

Review Article

Children's Inter-Individual Variability and Asthma Development

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Abstract:

Children of different ages vary in their response to environmental stressors due to their continuous development and changes in their bodies' anatomy, physiology, and biochemistry. Each age group of children has special biological features that distinguish their toxicokinetic and toxicodynamic characteristics from other age groups. The variability in responses extends to include children of the same age group. These intra- and inter- group differences in biological features explains the variability in responses to environmental exposures. Based on such differences in children's responses to exposures, adverse health outcomes and diseases develop differently in children. One of these diseases that are common in children is asthma. Asthma is a complex respiratory chronic disease that is multifactorial in origin. This paper discusses how variability in certain factors among children contributes to asthma occurrence or exacerbation, and links these factors to asthma in children of different ages. The importance of this review is to provide an insight on factors affecting asthma prevalence among children. These factors are usually overlooked in clinical or public health practice, which might significantly affect asthma management, and decrease the predictability of asthma detection measures. Therefore, keeping these factors into consideration can significantly improve asthma treatment and assist in asthma prevention amongst susceptible populations.

Key words: Toxicokinetics, Toxicodynamics, Genetic polymorphisms, Ventilation rates.

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Methodology

A literature review was conducted to identify factors that affect the variability in the occurrence and severity of asthma among children. All pertinent data in the literature, including review articles, original articles, and documents published by the U.S. Environmental Protection Agency (USEPA), and World Health Organization (WHO) is included in our search. Search engines used were google scholar, PubMed, and Web of Science. Statements used to search for potential publications include "Childhood asthma", "Childhood respiratory exposure", "child inhalational risk assessment", "asthma susceptibility". Only pertinent data in the literature were included in this review, and other information that is not directly related or is beyond the scope of this review was excluded.

Factors influencing asthma severity and occurrence among children

1. Age groups' variability

Childhood growth occurs over multiple stages. During each of these growth stages, children differ in regards to their physiological, biological, and behavioral features. Such differences demanded the consideration of age in the assessment of exposure levels and responses to environmental factors. In fact, children of different ages do not only differ in exposures' levels or responses, but also in their routes of exposure and sources of exposure. For instance: the habit of hand to mouth in the first two years of life, makes the oral route the major pathway of exposure in this age group. At the same time, indoor rather than outdoor exposures are the main source of inhalational exposures. That can be explained by the fact that children in this age group spend most of their time indoors. On the other hand, children who are 3-4 years old tend to play outside more often, which includes higher risk of outdoor dermal exposure from touching their surroundings. School age children have a relatively higher inhalational exposure risk from outdoor exposure because of increased physical activities. ⁽¹⁻³⁾

Therefore, an age-group classification based on the anatomic and physiologic development in children is needed when considering exposure and dose-response relationships. This classification can be better

outlined once these age-specific physiological and biochemical developmental aspects are explored. A definite classification might be difficult to determine because of rapid cell division and differentiation leading to continuous changes in physiological status in growing children. However, a broad classification is possible due to shared biochemical and anatomical characteristics at certain age stages. Such classification disregards some physiological and most behavioral changes, because otherwise, including many parameters in any classification will be difficult to study and analyze. A known classification was developed by the U.S. Environmental Protection Agency (USEPA); "Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants". ⁽¹⁾ It is as follows:

1. Birth – 1 year of age: Fast growth and weight gain, low oxygen that leads to high ventilation rate, rapid cell differentiation, low hepatic enzyme activity and incomplete maturation, as well as immature immune system.
2. 1 – 3 years of age: Almost complete maturity of the immune system, and higher function of hepatic enzymes.
3. 3 – 8 years of age: Complete and mature body systems, and stability in the body and skeleton's growth rate.
4. 8 – 16/18 years of age: High functionality and rapid growth of the reproductive and endocrine systems, and rapid musculoskeletal system growth.

Due to rapid cells division, differentiation, and maturation during a child's life, cells are more sensitive to several factors. Such factors include genetics, ethnicity, physical activity, body weight, socioeconomics, nutrition, education, geographical region, climate, and more. ⁽¹⁾ These factors influence body cells' growth, differentiation and maturation, and thus, making the whole body more or less vulnerable to environmental exposures by changing the body's pharmacokinetics (absorption, distribution, metabolism, and elimination) for any chemical or compound. This vulnerability means that for each age group, there is a wide variability in exposure and response due to these factors. It can be a daunting task to count for such variability in

each age group. Because of that, exposure assessments for children in each group is different, and there are some individuals in each age groups who are more sensitive than others. ^(1, 2)

