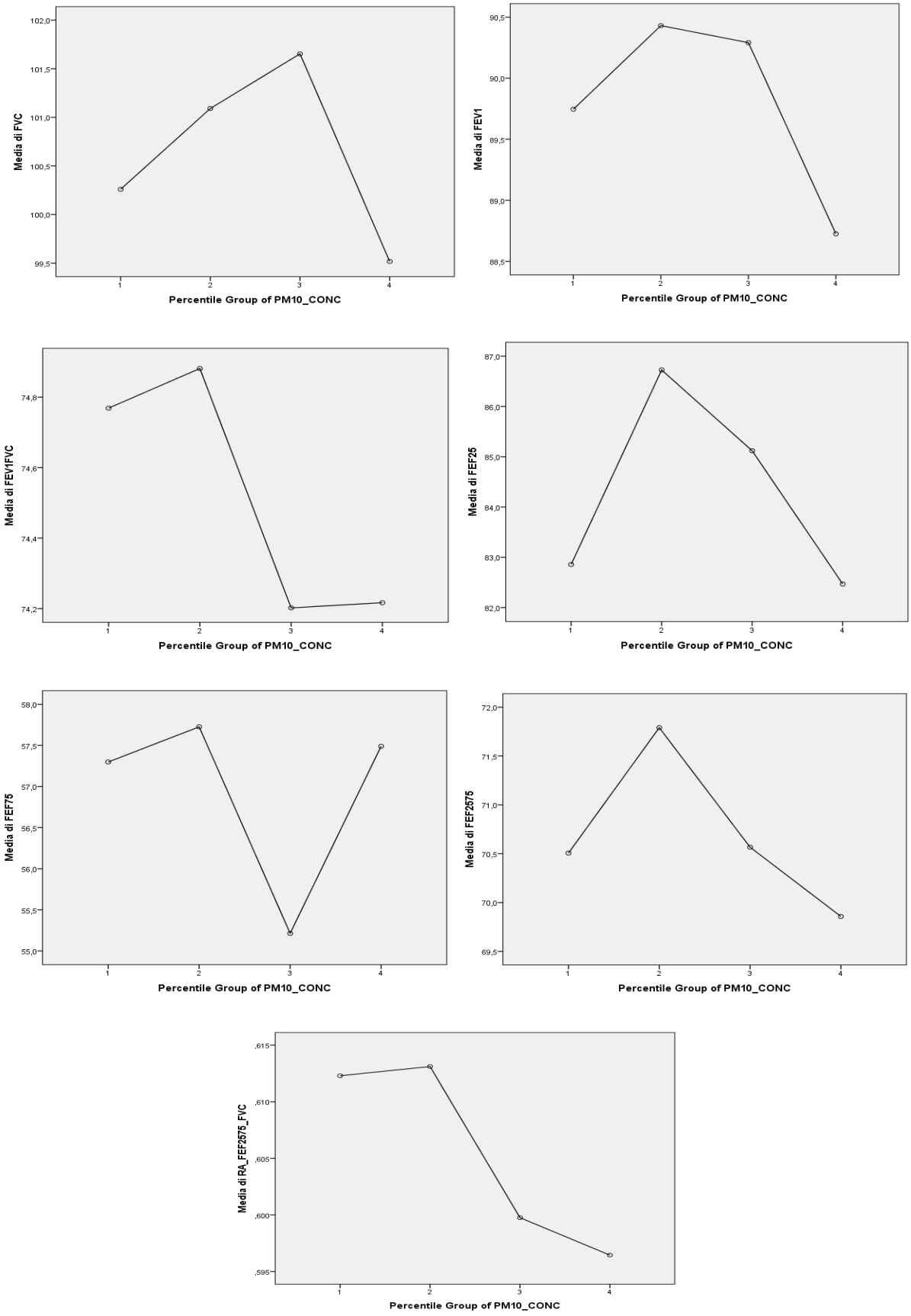

Figure 9: Changes of the respiratory parameters in relation to quartiles of PM10 concentrations. The analysis has been made on the entire sample of visits.

