

Quantification of airway deposition of intact and fragmented pollens

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Although pollen is one of the most widespread agents that can cause allergy, its airway transport and deposition is far from being fully explored. The objective of this study was to characterize the airway deposition of pollens and to contribute to the debate related to the increasing number of asthma attacks registered after thunderstorms. For the quantification of the deposition of inhaled pollens in the airways computer simulations were performed. Our results demonstrated that smaller and fragmented pollens may penetrate into the thoracic airways and deposit there, supporting the theory that fragmented pollen particles are responsible for the increasing incidence of asthma attacks following thunderstorms. Pollen deposition results also suggest that children are the most exposed to the allergic effects of pollens. Finally, pollens between 0.5 and 20 μm deposit more efficiently in the lung of asthmatics than in the healthy lung, especially in the bronchial region.

Keywords: airway deposition of pollens; Monte Carlo simulations; asthma modelling

Introduction

Allergy is a relatively modern disease. Although clinical conditions such as asthma and eczema have been known in the past, it has become a widespread disease only in the last decades. According to the American Academy of Asthma, Allergy and Immunology (AAAAI), asthma affects over 50 million people just in the US. This health disorder is characterized by an overreaction of the human immune system to a foreign substance (allergen) that is eaten, inhaled, injected or touched. Of all the agents that can cause allergy, pollen is one of the most pervasive. Pollen is a fine-to-coarse powder consisting of pollen grains, which produce the male gametes of seed plants. These particles are released from trees, weeds and grasses, hitch rides on currents of air and can be inhaled by humans, causing respiratory diseases like allergic rhinitis (hay fever) and asthma, diseases with increasing prevalence in the last decade (D'Amato et al. 1998; Pearce et al. 2000; Björkstén et al. 2008). While our

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physiological and immunopathological knowledge concerning the effects of pollens becomes more and more complete, airway transport and deposition of inhaled pollens is still far from being fully explored.

Deposition of inhaled pollens can be studied experimentally or by complex computational models. Extra- and intrathoracic particle deposition has been extensively studied using analytical (Yeh and Schum 1980; Koblinger and Hofmann 1990; Cassee et al. 1999; Asgharian et al. 2004) and numerical (Darquenne and Paiva 1996; Balásházy et al. 2003, 2008; Zhang et al. 2005; Farkas et al. 2006, Farkas and Balásházy 2007, Longest et al. 2006; Kimbell et al. 2007; Farkas and Balásházy 2008; Kleinstreuer et al. 2008) methods. However, the literature focusing on the special case of airway deposition of pollens is significantly less abundant. Although a relatively large number of experimental and clinical trial-based works on pollen deposition were published (Wilson et al. 1973; Michel et al. 1977; Guerico et al. 1980; Soler et al. 1982; Driessen and Quanjer 1991; Lewis et al. 1999; Martonen and O'Rourke 2002a, 2002b; O'Leary et al. 2005) there is, to the best of our knowledge, no study dealing with modeling airway deposition of large size range respirable pollens for various breathing modes. By the same token, although deposition of aerosol drugs in asthmatics has been addressed in a few simulation studies (Martonen et al. 2003; Longest et al. 2006), the authors of this work are not aware of any theoretical study concerning pollen retention in the asthmatic airways. Since there is experimental evidence that particle deposition in the airways may change dramatically during an asthma attack (Martonen et al. 2003; Chalupa et al. 2004), studies of pollen transport and deposition should address pollen retention in asthmatics as well.

The primary objective of this study was to use a computerized model of the human airways to characterize total, regional and generation-specific deposition of intact and fragmented pollens in the size range of 0.1–50 μm for different breathing modes in the case of healthy subjects and asthmatic patients. Furthermore, the work aimed to examine the effect of gender and age on pollen deposition. Finally, it attempted to contribute to the debate related to the increase in asthma attacks following thunderstorms (Murray et al. 1994; Bauman 1996) by providing useful information on lung deposition of intact and fragmented pollens.