2. Variability in Toxicokinetics and Toxicodynamics

Toxicokinetics (TK) is the process of absorption, metabolism, distribution, and elimination (ADME) of a certain chemical in the body. TK data for children is scarce, and TK variability information will be even harder to interpret or validate. TK in neonates and children is complicated if a judgment about their susceptibility to toxicants has to be made based on the TK of these toxicants. ^(4, 5) TK characteristics in children either increase or decrease their susceptibility following exposure to toxic chemicals. When breaking down the TK process into its four composing components: Absorption, Distribution, Metabolism, and Elimination, and describing them within children's physiological features, the reasons behind the complexity of the judgment become clearer. However, since asthma is a respiratory disease, it is important to consider ADME more within the boundaries of the respiratory system physiology, because the physiology of organs is different, and so is ADME. The description of ADME in the respiratory system of children is as follows:

- *Respiratory absorption*

Children of different ages have different respiratory volume per surface area. ⁽⁶⁾ This alters their exposure levels by affecting the deposition rate of any air pollutant. The difference of lung volume to its surface ratio between adults and children, leads to approximately two fold increase in respiratory exposure in young children compared to adults. ⁽⁴⁾

- *Respiratory distribution*

Distribution of chemicals in the body relies on the body's water and lipid composition, because chemicals are either hydrophilic or lipophilic in nature. Neonates usually have more water, less lipid, and less binding proteins in plasma than older children and adults. Less binding proteins in blood offer fewer binding sites for toxicants. This might be good for neonates since less binding sites result in more free chemicals in the plasma, and this decreases the systemic toxicity of a

chemical. ⁽⁴⁾ More water and less lipid composition offer smaller storage areas for lipophilic chemicals. Thus, chemicals of lipophilic affinity have lower burden in a child's body, and their possibility for toxicity becomes lower. ⁽⁴⁾

- *Respiratory metabolism and elimination*

Children, especially younger ones, have immature metabolic and renal clearance capacity. ⁽⁵⁾ The liver is the place where metabolic enzymes are formed, reside, and act. Cytochrome P450 is a major group of enzymes responsible for most of metabolic and detoxification actions in the liver. Other enzymes are also involved in such actions, including estrases, hydroxylases, carboxylases, hydrolases, sulfur transferases, and more. Some of these enzymes have a fetal form, while others are not completely mature until the age of six months, ⁽⁵⁾ and therefore, complete metabolism might not be available in neonates all the time.

The kidney doesn't function well in eliminating undesired material until weeks or even months (usually six months) after birth, probably because of incomplete maturation of renal glomerular filtration and tubular secretory functions. ⁽⁴⁾ After birth, kidney and liver enzymes start to increase in activity, and after the age of six months, some enzymes might be more active than those of adults. The higher enzymatic activity leads to higher metabolism and shorter half-life of chemicals compared to adults. ^(5, 7) It is crucial to understand that immaturity of metabolizing enzymes, and the lower capacity of renal clearance in young children and neonates lead to either less or more metabolism, thus, less or more detoxification. Such fact enhances or suppresses the toxic effects of a compound depending on where the toxicity of a compound exists; in the parent compound or in the metabolites.

Differences in TK between children and adults can provide information on the level of toxicity of certain chemicals in children compared to adults. Differences in TK do not exist only between children and adults, but also exist among children themselves. Variability among neonates in TK results in an uncertainty factor in risk assessment equal to or greater than 3.16, which is the default level of uncertainty used in adults. ⁽⁷⁾ The wide

variability in children's genetics, nutritional status, health conditions, and growth rates leads a substantial number of children in each age group to lie beyond the half-log TK variability range normally used in adults. ⁽⁵⁾ This changes the children's uncertainty factor to be higher than adults, which therefore, requires a new uncertainty factor for children. ⁽⁸⁾

Variability in TK among children is mainly based on information regarding individuals' enzymatic activity, organs' systems biology, and general physiological development during different life stages. ⁽⁹⁾ Each of these factors are important to form a variability TK framework for children, but not before understanding how children differ in such factors. ⁽¹⁾ Enzymatic activity is mainly affected by polymorphisms, while organs' systems biology and physiological development depend on the integration of genetic, nutritional, behavioral, and environmental factors. ⁽¹⁰⁾ These factors differ from one individual to the other, and therefore, TK varies among individuals. Toxicodynamics (TD) relates to the interaction of a chemical with a cellular or a biological compartment in the body, and the biological effect produced from this interaction. Based on physiological and TD differences among individuals, children express different biological responses and clinical manifestations.