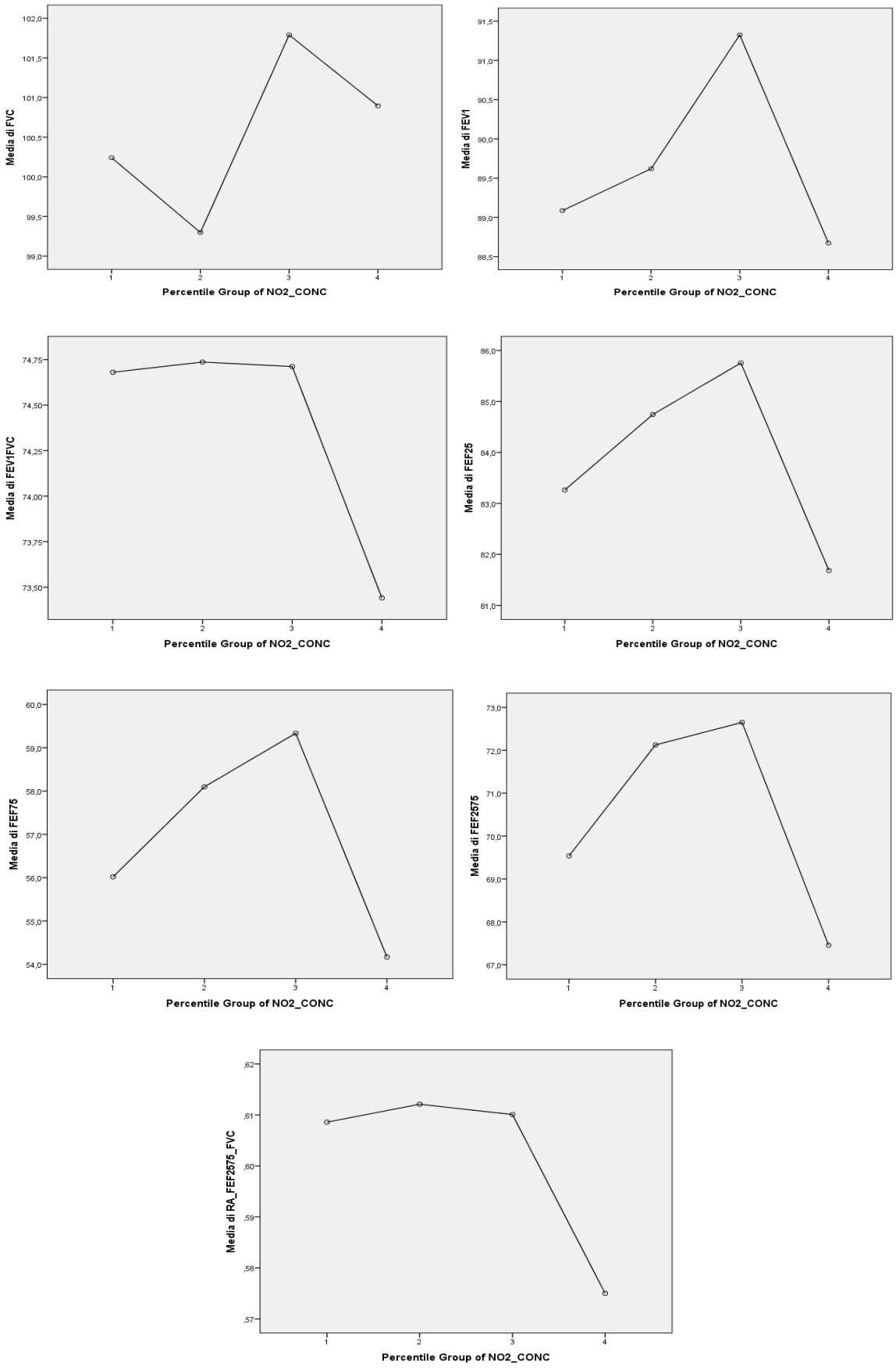

Figure 10: Changes of the respiratory parameters in relation to quartiles of NO_2 concentrations. The analysis has been made on the entire sample of visits.

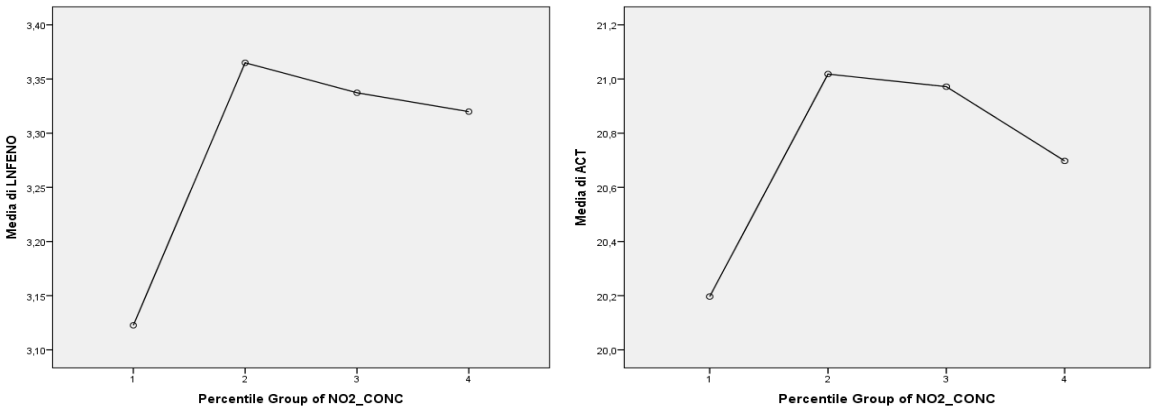

Figure 11: Changes of the ACT and FeNO in relation to quartiles of NO_2 concentrations. The analysis has been made on the entire sample of visits.

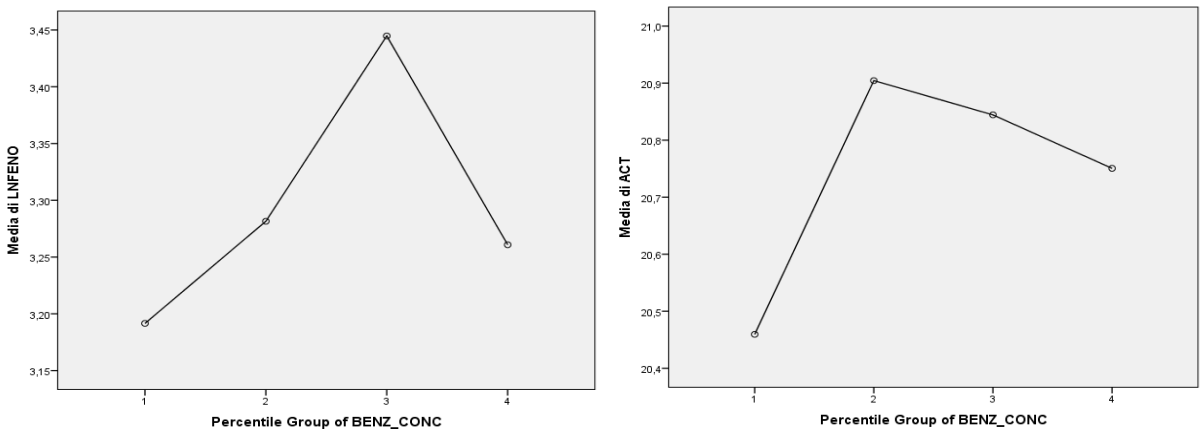

Figure 12: Changes of the ACT and FeNO in relation to quartiles of Benzene concentrations. The analysis has been made on the entire sample of visits.