Methods

For the modeling of transport and deposition of the inhaled pollens in the airways of healthy adults, the current version of the stochastic lung deposition model IDEAL of Koblinger and Hofmann was applied (Koblinger and Hofmann 1985, 1990; Hofmann and Koblinger 1992). The term “stochastic particle deposition” refers to the transport of inspired particles through a stochastic asymmetric lung structure by randomly selecting the sequence of airways for each individual particle and the application of stochastic modeling techniques, in this case the Monte Carlo method.

The currently used stochastic airway geometry is based on rigorous statistical analyses of the extensive morphometric data sets of bronchial (Raabe et al. 1980) and alveolar (Haefeli-Bleuer and Weibel 1988) airways. This stochastic lung morphology describes the inherent asymmetry and variability of the human airway system. The variability of airway diameters, lengths, branching and gravity angles, constrained by correlations among some of these parameters, is described

mathematically by probability density and correlation functions (Koblinger and Hofmann 1990). In agreement with the database of Raabe et al. (1980), in this model the bronchial airways contain both the bronchi and the bronchioli, starting from the trachea (as generation 1) and ending with the terminal bronchioles. The airway generation number of a terminal bronchiolus varies between 12 and 21. The airway structure is randomly selected by Monte Carlo techniques from the empirical distributions of geometric parameters of the Raabe et al. (1980) data. Similarly, the acinar airways start with the respiratory bronchioles, which have generation numbers between 13 and 22, and contain the alveolar ducts, the alveoli and the alveolar sacs. The maximum generation number, corresponding to alveolar sacs, varies between 18 and 33. In one region of the generation numbers (generations 13–21) one part of the airways is still bronchial but another part is already acinar. In this study, the joint bronchial and acinar airways are termed as lung or intrathoracic airways. For the simulation of particle transport through this stochastic lung structure, individual paths of inspired particles are randomly selected by Monte Carlo methods from mathematical functions. Flow splitting in an airway bifurcation between the two asymmetric daughter airways is assumed to be related to the peripheral air volume supported by each of the two daughter airways. Deposition of particles in a given airway generation is computed by analytical equations describing the average deposition of many particles in cylindrical airways due to inertial, gravitational and Brownian forces (Yeh and Schum 1980; Koblinger and Hofmann 1990).

In the oro- and nasopharyngeal region, particle deposition is computed by empirical equations derived from measurements in human volunteers (Yu et al. 1981; Stahlhofen et al. 1989). Due to the variability of the airway geometry and related flows, particle deposition may vary along different paths. Thus, penetration probabilities to a given airway generation, i.e., the probability of inhaled pollens to reach that airway generation, exhibits significant fluctuations, depending on the individual history of each particle in upstream airways. By simulating the random paths of many particles, typically of the order of tens of thousands, statistical means can be calculated for total, regional and generational deposition, providing also information on the underlying statistical distributions. The stochastic lung model was validated by comparison with the experimental total deposition data (Heyder et al. 1986; Schiller et al. 1988) for a wide range of particle sizes and breathing patterns.

The same mathematical model was applied in the case of women and children, but the airways were scaled down isotropically by the cubic root of the ratios of their functional residual capacities (FRC). FRC reference values, taken from the International Commission on Radiological Protection (ICRP66 1994) publication, were 3300, 2680 and 767 ml, characteristic of a healthy adult male, an adult female and a five year old child, respectively. Tidal volume (V_T) and breathing cycle time (BC) characteristic of different physical activities were derived from the same ICRP publication.

For the modeling of pollen transport and deposition in asthmatic airways, knowledge of both the specific breathing parameters and appropriate airway narrowing patterns is essential. To use as realistic as possible inputs, the authors collaborated with Dr Tamás Major of the Kaposi Mór Teaching Hospital, Hungary, who performed measurements on 50 asthmatic patients. Their measurements revealed that although tidal volume and breathing frequency values can vary from

person to person, an asymmetrical breathing pattern is most likely to characterize the breathing of asthmatic subjects during the asthma attack, and in many cases even between asthma episodes. In this study we proposed to simulate a severe asthma attack, characterized by 4500 ml functional residual capacity, 600 ml tidal volume, 35 min^{-1} breathing frequency and an exhalation time, which is twice as long as the inhalation time. Besides the uncertainties related to breathing parameters characterizing the asthma episode, there is a large intersubject scatter of airway narrowing rates depending upon age and gender, but intrasubject variability should also be noted. For the same person, both the average airway constriction and the distribution of narrowing rates throughout the bronchial tree may vary depending on the severity of an asthma attack. Based on the information retrieved in the open literature (Kraft 1999; Lutchen et al. 2001; Beigelman-Aubry et al. 2002; Samee et al. 2003; Tgavalekos et al. 2005; Venegas et al. 2005; Frey and Suki 2008; Kaminsky et al. 2008) and on measurement data concerning lung resistance and maximum inspiratory and expiratory flow provided by Dr Tamás Major, we have derived a hypothetical airway narrowing rate distribution.

