Session 3 Asthma and allergy

Asthma and allergies: The role of the home environment

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BACKGROUND

The incidence of asthma and allergy has increased throughout the developed world over the past forty years (1). The incidence is much higher for children than adults. From being a relatively uncommon disease, a few decades ago, allergies today, in many regions, are affecting a large part of the population. The European Allergy White Paper (1997) noted that with the exception of AIDS, only few diseases, besides allergies, have increased two- or three-fold within a short time (2). Allergic diseases are supposed to be caused by a complex interaction between genetic and environmental exposures. The temporal trends in allergy prevalence, the differences in the risk of allergy between urban and rural populations of the same ethnicity and the short time period for which the prevalence of allergic diseases have increased, indicate that changes in environmental exposures rather than genetic factors are the most likely explanation for the increase (3, 4).

But, what changes in environmental exposures are important for the increase in allergies?

In the search of causative factors it's important to note that small children are particularly at risk. Thus the exposure during pregnancy and first years of life seems more important than exposure later in life. Children have a higher metabolism and faster respiratory rate compared to adults resulting in higher intake of food, drink and air per unit of body volume, i.e. higher dose which is further enforced by their hand-to-mouth behaviour. The exposure (in mass) during pregnancy is defined by the exposure of the mother, while the exposure of babies mainly consist of indoor air (around 80%), and food, mainly breastmilk. In developed countries more than 50 % of the total exposure (in mass), during a 70 year life consists of air in the home, while outdoor air, food and liquids, and industrial air stands for around 7% each. The rest of the exposure is air in schools, day care, offices, and during travelling.

This review is based on multidisciplinary state-of-art reviews of the scientific literature on associations between indoor exposures and asthma and allergies (6, 7, 8, 9), and on results from two ongoing studies in Sweden and Bulgaria, DBH, and ALLHOME. The studies in Sweden and Bulgaria are basically identical, starting with a cross-sectional questionnaire study on small children, allergic manifestations and home environmental factors. The second step has been nested case-control studies including clinical examinations, inspections and environmental measurements.

CAUSES OF THE INCREASE IN ASTHMA / ALLERGIES

Even if genetic change is not the cause of the increase, **genetic predisposition** is an important factor for the risk of getting asthma and allergies. In a questionnaire study of 1,325 children, 7 years of age, Kjellman (10) observed the highest prevalence of atopic disease among children of parents with an identical type of atopic disease (with 72% risk), and the lowest among children of parents without an atopic disease (10% risk). Small boys have a higher prevalence of atopic diseases than small girls, but this changes during puberty.

As allergy means that a person reacts to an **allergen** (e.g. from cat, dog, pollen, mite, mould, cockroaches, specific food etc), the most simple explanation for the increase should be that we are exposed to more allergens today. Even if there are indications of increased allergen levels from mites and moulds (due to tighter, less ventilated, and thus more humid, buildings in northern climate), and, perhaps more pet contacts, there is no scientific data showing that this is an important factor behind the increase in allergies, worldwide.

If the allergen levels can not explain the increase, there must be other environmental changes that are the cause. Either our immune defence is changed (due to e.g. lack of microbial exposure), so that we react to harmless proteins, allergens, more than before (the hygiene hypothesis), or some other exposure (adjuvant factors) makes us more vulnerable (mechanisms not known) for exposure to allergens.

The **hygiene hypothesis** involving factors like family size and number of early infections is, by far, the most popular, discussed and studied explanation for the rising trends in allergy and asthma. It (11) suggests that exposure to infections early in life influences the development of a child's immune system along a "non allergic" pathway, leading to a reduced risk of asthma and other allergic diseases. However, despite numerous studies, (including up to 100 published state-of-the-art reviews), the area is controversial. E.g. the hypothesis does not fit for USA, where the allergy prevalence is very high among children in inner cities (Harlem.), where an increased hygiene is most certainly not a problem The summary of the state-of-the art reviews is that there is very little, if any, consistent evidence for this hypothesis.

If changed hygiene can not explain the increased morbidity, what about new environmental exposures?