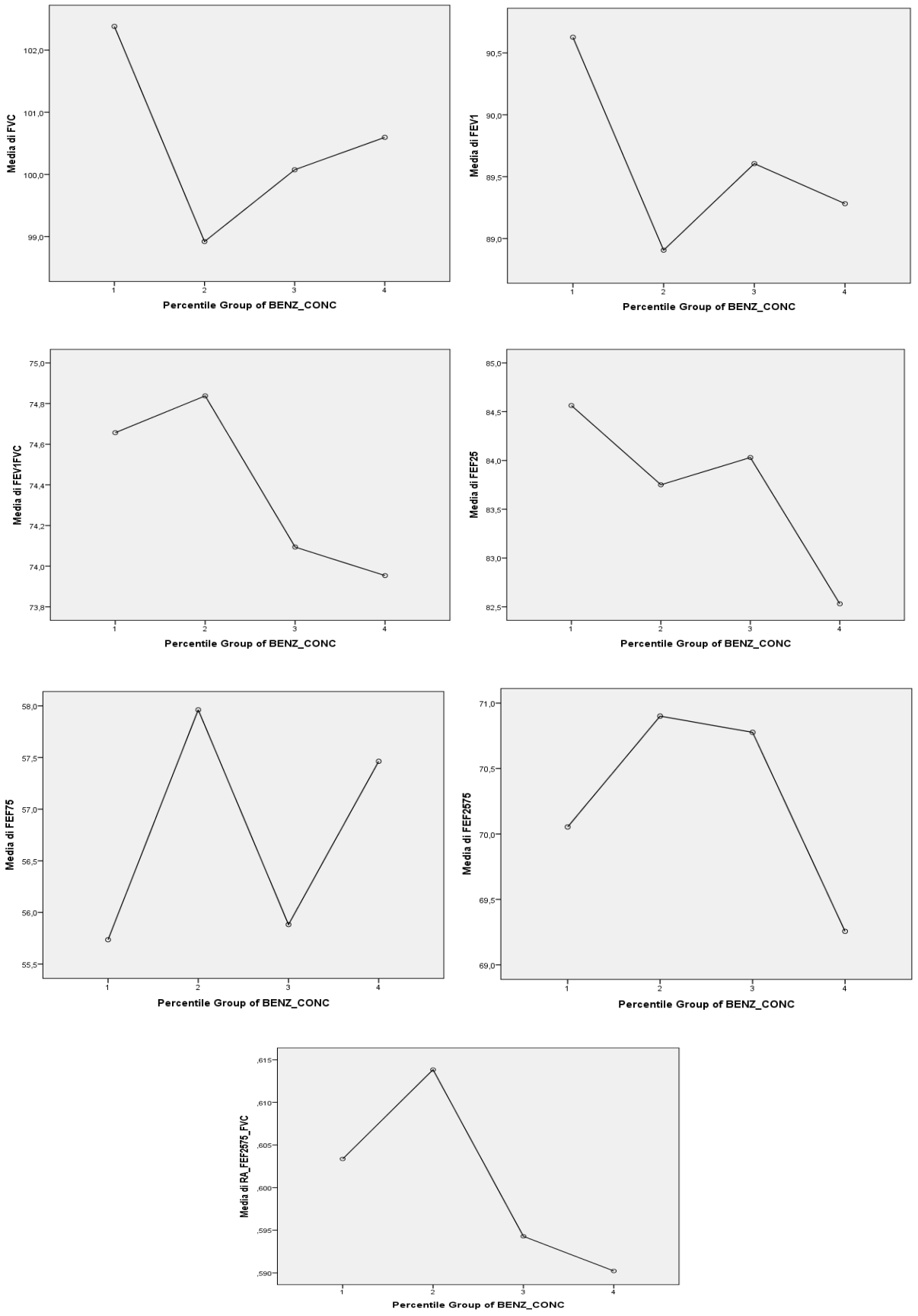

Figure 13: Changes of the respiratory parameters in relation to quartiles of Benzene concentrations. The analysis has been made on the entire sample of visits.

TABLES

Table 1: air quality principal limits imposed by DLgs 155/10

POLLUTANT	VALUE	µg/m³
Sulfur dioxide	*Average hourly limit ≤24*	350
	Alarm threshold 3 consecutive	500
Nitrogen dioxide	*Average hourly limit ≤18*	200
	Alarm threshold 3 consecutive	400
	Limit annual average	40
PM10	*Average daily limit ≤35*	50
	Limit annual average	40
PM2,5	*Limit annual average*	25
Ozone	*Information threshold*	180
	Alarm threshold	240
	Target value 8 consecutive	120
Carbon monoxide	*Limit average*	1000(= mg/m³)
Benzene	*Limit annual average*	5,0

Table 2: Descriptive of information about the sample of patients

TOTAL SUBJECT	249	%
SEX (M/F)	87/162	34,9/65,1
AGE (years)	46,3 (15,7)	14-85
BMI (Kg/m³)	24,9 (4,3)	17-40
ATOPY (NO/YES)	71/178	28,5/71,5
FAMILIARITY (NO/YES)	170/79	68,3/31,7
SMOKE (NO/YES)	220/27	89,2/10,8
THERAPY (NO/YES)	44/205	17,7/82,3
BRONCHODILATORS	71/178	28,5/71,5
STEROIDS (NO/YES)	44/205	17,7/82,3

Dichotomous variables are expressed as frequency, continuous variables as mean, standard deviations and minimum and maximum values