3. The effects of genetics on asthma susceptibility

- *Etiology*

Differences in genetic formations in a population are linked to the development of certain diseases, especially diseases known to exist among the same family members. The existence of asthma in certain families compared to others supports that genetic predisposition might have a role in asthma development. Indeed, some epidemiological and immunological evidence in studies conducted during the last few decades show the influence of genetics on the development of asthma. Epidemiological studies show an environmental as well as a genetic component in asthma etiology. Studies on monozygotic and dizygotic twins were the corner stone for such conclusions. Some studies showed that monozygotic and dizygotic twins have asthma developed due to similar genetic skeleton,

which carried out the emergence of asthma in a comparable way in each twin individuals. ⁽¹¹⁻¹⁶⁾ Other studies on monozygotic and dizygotic twins noticed the necessity of an external insult to promote asthma occurrence. These studies indicated that an interaction should exist between the environment and different genetic variants to develop asthma. ^(14, 16-19) Immunological evidence is mainly characterized by twin studies that used IgE measurements, as an immunologic factor with a good genetic indication. ^(20, 21) The genetic component of IgE levels exhibits itself mainly as an autosomal-recessive inheritance pattern, and not as a Mendelian pattern. This was discovered during the process of IgE segregation, conducted on many families involved in the analysis. ⁽²²⁻²⁷⁾

Advances in genetic testing continued to reveal some of the obscurity surrounding the etiology of many diseases, including asthma. Understanding genetic components of certain diseases helped to know more about the complexity of these conditions. After two decades of cloning genes related to asthma, six genes have been identified as novel genes for asthma. These genes play a key role in asthma occurrence. ⁽²⁸⁻³²⁾ Subsequently, more genes have been identified as having a role in asthma occurrence. One study identified over 100 polymorphic genes related to asthma after reviewing about 500 papers. Among the identified genes, 64 were found to have had a positive association by at least one study, and among these 64 genes, 42 genes were replicated in two or more studies. ⁽³³⁾ Some of the studied genes are linked to environmental exposures (*CD14*, *TIM1*). They are activated when an exposure to an environmental stimulator occurs. ⁽³⁴⁻³⁶⁾ More recently, additional susceptible loci have been identified in many other studies, indicating that genetics are deeply rooted in asthma and asthma-related phenotypes. ⁽³⁷⁻⁴⁰⁾ While the majority of genome-wide association studies were conducted on people of European origins, ⁽⁴¹⁻⁴³⁾ some studies included other populations and identified susceptible loci related to asthma. These studies included asthma patients from African American origins, ⁽⁴⁰⁾ Puerto Rican origins ⁽⁴¹⁾ and Mexican origins, ⁽³⁷⁾

- *Susceptibility and response*

The chronic inflammatory process, which precedes the development of asthma,

includes many structural and functional changes in the lung, which remodel the lung shape and capability. The inflammatory reaction involves numerous cellular and mechanical components participating throughout the whole process. Inflammatory cells include mast cells, eosinophils, neutrophils, macrophages, and T-lymphocytes. In addition, specific inflammatory mediators are involved in the process, which include interleukins, leukotriene, cytokines, and interferons. Variations in the function of the inflammatory cells or mediators exist among individuals. Genetic polymorphisms in any of the inflammatory factors can contribute to the increase or to the decrease of a function during an inflammatory reaction, and therefore alter an individual response. ^(22, 44-50)

Other potential contributors to genetic polymorphisms are changes in lung growth factors or their regulators, which in turn affect the way remodeling happens. ⁽⁵¹⁻⁵⁴⁾ Lung remodeling is also affected by variations in the lung's defense system. Some studies showed that glutathione or glutathione transferase allelic variations could alter the response of the lung to inflammatory stimuli. Thus, increase the lung sensitivity during development, which contributes to lung remodeling. ⁽⁵⁵⁻⁶¹⁾

The different clusters of genetic variations have a wide range of interactions with environmental exposures, which might increase or decrease the likelihood of asthma development. ⁽⁶²⁾ Such phenomenon was observed in volunteers who responded differently following their exposure to ozone gas in closed chambers. Authors of these studies provided an explanation that genetic polymorphisms exist among individuals, which caused different responses to ozone. ⁽⁶³⁻⁶⁵⁾

4. The effects of nutritional variability on asthma

Normal body development and maintenance of good health rely on a balanced and an appropriate nutrition. Imbalanced or insufficient nourishment have detrimental effects on children's health, which predisposes disease development. Children with malnutrition do not only have slower growth, but also lack a sufficient and a complete self-defense system, and possess an ineffective metabolism. ⁽⁶⁶⁻⁷²⁾