Some **outdoor** exposures, such as ozone, nitrogen dioxide, sulphur oxides and particulate matter are known to exacerbate asthma (12, 13, 14, 15, 16). In Bulgaria, Lubomirova et al. (17) reported a higher prevalence of respiratory and allergic diseases among children exposed to air pollution (organic solvents) from refinery and petrochemical plant compared to control children. Outdoor air also constitutes a main source of exposure to air-borne allergens, such as ***pollen*** from plants and ***moulds***. However the role of outdoor air pollution in causing asthma remains controversial (ATS, 2000 (18)). E.g. the prevalence of allergic sensation was three times higher in low polluted Sundsvall (Sweden) than in Konin (Poland), where the levels of common industrial pollutants, SO_2 and smoke particles were much higher (19). In a review of the evidence regarding the link between environmental exposures and the prevalence of asthma, Etzel (3) concluded that outdoor air exposures are not likely to cause the increase in asthma prevalence.

Diet (20), lack of **breastfeeding** (21), **less physical activity** (22) and **obesity** (23) are factors discussed as possible causes behind the increase in asthma/allergies. It is shown that breast-feeding has a protective effect. Otherwise there is no good scientific data behind these ideas.

INDOOR AIR

The air indoor comes from the air outdoor. Outdoor air contains pollutants that are present due to e.g. traffic, soil, vegetation (pollens) and industries. Inside the room, the air receives further contaminations from people, animals, furniture, furnishings and building materials, cooking, vacuum cleaning, combustion processes and smoking as well as from cleaning products, microbial growth, etc.

In two multidisciplinary reviews on moisture related problems in buildings (dampness) and associated health effects it was concluded that **"dampness**" do increase the risk for several health effects such as asthma and allergies, sick building syndrome and airway infections (7, 8). Identified health relevant moisture problems were e.g. visible mould and damp spots, detached or miss-colored flooring materials, condensation on inside of window panes, flooding and bad odor. However, the literature did not show what dampness related exposures that were responsible for the health effects

The results from the DBH and ALLHOME studies are well in line with earlier major studies on dampness and health. In both studies strong and consistent associations were found between moisture related problems indoor and symptoms among children. The risk for symptoms was more than doubled for children living in a home with self reported "dampness" (24, 25).

In Sweden **visible mould or damp spots** were reported from the index child bedroom in 1.4% of homes compared to 35% in Bulgaria. In general no association was found in Sweden between health effects and type of mould, a mouldy odour in the room, glucan, ergosterol, and mVOC. However an association between symptoms and Penicillium in dust, and a strong dose-response relationship between rhinitis and

eczema and inspectors perceptions of a mouldy odour along the skirting board (28). Results from Bulgaria are pending analyses.

The Nordic interdisciplinary review, NORDPET (5), concluded that **pet** exposure in infancy increases the risk for sensitization (OR 1.0-1.5). Pet keeping as a risk factor for asthma and wheezing in children was also reported in the review by Apelberg et al. (27). However, in a study by Lau et al. (28) no relation was found between early indoor pet allergen exposure and prevalence of asthma, wheeze, and bronchial hyper-responsiveness. In a number of studies (28, 29, 30) an inverse relationship between early pet exposure and allergic diseases later in life has been found, suggesting a "protective" effect of pet keeping. Such inverse associations between current or early life pet ownership and symptoms are, however, mainly due to avoidance behaviour in the families (31, 32), i.e. a "healthy pet keeping" effect. In Sweden where a number of information campaigns to the general public, about risk factors for asthma and allergies, there is a strong "protective effect" of pet exposure, while in Bulgaria with no such campaigns, there is no "protection" from pet keeping. Meaning, in countries with a good knowledge about the risk for allergies related with pets, families with allergies tend to get rid of pets, while that is not the case in countries without such public knowledge.

Reduced ventilation rates means increased concentrations of building related pollutants, including moisture. Only few studies on the association between health effects and ventilation rates in homes have been reported (e.g. 36, 37, 38). Oie et al. (33) found that the risk of bronchial obstruction not directly was associated with the ventilation rate in the homes, but that the risk associated with e.g. dampness was greatly increased in homes with a low ventilation rate. Emenius et al. (34) reported that air change rate and type of ventilation system did not affect the risk of recurrent wheezing. However, in a study by Bornehag et al. (35) case children had significantly lower ventilation rates at home than controls and a dose-response relationship was indicated. An important difference between these studies are that the ventilation rate in the study by Emenius et al. are reported to be about the double of that in the study by Bornehag et al. The literature on HDM (36, 37) indicates that inadequate ventilation in homes in cold climate constitutes a major risk factor for infestation of mites and subsequent health effects.

It is well established that ventilation rates in homes in northern Europe have been reduced during the last decades, as a result of energy conservation measures. About 60% of the multi-family houses and about 80% of the single-family houses in Sweden (38) and 36% of all residences in Oslo, Norway (33) had lower than 0.5 air changes per hour.