Table 3: Subdivision of the pollutants considered for quartiles of concentration

	Q1	Q2	Q3	Q4	Mean	Min-max
PM10	≤23	23,1-42,5	42,6-71,2	≥71,3	40,8	9-139
NO_2	≤36,7	36,8-50,3	50,4-60,7	≥60,7	50,3	18,5-102,4
Benzene	≤1,1	1,2-1,8	1,9-2,9	≥2,9	2,1	0,40-5,8

Table 4: Stratification of the respiratory parameters as a function of age and BMI

		ETA'	BMI
FEV1%	***p***	0,001	0,001
	r²	0,068	0,010
FVC%	***p***	0,001	0,001
	r²	0,012	0,010
FEV1/FVC%	***p***	0,001	0,001
	r²	0,211	0,012
FEF25%	***p***	0,001	0,098
	r²	0,095	0,003
FEF75%	***p***	0,001	0,001
	r²	0,209	0,037
FEF25-75%	***p***	0,001	0,051
	r²	0,097	0,004
FEF25-75/FVC	***p***	0,001	0,006
	r²	0,212	0,007
FeNO (ln)	***p***	0,741	0,001
	r²	0,001	0,018
ACT	***p***	0,003	0,001
	r²	0,017	0,018

Table 5: stratification of FVC, FEV1, FEV1/FVC, FeNO e ACT, as a function of sex, familiarity, atopy and therapy.

		FEV1%	*P*	**FVC%**	*P*	**FEV1/ FVC%**	*P*	**FeNO (ln)**	*P*	**ACT**	*P*
SEX	M	91,14 (16,97)	0,63	101,16 (17,42)	0,43	73,49 (9,26)	0,01	3,47 (0,79)	0,001	21,74 (3,30)	0,001
	F	89,1 (17,27)		100,25 (17,98)		74,93 (8,76)		3,21 (0,85)		20,19 (4,49)	
FAMILIARITY	No	91,16 (17,27)	0,001	101,12 (18,05)	0,12	75,25 (8,76)	0,001	3,23 (0,82)	0,01	20,67 (4,33)	0,97
	YES	86,83 (16,70)		99,37 (17,26)		72,93 (9,11)		3,41 (0,87)		20,68 (3,97)	
ATOPY	NO	84,87 (18,75)	0,001	96,71 (18,98)	0,001	72,41 (8,97)	0,001	3,20 (0,83)	0,09	20,02 (4,96)	0,03
	YES	91,48 (16,26)		101,92 (17,16)		75,22 (8,82)		3,33 (0,85)		20,93 (3,86)	
THERAPY	NO	93,131 (16,44)	0,001	102,34 (16,71)	0,007	76,191 (8,62)	0,001	3,46 (0,80)	0,001	21,702 (3,72)	0,001
	YES	87,553 (17,34)		99,359 (18,38)		73,398 (8,98)		3,16 (0,85)		19,856 (4,41)	
BRONCHODILATORS	NO	93,18 (16,51)	0,001	102,60 (17,25)	0,001	76,06 (8,16)	0,001	3,45 (0,79)	0,001	21,48 (3,70)	0,001
	YES	86,30 (17,21)		98,45 (18,11)		72,92 (9,40)		3,11 (0,86)		19,69 (4,59)	
STEROIDS	NO	92,81 (16,48)	0,001	102,06 (16,89)	0,02	76,11 (8,64)	0,001	3,47 (0,80)	0,001	21,61 (3,76)	0,001
	YES	87,67 (17,38)		99,5 (18,33)		73,40 (8,98)		3,15 (0,85)		19,89 (4,42)	

Values are expressed as mean (sd)

Table 6: Stratification of FEF25, FEF75, FEF25-75 e FEF25-75/FVC, as a function of sex, familiarity, atopy and therapy.

		FEF25%	*P*	**FEF75%**	*P*	**FEF25-75%**	*P*	**FEF25-75/ FVC**	*P*
SEX	M	80,81 (24,07)	0,007	64,37 (30,88)	0,001	73,10 (25,79)	0,04	0,58 (0,24)	0,078
	F	85,6 (28,47)		53,6 (27,94)		69,51 (27,15)		0,61 (0,25)	
FAMILIARITY	NO	86,44 (27,39)	0,001	59,55 (29,94)	0,001	73,23 (26,68)	0,001	0,62 (0,25)	0,001
	YES	79,34 (26,36)		51,98 (27,42)		65,48 (26,21)		0,56 (0,24)	
ATOPY	NO	76,8 (28,25)	0,001	47,13 (23,20)	0,001	64,34 (27,72)	0,001	0,54 (0,22)	0,001
	YES	86,69 (26,40)		60,54 (30,47)		72,90 (26,06)		0,63 (0,25)	
THERAPY	NO	89,175 (28,74)	0,001	62,941 (30,07)	0,001	76,213 (26,86)	0,001	0,65 (0,25)	0,001
	YES	80,811 (25,73)		53,205 (28,20)		67,067 (26,11)		0,57 (0,24)	
BRONCHODILATORS	NO	89,19 (27,77)	0,001	62,11 (29,34)	0,001	75,56 (25,74)	0,001	0,64 (0,24)	0,001
	YES	78,98 (25,73)		51,93 (28,43)		65,74 (26,89)		0,56 (0,25)	
STEROIDS	NO	88,6 (28,67)	0,001	62,67 (30,10)	0,001	75,94 (26,78)	0,001	0,65 (0,26)	0,001
	YES	81,05 (25,81)		53,21 (28,18)		67,08 (26,19)		0,57 (0,24)	

Values are expressed as mean (sd)

Table 7: Changes of the respiratory parameters in relation to quartiles of PM10 concentrations. The analysis has been made on the entire sample of visits.