Inhalability and airway deposition of pollen particles are influenced, among others, by their size and shape. Pollen grains come in a wide variety of shapes and sizes but most of them are nearly spherical. Pollen diameters cover a wide range from 6–100 μm , but most of them are between 20 and 50 μm . Table 1 presents the names and mean diameters of some common pollen particles gleaned from the published literature. Since pollen size is influenced by the measurement method applied, and/or by the water content of the pollen grains, the values in this table are only reference values. In addition, pollen size distributions vary from site to site and from year to year. The values in Table 1 refer to geometric and not the aerodynamic diameters, but this does not affect the simulation results, and even less the general trends. Thus

Table 1. Names and mean diameters of some widespread pollens.

Name	Latin name	Mean diameter (μm)	Source
Chestnut	<i>Castanea</i>	12	Feliziani (1986)
Paper mulberry	<i>Broussonetia papyrifera</i>	12.4	Kang et al. (2007)
Nettle	<i>Urtica</i>	14.5	Feliziani (1986)
Plantain	<i>Plantago</i>	17	Feliziani (1986)
Mulberry	<i>Morus</i>	14.5	Martonen and O'Rourke (2002a)
Willow	<i>Salix</i>	19	Feliziani (1986)
Sycamore	<i>Platanus</i>	19.5	Feliziani (1986)
Ragweed	<i>Ambrosia</i>	20	Cecchi et al. (2007)
Hazel	<i>Corylus</i>	20	Feliziani (1986)
Birch	<i>Betula</i>	25	Rantio-Lehtimäki et al. (1987)
Bermuda grass	<i>Cynodon</i>	27.1	Kang et al. (2007)
Pine	<i>Pinus</i>	100	Feliziani (1986)
Maize (corn)	<i>Zea mays</i>	78	van Hout and Katz (2004)
Oat	<i>Avena</i>	47.1	Joly et al. (2007)
Trefoil	<i>Trifolium</i>	42.5	Feliziani (1986)
Nut	<i>Juglans</i>	41	Feliziani (1986)
Hornbeam	<i>Carpinus</i>	36	Feliziani (1986)
Linden	<i>Tilia</i>	32.5	Feliziani (1986)

tracking of unit density spherical particles is a fairly reasonable approach. In this study, each particle deposition computation was performed for 10^5 inhaled monodisperse pollen particles in order to achieve statistically relevant results. The deposition of pollens was quantified in terms of deposition fractions. By definition, deposition fraction is the ratio of the number of particles deposited in a certain region of the airways to the number of particles entering the respiratory system.

Results and discussion

To study the effect of breathing mode on the airway deposition of pollens, inhalation by nasal and oral breathing routes during different physical exercises were studied. The resulting total airway deposition fractions are presented in Figure 1. The three specific flow rates in this Figure correspond to resting, light physical activity and heavy exercise breathing conditions. According to ICRP 66 (1994), most of the people breathe via the nose during resting and moderate physical activity and about half of the subjects continue breathing through the nose even during heavy exercise. However, in some special cases when, for any reason, nasal passages are narrowed or occluded, switching to mouth breathing is the most likely and logical option. Therefore, in order to reveal the general tendencies, mouth breathing was also considered in our simulations.