Prenatal well-balanced nutrition is as important as postnatal. Anemia that results from protein insufficiency in a pregnant mother negatively affects the child's growth and development. Anemia is a global problem affecting two billion people, and accounts for 20% of perinatal mortality, which mainly resulted from iron deficiency. ⁽²⁾ Iron deficiency in children causes several health issues including anemia. Anemia produces higher cardiac and inhalation rates, thereby affecting the lung's absorption and deposition rates of air pollutants. ⁽⁷³⁾

Numerous dietary components have been linked to asthma. Some studies observed a relationship between asthma and anti-oxidants in fruits and vegetables. Fruits are a good source of vitamins, like Vitamin C, which helps improve lung function and ameliorate the symptoms of asthma. ^(74, 75) Vitamin E, which is found in fruits, decreases IgE levels in plasma and therefore, lessens the inflammatory reaction in asthma. ⁽⁷⁶⁾ The positive effects of certain nutrients is not exclusive to Vitamins C and E, but also other elements like carotenoids, selenium, polyphenols, vitamin D, and zinc. All of these beneficial elements are linked to asthma enhancement. Some studies showed that deficiency in these elements is related to asthma exacerbation. ⁽⁷⁷⁾

Many studies support the positive effects of fruits and vegetables in the control of asthma. A meal of more vegetables and/or fruits and less saturated fatty acids is more beneficial for an asthmatic patient. Some studies that were conducted in different Mediterranean countries showed how contents of a meal affect asthma status. Two studies in Spain ^(78, 79) revealed the pleasant and mollifying effects of Mediterranean food on asthma. In agreement with the findings of these two studies, other studies found similar results, one done in Crete ⁽⁸⁰⁾ and the other one in Mexico. ⁽⁸¹⁾ The reason for this positive effect is the high fruits and vegetables contents in the Mediterranean diet and the low saturated fatty acids from animal sources. Other studies examined the effects of an opposite diet composition, low fruits and vegetables, on pulmonary function. The conclusion for one of these studies was a reduced lung function for children aged 9 to 11 years. ⁽⁷⁵⁾

Fast food is suggested as a factor that contributes to increased asthma prevalence,

⁽⁸²⁾ and may weaken the protective effect of breast-feeding on reducing asthma occurrence. ⁽⁸³⁾ Trans-fatty acids from ground meat, meat from ruminated animals, and industrially hydrogenated vegetable oils, can worsen wheezing in asthmatic children, and exacerbates asthma overall. ⁽⁸⁴⁾ It would be prudent to consider nutritional factors in asthma management, especially for those who have frequent asthma attacks.

5. Variability in respiratory function among children

The function of the lung varies among children because of difference in age, physiology, physical activity, body weight, and genetics. The lung continues to increase in size and change in structure after birth. Many factors can affect a growing lung by affecting its capacity or its function. Such factors might be internal or external. Internal factors include genetics, age, body weight, physical activity, and the general health status of the body. External factors are mainly nutrition, and chemical and non-chemical environmental stressors.

Intra-species differences (differences among individuals of the same species in certain characteristics) in ventilation rates was first described by the USEPA in 1997. ⁽⁸⁵⁾ The USEPA released a handbook titled "Exposure Factors handbook". In this handbook, the USEPA adapted a method, previously developed by Layton in 1993 to describe the ventilation rates at different age groups. This method considered "ventilatory equivalent" to differentiate ventilation rates of different individuals. Ventilatory equivalent is the ratio of ventilation to oxygen intake. A major limitation in this methodology relates to factors that result in differences among individuals in the values of "ventilatory equivalent". Differences in "ventilatory equivalent" refer to differences in metabolic and oxygen uptake efficiency, which are affected by the lung structure and physiology. ⁽⁸⁵⁾

Subsequently, the USEPA developed another methodology different from Layton's methodology. This newer methodology facilitates the calculation of "ventilatory equivalent" directly from oxygen consumption rate. The description of the methodology is found in the "revision of the metabolically-derived ventilation rates" within the "Exposure