PM10					
PARAMETERS	**QUARTILES**	**THERAPY YES**	***p***	**THERAPY NO**	***p***
FVC%	**0**	99,39 (18,41)	0,639	103,51 (16,47)	0,009
	1	100,18 (17,80)		98,50 (17,18)	
FEV1%	**0**	87,70 (17,21)	0,965	94,08 (15,99)	0,04
	1	87,77 (16,47)		90,19 (17,75)	
FEV1/FVC%	**0**	73,51 (8,90)	0,526	76,41 (8,74)	0,755
	1	72,99 (9,19)		76,98 (8,52)	
FEF25%	**0**	81,44 (24,79)	0,391	90,30 (28,81)	0,329
	1	79,43 (26,76)		87,06 (29,18)	
FEF75%	**0**	53,00 (27,58)	0,939	62,60 (29,58)	0,696
	1	53,20 (28,08)		63,96 (32,38)	
FEF25-75%	**0**	67,16 (25,36)	0,795	76,94 (26,81)	0,505
	1	66,54 (26,46)		74,86 (27,89)	
FEF25-75/FVC	**0**	0,58 (0,24)	0,378	0,66 (0,25)	0,915
	1	0,56 (0,25)		0,65 (0,25)	
FeNO (ln)	**0**	3,12 (0,85)	0,184	3,42 (0,78)	0,394
	1	3,26 (0,82)		3,52 (0,86)	
ACT	**0**	19,66 (4,36)	0,291	21,55 (3,30)	0,253
	1	20,34 (4,67)		22,24 (4,81)	

Values are expressed as mean (sd); 0=Q1-Q3, 1=Q4

Table 8: Changes of the respiratory parameters in relation to quartiles of NO_2 concentrations. The analysis has been made on the entire sample of visits.

NO_2					
PARAMETERS	**QUARTILES**	**THERAPY YES**	***p***	**THERAPY NO**	***p***
FVC%	**0**	98,64 (18,07)	0,060	103,33 (16,63)	0,044
	1	101,76 (19,08)		99,52 (16,48)	
FEV1%	**0**	87,54 (17,19)	0,887	93,98 (15,71)	0,038
	1	87,76 (17,97)		90,11 (17,99)	
FEV1/FVC%	**0**	73,78 (9,03)	0,033	76,19 (8,63)	0,562
	1	72,05 (8,69)		75,62 (8,60)	
FEF25%	**0**	81,44 (25,16)	0,261	89,56 (27,58)	0,309
	1	78,80 (27,44)		86,23 (31,45)	
FEF75%	**0**	54,45 (28,56)	0,088	63,13 (30,46)	0,474
	1	50,05 (27,66)		60,67 (28,61)	
FEF25-75%	**0**	68,15 (26,13)	0,062	76,66 (26,49)	0,276
	1	63,74 (25,46)		73,32 (27,58)	
FEF25-75/FVC	**0**	0,59 (0,24)	0,019	0,65 (0,25)	0,716
	1	0,53 (0,23)		0,64 (0,25)	
FeNO (ln)	**0**	3,15 (0,89)	0,800	3,43 (0,78)	0,368
	1	3,18 (0,77)		3,54 (0,89)	
ACT	**0**	19,92 (4,40)	0,715	21,78 (3,21)	0,935
	1	19,69 (4,58)		21,82 (4,77)	

Values are expressed as mean (sd); 0=Q1-Q3, 1=Q4

Table 9: Changes of the respiratory parameters in relation to quartiles of Benzene concentrations.

The analysis has been made on the entire sample of visits.

BENZENE					
PARAMETERS	**QUARTILES**	**THERAPY YES**	***p***	**THERAPY NO**	***p***
FVC%	**0**	98,34 (18,53)	0,030	103,60 (16,70)	0,006
	1	101,94 (17,90)		98,37 (16,28)	
FEV1%	**0**	86,85 (17,45)	0,206	94,04 (16,19)	0,033
	1	88,84 (17,18)		90,01 (17,23)	
FEV1/FVC%	**0**	73,55 (8,67)	0,220	76,03 (8,80)	0,844
	1	72,57 (9,60)		76,23 (8,08)	
FEF25%	**0**	80,24 (25,20)	0,831	90,00 (28,53)	0,162
	1	80,74 (27,46)		85,38 (29,30)	
FEF75%	**0**	52,62 (27,78)	0,652	62,45 (28,78)	0,804
	1	53,78 (29,02)		63,31 (33,97)	
FEF25-75%	**0**	66,57 (25,27)	0,922	76,67 (26,38)	0,380
	1	66,34 (27,81)		73,96 (28,32)	
FEF25-75/FVC	**0**	0,57 (0,23)	0,359	0,65 (0,25)	0,975
	1	0,55 (0,24)		0,65 (0,24)	
FeNO (ln)	**0**	3,19 (0,88)	0,242	3,44 (0,77)	0,434
	1	3,07 (0,74)		3,53 (0,89)	
ACT	**0**	19,97 (4,45)	0,593	21,70 (3,23)	0,712
	1	19,60 (4,21)		21,93 (5,10)	

Values are expressed as mean (sd); 0=Q1-Q3, 1=Q4

Table 10: Changes of the respiratory parameters in relation to minimum and maximum concentrations of PM10 in two visits. The analysis has been made on the totality of patients as a sample.