Due to the higher filtering efficiency of the nose, deposition fractions in the whole respiratory system are usually higher in the case of nose breathing than those computed for mouth breathing. In addition, total airway deposition fractions of large particles increase with increasing flow rate due to inertial impaction, the dominant deposition mechanism for large particles. In the case of smaller pollens or

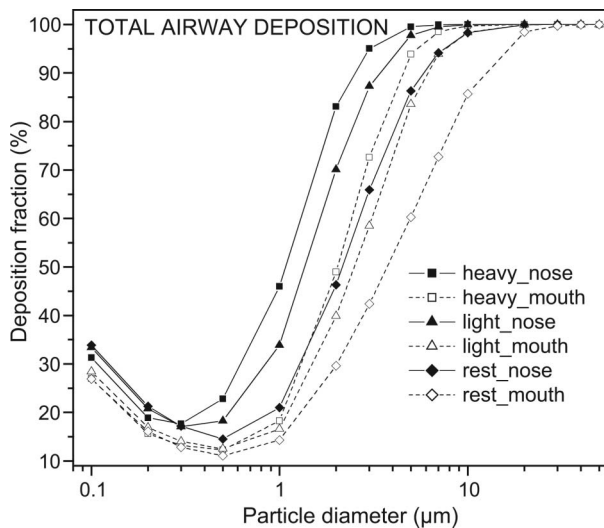


Figure 1. Total airway deposition fractions of pollen aerosols inhaled through oral and nasal airway passages in adult males during different physical activities as a function of pollen diameter. Breathing parameters: FRC = 3300 ml; resting: V_T = 625 ml, BC = 5 s; light physical activity: V_T = 1250 ml, BC = 3 s; heavy exercise: V_T = 1923, BC = 2.31 s.

tiny pollen fragments, say below $0.3\ \mu\text{m}$, lower flow rates result in higher deposition fractions due to Brownian motion.

As far as health consequences are concerned, regional deposition fractions provide more useful information than the total respiratory system deposition fraction. The type and severity of health disorders induced by the deposited pollens depend on the primary deposition sites. There is medical evidence that allergens filtered by the upper airways cause less severe effects than those depositing in the thoracic airways. Figure 2 depicts the upper and thoracic airway (lungs) deposition fraction curves computed for parameters characteristic of an adult man during resting.

Figure 2 demonstrates that while most of the pollen particles are too large to enter the lung, smaller pollens and pollen fragments can reach the lung and deposit there. Since the nasopharynx is a more efficient filter than the oropharynx, lung deposition is enhanced in the case of oral breathing for practically all studied particle sizes. It is worth mentioning that although the penetration probability of intact pollen particles into the deeper airways is not zero (see Michel et al. 1977 for experimental evidence) most of the pollen particles are too large to enter the lung (see Table 1 and Figure 2). This fact triggered a scientific debate concerning allergic reactions from the thoracic airways (especially seasonal asthma), namely, how can pollens cause allergic reactions in regions, which are not reached by them. It has been hypothesized that pollen asthma probably results from a gradual cumulative effect of deposition of small amounts of allergen in intrathoracic airways (Driessen and Quanjer 1991). At the same time, it is well documented in the literature that the number of asthma attacks can increase significantly after thunderstorms, although the rain should “wash out” the pollen particles from the air (Murray et al. 1994; Bauman 1996). For the explanation of this apparent controversy, detailed

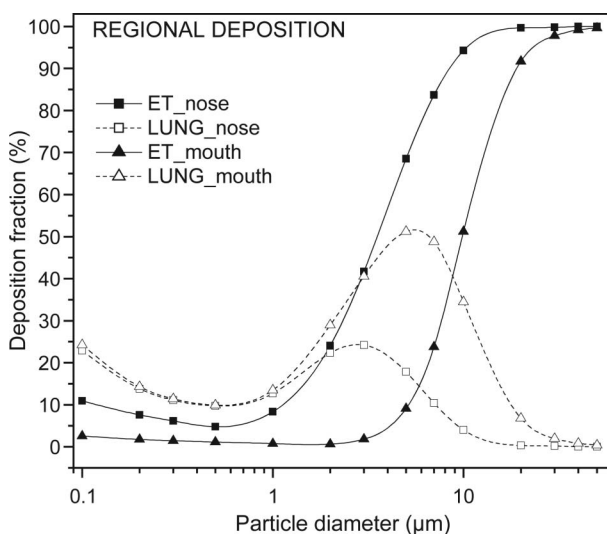


Figure 2. Extrathoracic and lung deposition fractions of pollen particles inhaled through oral and nasal airway passages in adult males during resting (sleeping) as a function of particle diameter. Breathing parameters: FRC = 3300 ml, V_T = 625 ml, BC = 5 s. No breath-hold is assumed.