Factors Handbook" of 2006. ⁽⁸⁶⁾ The handbook describes an approach examining the variability of ventilation rates in individuals based on age, gender, and metabolic rate differences. Oxygen consumption rate used to extract "ventilatory equivalent" was estimated by measuring "Metabolic Equivalent Task (MET)" and "Basal Metabolic Rate (BMR)". MET is the ratio of energy consumed during physical activity to the energy needed for life sustenance. Estimation of MET helps to estimate ventilation rate. On the other hand, BMR is the energy consumed at rest. USEPA used this approach to test data taken from 1999-2002 NHANES and CHAD national studies. ⁽⁸⁶⁻⁸⁸⁾ NHANES – National Health and Nutrition Examination Survey – database has records for 19,022 individuals, while CHAD – Consolidated Human Activity Database – has records 23,000 individuals including location, time, and activity. The assessment shows that young children have higher ventilation rates than adults after adjustment for body weight. Ventilation rates keep changing after birth until the child reaches adulthood. Most of the changes of ventilation rates occur between the ages of 5 to 15 years. For example, a one-year old child has an adjusted ventilation rate of about 1.2 m³/kg-d, while a 41-51 years old adult has an adjusted ventilation rate of 0.24 m³/kg-d. This five-fold difference in ventilation rate can increase to reach six-fold difference if the child age is less than one. This approach of the EPA also showed a variation in ventilation rate by some factors, such as age and activity level, but not by gender. Comparing EPA assessment with Layton assessment indicates a difference in the assessment for younger children. Both assessments were consistent for children above 6 years of age, but were different for children below 6 years of age. ⁽⁸⁶⁾

Variations in ventilation rates among children affect their lungs' affinity for particulate matter's deposition. Among different children examined for the ratio of particles they exhale to particles they inhale (deposition fraction), the tidal volume was the main factor for variation in deposition fraction. ⁽⁸⁸⁾ In addition, children at resting state had greater normalized deposition rate than adolescents and adults, when grouped together, by 35%. ⁽⁸⁸⁾ Findings revealed that tidal volume was highly correlated with deposition factor when analyzed with the consideration of other

variables; age, height, and body mass index (BMI). The correlation between tidal volume and deposition factor was ($r=0.79$) and BMI was the best predictor for tidal volume compared to age and height. ⁽⁸⁹⁾ BMI was also a factor in deposition rate. Results by Bennett and Zeman (2004) showed that overweight children had 2.7 times higher deposition rate than those with normal weight and below. The correlation between BMI and deposition rate was $r=0.46$. ⁽⁸⁹⁾

The information provided by the analysis of the EPA approach for the variability of ventilation rates among individuals is useful, along with Bennet and Zeman (1998, 2004) findings on the relations between deposition rates, tidal volume, and BMI. Activity level, age, BMI, and tidal volumes were important factors of ventilation rates. Gender was not a factor for differences in ventilation rates.

6. The effect of residential history on inter-individual susceptibility

Children living in different areas are exposed to different kinds of exposures. Exposures including chemical exposures do not only exist outdoors, but also indoors. Both indoor and outdoor exposures affect children's health and might cause diseases.

For any exposure, distance to the source of contamination is a key factor in the magnitude of exposure. In addition, different areas have different kinds of contaminants. For example, agricultural areas are commonly contaminated with pesticides and fertilizers' residuals, which is found in soil, water, air, and biota. Therefore, children living close to agricultural areas are more susceptible to such chemicals. Further, different regions might have different kinds of exposures. For example, areas of a thinning layer of ozone produce a relatively higher risk to Ultra Violet (UV) radiation exposure. This kind of exposure exists in Chile and New Zealand. ⁽⁹⁰⁾ Other examples are areas contaminated with metals in soil or water, fluoride in water, or radon from natural resources with radium in soil, which increases risk to diseases produced from exposures to these materials. ⁽⁹¹⁾

Dose-response relationships and exposures' assessment should not be the same for children who reside in recently contaminated areas and those living in areas that are contaminated for a long period.

Chronically exposed children have altered susceptibility to chemicals because of the structural and functional changes that happen to their bodies over the years. A pre-existing damage will make the body fragile and more susceptible to any further exposure.

Therefore, the geographical residence is very important when comparing exposure in two groups or two individuals. Twin studies show that environmental factors can be more important than genetic factors in health outcomes. The findings of these studies concluded that the environment modifies the epigenetics of an individual, and thus, result in an altered responses or health outcomes. ^(92,93) Epigenetic modifications change the individual susceptibility to environmental stressors. However, formation of such susceptibility during a person's life is believed to be more dominant and influential during cells division, differentiation and maturation. ^(92, 94-99)

Conclusions and significance to public health

The variability among children in their response to environmental stressors and in expressing health outcomes is explained by their continuous development during childhood. In addition, children of the same age are impacted by other factors affecting their expression to chronic diseases, as noticed in asthma. These factors include nutrition, genetics, respiratory system susceptibility, and residential history. These factors do not only influence asthma occurrence, but also the frequency and severity of asthma attacks and exacerbations. Special considerations to these factors are important in asthma management at the individual and public levels.

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