PARAMETERS	THERAPY	PM10		*p*
		MIN	MAX	
FVC%	**Yes**	101,55 (18,51)	100,78 (17,61)	0,435
	No	104,18 (17,13)	101,91 (16,10)	0,075
FEV1%	**Yes**	89,80 (18,31)	88,40 (16,73)	0,106
	No	94,27 (16,48)	92,55 (15,76)	0,145
FEV1/FVC%	**Yes**	73,59 (9,48)	73,36 (9,50)	0,653
	No	75,72 (8,77)	76,15 (8,99)	0,446
FEF25%	**Yes**	82,99 (26,99)	80,94 (26,03)	0,133
	No	89,18 (28,34)	87,46 (28,22)	0,318
FEF75%	**Yes**	55,52 (29,75)	55,23 (31,10)	0,874
	No	62,52 (31,25)	64,45 (33,78)	0,387
FEF25-75%	**Yes**	69,77 (28,39)	66,84 (26,89)	0,049
	No	75,94 (26,94)	75,98 (28,11)	0,984
FEF25-75/FVC	**Yes**	0,59 (0,25)	0,58 (0,27)	0,410
	No	0,64 (0,24)	0,65 (0,26)	0,338
FeNO (ln)	**Yes**	3,03 (0,84)	3,06 (0,78)	0,773
	No	3,53 (0,79)	3,64 (0,89)	0,255
ACT	**Yes**	19,72 (4,69)	20,94 (4,05)	0,122
	No	22,02 (3,20)	22,33 (4,88)	0,735

Values are expressed as mean (sd)

Table 11: Changes of the respiratory parameters in relation to minimum and maximum concentrations of NO_2 in two visits. The analysis has been made on the totality of patients as a sample.

PARAMETERS	**THERAPY**	**NO_2**		***p***
		MIN	**MAX**	
FVC%	**Yes**	100,73 (17,99)	100,38 (18,01)	0,751
	No	104,87 (17,16)	102,22 (17,16)	0,045
FEV1%	**Yes**	89,09 (18,22)	87,88 (17,06)	0,193
	No	94,07 (17,45)	92,82 (16,21)	0,265
FEV1/FVC%	**Yes**	73,52 (9,75)	73,03 (9,43)	0,382
	No	75,39 (9,03)	75,85 (8,93)	0,455
FEF25%	**Yes**	82,72 (28,02)	79,56 (25,19)	0,017
	No	88,06 (28,52)	87,73 (27,22)	0,826
FEF75%	**Yes**	54,10 (29,64)	54,35 (31,09)	0,896
	No	60,97 (30,08)	62,92 (33,12)	0,337
FEF25-75%	**Yes**	68,76 (68,76)	66,04 (26,53)	0,093
	No	74,73 (27,56)	75,68 (26,73)	0,573
FEF25-75/FVC	**Yes**	0,58 (0,26)	0,56 (0,24)	0,160
	No	0,62 (0,25)	0,65 (0,25)	0,076
FeNO (ln)	**Yes**	2,96 (0,84)	3,06 (0,80)	0,215
	No	3,47 (0,84)	3,57 (0,87)	0,330
ACT	**Yes**	19,61 (4,31)	18,91 (5,04)	0,401
	No	22,61 (2,69)	22,68 (4,88)	0,933

Values are expressed as mean (sd)

Table 12: Changes of the respiratory parameters in relation to minimum and maximum concentrations of Benzene in two visits. The analysis has been made on the totality of patients as a sample

PARAMETERS	**THERAPY**	**BENZENE**		***p***
		MIN	**MAX**	
FVC%	**Yes**	101,70 (17,44)	99,98 (19,11)	0,136
	No	105,90 (16,35)	101,19 (16,73)	0,001
FEV1%	**Yes**	89,86 (17,57)	87,66 (17,04)	0,012
	No	94,74 (16,70)	91,87 (16,46)	0,009
FEV1/FVC%	**Yes**	73,65 (9,64)	72,99 (9,32)	0,213
	No	75,41 (8,72)	75,92 (8,76)	0,340
FEF25%	**Yes**	83,59 (27,30)	79,74 (26,37)	0,008
	No	88,29 (29,03)	86,41 (27,61)	0,215
FEF75%	**Yes**	54,12 (27,88)	54,16 (28,61)	0,982
	No	60,66 (29,33)	63,06 (33,38)	0,230
FEF25-75%	**Yes**	68,95 (27,41)	65,58 (26,06)	0,043
	No	74,97 (27,23)	74,98 (27,04)	0,996
FEF25-75/FVC	**Yes**	0,58 (0,25)	0,56 (0,26)	0,20
	No	0,62 (0,24)	0,64 (0,25)	0,201
FeNO (ln)	**Yes**	3,13 (0,89)	3,13 (0,79)	0,987
	No	3,41 (0,84)	3,55 (0,89)	0,214
ACT	**Yes**	20,50 (3,60)	20,44 (4,33)	0,940
	No	22,59 (2,69)	22,86 (4,88)	0,767

Values are expressed as mean (sd)

Table 13: Changes of respiratory parameters in relation to the pollutants concentrations, on equal BMI and assumption of therapy.

PARAMETERS	**PM10**	***p***	**NO2**	***p***	**BENZENE**	***p***
FVC%	-0,036	0,237	0,031	0,312	-0,010	0,741
FEV1%	-0,050	0,104	0,006	0,850	-0,015	0,624
FEV1/FVC%	-0,035	0,255	-0,039	0,195	-0,033	0,274
FEF25%	-0,054	0,080	-0,019	0,543	-0,026	0,402
FEF75%	0,011	0,719	0,008	0,803	-0,025	0,403
FEF25-75%	-0,032	0,292	-0,014	0,646	-0,014	0,650
FEF25-75/FVC	-0,027	0,372	-0,037	0,222	-0,034	0,263
FeNO (ln)	0,045	0,264	0,087	0,031	0,058	0,150
ACT	0,024	0,587	0,035	0,417	0,045	0,304

Table 14: Changes of the respiratory parameters in relation to quartiles of PM10 concentrations.