investigations have been conducted concerning the effects of meteorological conditions on pollen release and transport and the possible synergistic effects of other environmental pollutants (Celenza et al 1996; Newson et al 1997). One of the proposed mechanisms responsible for the increase of asthma attacks following thunderstorms is related to the increase in the charge resident on pollen particles due to special meteorological conditions. Deposition efficiencies in the lower airway regions, where provocation of an allergic response is most likely, were found to increase with particle charge (O'Leary et al. 2005). Another possible explanation is related to the fragmentation of pollen particles. As described in the literature (Celenza et al. 1996) the persisting increase of humidity above 50–80% (for more than 2 h at 27°C), quick temperature drops, strong winds and increased electric activity together with a high pollen concentration can lead to significant fragmentation of pollens and release of cytoplasm, which contains allergens. These fragments have various dimensions, most of them with diameters smaller than 5 μm . At the same time, some data suggest that the smallest fragments are as small as 0.1 μm (Taylor et al. 2002). Figure 2 provides a useful contribution to the debate related to enhanced asthma attacks following thunderstorms, clearly supporting the hypothesis of fragmented pollens. It demonstrates that small size fragmented pollen particles may indeed penetrate and deposit in the lung. Since our model at its current stage does not consider electrostatic deposition, it does not support nor contradict the theory of enhanced lung deposition due to pollen charges.

Simulation results presented in Figures 1 and 2 refer to a healthy adult man, but upper airway deposition fractions are generally comparable for both men and women, for any breathing mode and particle size. To study pollen deposition in the lungs, airway generation-specific deposition fractions characteristic for men and women during resting and heavy exercise breathing conditions were computed. Since some people switch to mouth breathing during heavy exercise, both oral and nasal breathing modes were considered (see Figure 3).

Figure 3 demonstrates that deposition fractions characteristic of female and male subjects are slightly different. For smaller particles (0.1 μm and 1 μm) the deposition fractions are higher for males, while for large particles (10 μm) they seem to be the same during heavy exercise and slightly higher for women during resting. In spite of the differences mentioned above, it is clear that the general tendencies regarding pollen deposition are identical for men and women. Therefore, the general conclusions of Figures 1 and 2 remain valid for women as well.

Children are certainly at the highest risk due to environmental pollutants and allergens, and pollens are one of the most frequent triggers of asthma attacks. In Figure 4, bronchial deposition fractions for an adult man and a five-year-old child are compared for resting and sitting breathing conditions.

According to the deposition curves (rectangular symbol in Figure 4), deposition fractions are significantly higher for adults for all particle sizes below 7–10 μm during one breathing cycle, but if normalized to the same time interval, deposited fractions are higher in children for all particle sizes above 2–5 μm , depending on the physical activity (see the unit time deposition ratio curves marked with filled circles). Moreover, deposition fraction densities in children, defined below, are higher than those computed for adults for particles larger than 2 μm during resting and for all studied particle sizes during sitting (curves with filled triangles). Deposition fraction densities were computed by dividing the simulated deposition fraction values by the total inner surface area of the bronchial tree. Although the exact relationship

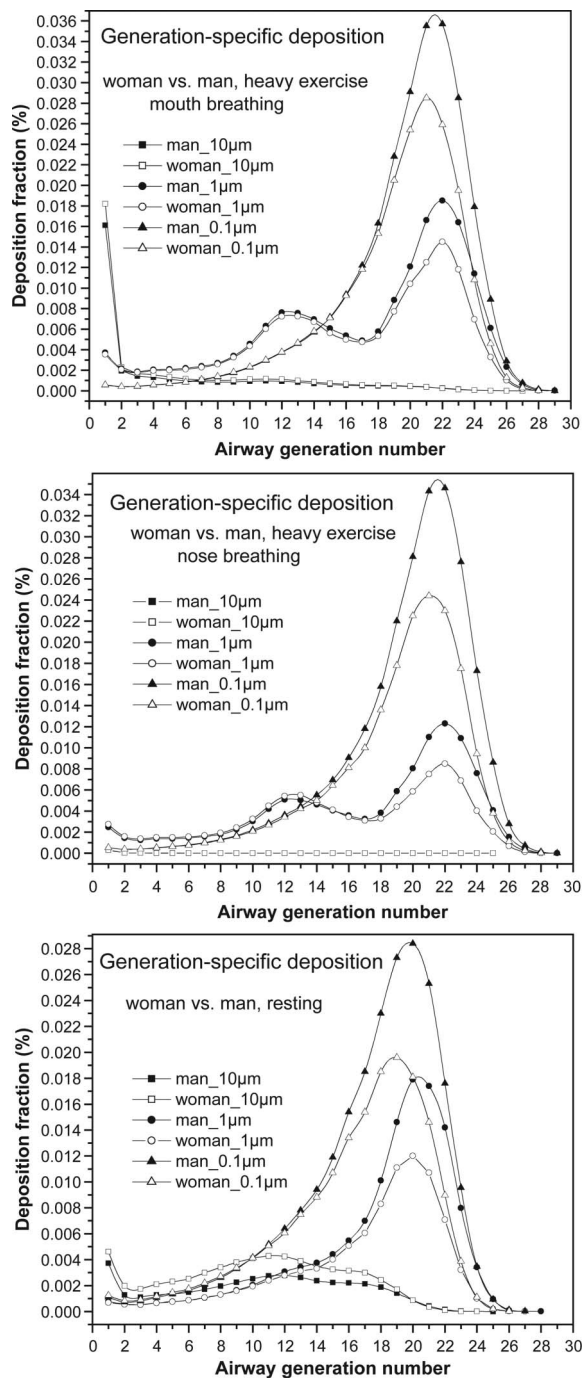


Figure 3. Airway generation-specific deposition fractions of 0.1, 1 and 10 μm particles inhaled by adult females and males during heavy exercise (upper and middle panels) and resting (bottom panel), without breath-hold. Breathing parameters: Woman, resting: $\text{FRC} = 2680 \text{ ml}$, $V_T = 444 \text{ ml}$, $\text{BC} = 5 \text{ s}$; woman, heavy exercise: $\text{FRC} = 2680 \text{ ml}$, $V_T = 1364 \text{ ml}$, $\text{BC} = 1.82 \text{ s}$; man, resting: $\text{FRC} = 3300 \text{ ml}$, $V_T = 625 \text{ ml}$, $\text{BC} = 5 \text{ s}$; man, heavy exercise: $\text{FRC} = 3300 \text{ ml}$, $V_T = 1923 \text{ ml}$, $\text{BC} = 2.31 \text{ s}$.