The analysis has been made on the entire sample of visits.

PM10					
PARAMETERS	**QUARTILES**	**STEROIDS YES**	***p***	**STEROIDS NO**	***p***
FVC%	**0**	99,41 (18,44)	0,434	103,37 (16,50)	0,003
	1	100,73 (17,43)		97,74 (17,65)	
FEV1%	**0**	87,71 (17,33)	0,723	93,89 (15,87)	0,016
	1	88,27 (16,24)		89,40 (18,11)	
FEV1/FVC%	**0**	73,53 (8,94)	0,457	76,29 (8,69)	0,861
	1	72,91 (9,02)		76,11 (8,77)	
FEF25%	**0**	81,62 (24,91)	0,470	89,78 (28,67)	0,268
	1	79,90 (26,76)		86,17 (29,30)	
FEF75%	**0**	53,07 (27,77)	0,973	62,22 (29,32)	0,611
	1	52,99 (27,32)		63,96 (33,14)	
FEF25-75%	**0**	67,13 (25,49)	0,861	76,70 (26,61)	0,448
	1	66,71 (26,35)		74,39 (28,11)	
FEF25-75/FVC	**0**	0,58 (0,24)	0,214	0,65 (0,25)	0,789
	1	0,55 (0,23)		0,66 (0,28)	
FeNO (ln)	**0**	3,11 (0,85)	0,206	3,42 (0,78)	0,349
	1	3,25 (0,81)		3,54 (0,86)	
ACT	**0**	19,66 (4,38)	0,205	21,50 (3,31)	0,405
	1	20,49 (4,62)		21,99 (4,93)	

Values are expressed as mean (sd); 0=Q1-Q3, 1=Q4

Table 15: Changes of the respiratory parameters in relation to quartiles of NO_2 concentrations. The analysis has been made on the entire sample of visits.

NO_2					
PARAMETERS	**QUARTILES**	**STEROIDS YES**	***p***	**STEROIDS NO**	***p***
FVC%	**0**	98,70 (18,12)	0,038	103,12 (16,62)	0,029
	1	102,17 (18,68)		99,01 (17,17)	
FEV1%	**0**	87,58 (17,32)	0,746	93,74 (15,60)	0,021
	1	88,10 (17,76)		89,52 (18,35)	
FEV1/FVC%	**0**	73,81 (9,07)	0,024	76,09 (8,59)	0,633
	1	71,96 (8,53)		75,63 (8,81)	
FEF25%	**0**	81,68 (25,29)	0,266	88,99 (27,47)	0,294
	1	79,03 (27,42)		85,62 (31,44)	
FEF75%	**0**	54,53 (28,73)	0,071	62,80 (30,23)	0,517
	1	49,82 (26,97)		60,61 (29,49)	
FEF25-75%	**0**	68,15 (26,25)	0,068	76,45 (26,34)	0,240
	1	63,76 (25,41)		72,92 (27,66)	
FEF25-75/FVC	**0**	0,59 (0,24)	0,006	0,64 (0,25)	0,978
	1	0,53 (0,21)		0,64 (0,28)	
FeNO (ln)	**0**	3,14 (0,89)	0,954	3,44 (0,78)	0,273
	1	3,15 (0,76)		3,56 (0,89)	
ACT	**0**	19,94 (4,41)	0,776	21,71 (3,24)	0,923
	1	19,76 (4,57)		21,65 (4,82)	

Values are expressed as mean (sd); 0=Q1-Q3, 1=Q4

Table 16: Changes of the respiratory parameters in relation to quartiles of NO_2 concentrations. The analysis has been made on the entire sample of visits.

BENZENE					
PARAMETERS	**QUARTILES**	**STEROIDS YES**	***p***	**STEROIDS NO**	***p***
FVC%	**0**	98,26 (18,56)	0,011	103,60 (16,68)	0,002
	1	102,50 (17,49)		97,60 (16,81)	
FEV1%	**0**	86,82 (17,53)	0,113	93,93 (16,09)	0,011
	1	89,33 (16,94)		89,20 (17,61)	
FEV1/FVC%	**0**	73,59 (8,70)	0,174	75,92 (8,77)	0,744
	1	72,49 (9,46)		76,24 (8,36)	
FEF25%	**0**	80,34 (25,28)	0,711	89,64 (28,44)	0,115
	1	81,22 (27,45)		84,51 (29,37)	
FEF75%	**0**	52,72 (27,92)	0,738	62,09 (28,64)	0,717
	1	53,59 (28,34)		63,33 (34,67)	
FEF25-75%	**0**	66,60 (25,38)	0,964	76,40 (26,27)	0,340
	1	66,49 (27,73)		73,50 (28,51)	
FEF25-75/FVC	**0**	0,58 (0,23)	0,199	0,64 (0,25)	0,735
	1	0,55 (0,23)		0,65 (0,27)	
FeNO (ln)	**0**	3,19 (0,88)	0,194	3,44 (0,77)	0,380
	1	3,04 (0,73)		3,55 (0,89)	
ACT	**0**	19,98 (4,48)	0,758	21,65 (3,25)	0,953
	1	19,76 (4,15)		21,68 (5,20)	

Values are expressed as mean (sd); 0=Q1-Q3, 1=Q4

Table 17: Changes of the respiratory parameters in relation to minimum and maximum concentrations of PM10 in two visits. The analysis has been made on the totality of patients as a sample.