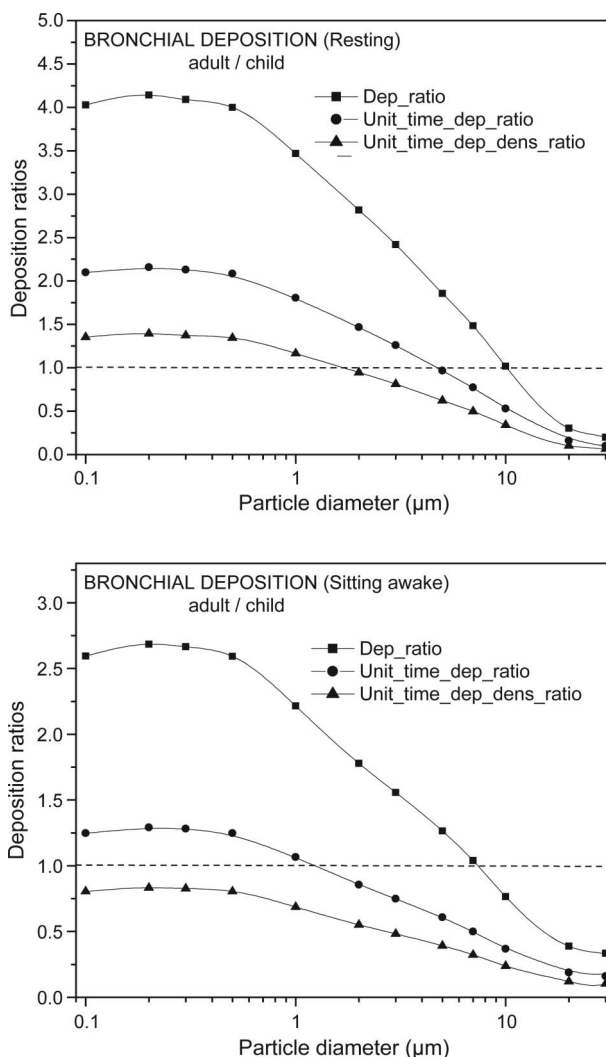


Figure 4. Ratios of deposition fractions, time normalized deposition fractions, and time normalized deposition densities of a healthy adult male and a five-year-old child as a function of particle diameter, during resting (upper panel) and sitting awake (bottom panel), assuming nose breathing, without breath-hold. Breathing parameters: Adult, resting: FRC = 3300 ml, V_T = 625 ml, BC = 5 s; adult, sitting awake: FRC = 3300 ml, V_T = 750 ml, BC = 5 s; child, resting: FRC = ml, V_T = 174 ml, BC = 2.61 s; child, sitting awake: FRC = ml, V_T = 213, BC = 2.4 s.

between primary pollen deposition and the related health effects cannot be simulated by the present model, it allows us to demonstrate that pediatric bronchi are more exposed to pollens than the bronchi of adults, especially during physical activities characterized by higher flow rates.

In Figures 1–4, which refer to healthy subjects, gender- (Figure 3) and age- (Figure 4) related differences in pollen deposition are caused by different airway geometries and breathing parameters, suggesting that changes in both airway geometry and breathing parameters during an asthma attack may also affect particle

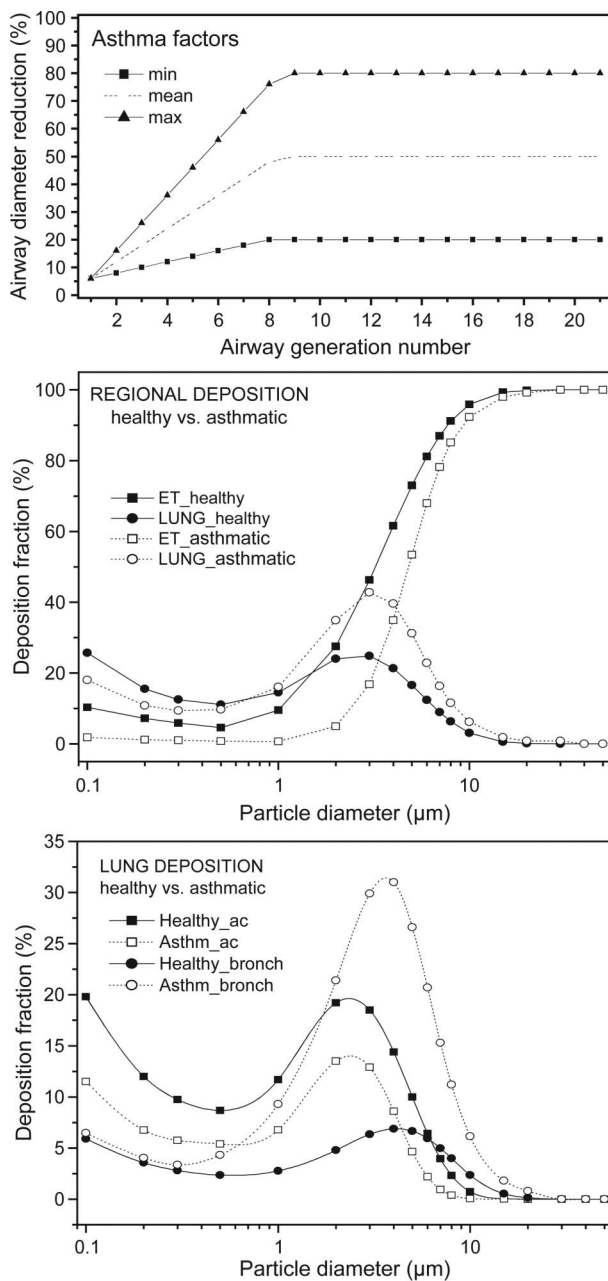


Figure 5. Bronchial asthma factors (upper panel), extrathoracic and lung deposition fractions (middle panel), and bronchial and acinar deposition fractions of pollens inhaled through the nose for healthy and asthmatic adult male subjects. Breathing parameters: Healthy subjects: $\text{FRC} = 3300 \text{ ml}$, $V_T = 750 \text{ ml}$, $\text{BC} = 5 \text{ s}$, nose breathing; asthmatics: $\text{FRC} = 4500 \text{ ml}$, $V_T = 600 \text{ ml}$, $\text{BC} = 1.71 \text{ s}$, with 0.57 s inhalation time and 1.14 s exhalation time, mouth breathing.