PARAMETERS	STEROIDS	PM10		*p*
		MIN	MAX	
FVC%	**Yes**	101,26 (18,43)	100,61 (17,52)	0,523
	No	103,68 (17,99)	101,26 (16,85)	0,109
FEV1%	**Yes**	89,54 (18,33)	88,67 (16,65)	0,286
	No	93,81 (16,81)	91,94 (16,28)	0,165
FEV1/FVC%	**Yes**	73,55 (9,61)	73,61 (9,51)	0,907
	No	75,78 (9,03)	76,14 (9,24)	0,524
FEF25%	**Yes**	82,90 (27,22)	81,40 (25,99)	0,272
	No	88,11 (28,16)	86,52 (28,19)	0,385
FEF75%	**Yes**	55,74 (30,15)	56,18 (30,81)	0,804
	No	62,63 (31,28)	64,77 (34,32)	0,337
FEF25-75%	**Yes**	69,60 (28,53)	67,74 (26,86)	0,178
	No	75,61 (26,66)	75,90 (28,28)	0,879
FEF25-75/FVC	**Yes**	0,59 (0,26)	0,58 (0,26)	0,735
	No	0,64 (0,25)	0,66 (0,29)	0,265
FeNO (ln)	**Yes**	3,11 (0,84)	3,09 (0,78)	0,894
	No	3,56 (0,80)	3,60 (0,88)	0,601
ACT	**Yes**	19,74 (4,70)	20,64 (4,49)	0,304
	No	22,05 (3,23)	22,10 (3,04)	0,939

Values are expressed as mean (sd)

Table 18: Changes of the respiratory parameters in relation to minimum and maximum concentrations of NO_2 in two visits. The analysis has been made on the totality of patients as a sample.

PARAMETERS	**STEROIDS**	**NO_2**		***p***
		MIN	**MAX**	
FVC%	**Yes**	100,75 (18,21)	100,99 (17,77)	0,833
	No	104,37 (18,12)	101,79 (17,60)	0,045
FEV1%	**Yes**	89,19 (18,30)	88,52 (17,14)	0,467
	No	93,62 (17,63)	92,16 (16,44)	0,178
FEV1/FVC%	**Yes**	73,55 (9,74)	73,04 (9,31)	0,347
	No	75,43 (9,16)	75,64 (9,24)	0,718
FEF25%	**Yes**	83,12 (28,07)	80,42 (25,45)	0,046
	No	87,20 (28,52)	86,77 (27,26)	0,763
FEF75%	**Yes**	54,33 (29,65)	54,46 (30,67)	0,942
	No	60,80 (29,70)	62,69 (33,38)	0,340
FEF25-75%	**Yes**	68,93 (28,31)	66,79 (26,98)	0,175
	No	74,57 (27,14)	75,15 (26,73)	0,724
FEF25-75/FVC	**Yes**	0,58 (0,26)	0,56 (0,24)	0,160
	No	0,62 (0,25)	0,65 (0,28)	0,092
FeNO (ln)	**Yes**	2,98 (0,83)	3,06 (0,81)	0,330
	No	3,48 (0,83)	3,58 (0,87)	0,310
ACT	**Yes**	19,19 (4,62)	18,87 (5,12)	0,700
	No	22,64 (2,66)	22,69 (4,81)	0,957

Values are expressed as mean (sd)

Table 19: Changes of the respiratory parameters in relation to minimum and maximum concentrations of NO_2 in two visits. The analysis has been made on the totality of patients as a sample.

PARAMETERS	**STEROIDS**	**BENZENE**		***p***
		MIN	**MAX**	
FVC%	**Yes**	101,99 (17,62)	100,38 (19,27)	0,161
	No	105,18 (17,45)	101,23 (16,93)	0,001
FEV1%	**Yes**	90,09 (17,64)	88,16 (17,27)	0,023
	No	94,08 (17,10)	91,60 (16,72)	0,023
FEV1/FVC%	**Yes**	73,62 (9,68)	73,11 (9,34)	0,329
	No	75,47 (8,97)	75,78 (9,12)	0,550
FEF25%	**Yes**	84,00 (27,38)	80,30 (26,61)	0,010
	No	87,76 (29,34)	85,92 (27,77)	0,223
FEF75%	**Yes**	54,32 (27,89)	54,75 (28,26)	0,787
	No	60,95 (29,24)	63,35 (33,87)	0,233
FEF25-75%	**Yes**	69,15 (27,37)	66,39 (26,50)	0,090
	No	74,74 (27,12)	74,80 (27,17)	0,971
FEF25-75/FVC	**Yes**	0,58 (0,25)	0,57 (0,25)	0,264
	No	0,62 (0,02)	0,64 (0,28)	0,204
FeNO (ln)	**Yes**	3,15 (0,87)	3,13 (0,80)	0,826
	No	3,44 (0,84)	3,56 (0,87)	0,265
ACT	**Yes**	20,12 (4,03)	20,45 (4,39)	0,661
	No	22,64 (2,63)	22,87 (4,75)	0,790

Values are expressed as mean (sd)

Table 20: Changes of respiratory parameters in relation to the pollutants concentrations, on equal BMI and assumption of steroid.

PARAMETERS	**PM10**	***p***	**NO2**	***p***	**BENZENE**	***p***
FVC%	-0,037	0,236	0,031	0,316	-0,010	0,734
FEV1%	-0,050	0,103	0,005	0,862	-0,015	0,612
FEV1/FVC%	-0,035	0,251	-0,040	0,189	-0,034	0,268
FEF25%	-0,054	0,079	-0,019	0,536	-0,026	0,394
FEF75%	0,011	0,727	0,007	0,816	0,025	0,410
FEF25-75%	-0,033	0,287	-0,015	0,633	-0,014	0,640
FEF25-75/FVC	-0,028	0,367	-0,038	0,215	-0,034	0,259
FeNO (ln)	0,045	0,259	0,088	0,029	0,058	0,147
ACT	0,024	0,588	0,036	0,410	0,045	0,307

…Thanks

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