deposition. To evaluate and to quantify these changes, the deposition of inhaled pollens in the upper and thoracic airways in healthy and asthmatic subjects were compared with each other. Airway narrowing was bound by the two curves presented in Figure 5, upper panel. The asthma factor is a measure of airway constriction in percentage. For example, in the case of blocked airways, this factor is 100% and for a healthy airway it is 0%. Asthma factors are applied only to the bronchial airways. At each bronchial airway generation and for each individual particle trajectory calculation, the code randomly selects with the help of Monte Carlo techniques, an asthma factor value from a uniform distribution bound by minimum and maximum values. The applied minimum and maximum asthma factor values in each bronchial airway generation in this study characterize a severe asthma attack. These values are presented in the upper panel of Figure 5.

In the case of healthy subjects, the breathing parameters characteristic of adult males during sitting awake were applied. The middle panel of Figure 5 presents extrathoracic and lung deposition fraction curves characterizing healthy and asthmatic patients. The Figure reveals that deposition fractions in the upper airways of healthy individuals are systematically higher than those of asthmatic subjects, due to different breathing modes, i.e., nasal breathing in the case of healthy individuals and mouth breathing in the case of asthmatics. However, the difference is not significant for most of the intact pollens, which are trapped in the upper airways with a probability close to 100%. Regarding asthma, lung deposition is more important than extrathoracic deposition, therefore lung deposition fractions of healthy and asthmatic individuals versus particle diameter are plotted in the same panel. As mentioned above, large pollens have a small chance to reach the lung. Particles between 0.5 and 20 μm deposit more efficiently in the lung of asthmatics than in the healthy lung, while the opposite is true for the smallest particles. To find an explanation for the complex nature of the deposition, bronchial and acinar deposition fractions were computed (see Figure 5, bottom panel). According to the plot, bronchial deposition fractions increase, while acinar deposition fractions decrease during an asthma attack. Since the air velocity in the bronchi of asthmatics is higher than in healthy bronchi, bronchial deposition by impaction is enhanced in asthmatic patients. For smaller particles impaction is less important, thus the increase in deposition is less significant. Concluding from the results of Figure 5, deposition of most of the intact (large) pollens in asthmatic airways is not significantly different from their deposition in healthy subjects, but smaller pollen grains and fragmented pollen deposit more efficiently in the bronchial airways during an asthma attack and may thus cause further contractions. At the same time, aerosolized bronchodilators and inhalable steroids also deposit with a higher efficiency in the narrowed bronchi.

Conclusions

Our simulation results demonstrated that although the upper airways (especially the nasal passages) act as an efficient filter for most of the intact pollens, some smaller ones and fragmented pollen particles may penetrate into the thoracic airways and deposit there. According to our computations, fragmented pollens between 1 and 10 μm sizes have the highest probability to deposit in the lung, supporting the hypothesis that fragmented pollens are responsible for the increase in the number of asthma attacks after thunderstorms. Airway generation-specific deposition fractions

calculated for healthy women and men, although slightly different, were comparable for both nasal and oral breathing, for all flow rates, and for most of the pollen sizes. At the same time, bronchial deposition fractions computed in the pediatric airways, normalized to unit time and surface area, were systematically higher than the corresponding values of adult subjects, suggesting that children are the most exposed to the allergic effects of pollens. While bronchial deposition fractions increased, acinar deposition fractions decreased during a simulated asthma attack.

Although the results presented here may be slightly modified by the inclusion of more deposition mechanisms, such as electrostatic deposition and hygroscopicity, it is unlikely that the general trends observed in this study will be modified substantially.

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