Indoor smoke from solid fuels (38) and environmental tobacco smoke (39) are significant triggers for asthma symptoms and attacks. The situation with regard to smoking is totally different between Sweden and Bulgaria. In Sweden smoking among pregnant women is rare, and "no one" smokes in a room with a baby, while in Bulgaria 31% of the pregnant women were smoking, and 73% of the children had at least one family member smoking. Smoking is a risk factor for asthma in both countries, but much more pronounced in Bulgaria. Especially a mother smoking during pregnancy, and first year of life of the child were significantly associated with most of the health effects among the children. Adverse effects of both pre- and

postnatal parental smoking on children's respiratory health were recently confirmed by Pattenden et al. (40). Asthma was most strongly associated with maternal smoking during pregnancy, but postnatal exposure showed independent associations with a range of other respiratory symptoms.

CHEMICAL EXPOSURES INDOORS

The home environment has changed considerably during the past 3-5 decades because of the introduction of new building technology, as well as new building materials. Some new surface materials are emitters of chemical compounds with potential allergic properties.

Commonly measured **VOCs** have not been strongly and consistently associated with asthma/allergies. There is, however, some epidemiological evidence for associations between **phthalates** or plasticized products such as PVC and allergic symptoms in the airways (e.g. asthma), nose and skin. Jaakkola et al. (41) found that the total area of PVC surface materials in homes was associated with development of bronchial obstruction in small children in Norway. In another study from Finland lower respiratory tract symptoms, like persistent wheezing, cough and phlegm in children, were associated with the presence of plastic wall materials, while upper respiratory tract symptoms were not (42). Also the relative risk estimated for pneumonia, bronchitis and otitis media were slightly increased in the presence of plastic wall materials. In the first phase of the Swedish DBH-study it was found that PVC as flooring material in combination with moisture problems in the floors was associated with e.g. asthma among children aged 1-6 years (48), the same is valid for Bulgaria. Furthermore, in the second phase of the DBH-study a strong dose-response relationship was found between asthma and di(2-ethyl-hexyl)-phthalate (DEHP) concentration in indoor dust and between eczema and rhinitis and butyl-benzyl-phthalate (BBzP) (43). Oie et al. (1997) (33) elaborated possible mechanisms of respiratory effects by inhalation exposure and concluded that deposition of DEHP in the lungs may increase the risk of inflammation in the airways which is a characteristic feature of asthma. In a population-based incident case-control study among adults (21-63 years), Jaakkola et al (2006) (45) reported that the use of self leveling compounds at home during the past 12 months was a determinant of onset of asthma. They also found that the risk of asthma was significantly related to the presence of plastic wall materials at work. Reviewing existing literature, Nielsen et al (2006) supported the hypothesis that some phthalates may act as adjuvants (46). An adjuvant effect of phthalates for sensitization to common allergens was tested by Glue et al. (2005) (47). None of the phthalates tested was found to induce histamine release per se, however, higher histamine release was observed when the cells first were treated with phthalates and then exposed for allergen. Lee et al. (48) reported that DEHP and DINP (di-isononyl phthalate) enhance allergic responses by enhancement of IL-4 production in CD4+ T cells via stimulation of NF-AT-binding activity which is in line with the discussion in the paper by Chalubinski et al. (2006) (49).

The sources of phthalate esters indoor are ubiquitous plasticized polyvinyl chloride (PVC) materials (floor and wall covering materials), shower curtains, adhesives, synthetic leather, toys, cosmetics and very many other consumer products.

DISCUSSION AND CONCLUSIONS

The increase in asthma/allergies has been dramatic all over the world, in a short time period (decades). The causes must be environmental, as the time period is to short for major **genetic changes**. An easy explanation would be that there has been a major increase in exposure to **allergens**. We are still becoming sensitized to birch, cat, dog, mites etc, and there is no scientific evidence that such sources have increased drastically the last decades. So the cause should be searched for in the way we are reacting more often to pollens, cat dander, mites today.
The most common explanation is the **"hygiene hypothesis".** Our environment is too clean; we are not exposed to "dirt", including microbes, occupying the immune defense. Instead the immune system reacts to harmless proteins, allergens, inducing asthma/allergies. In spite of two decades of research on this hypothesis, no consistent positive confirmation has been found, rather the contrary. Probably many of the findings can be explained by selection bias. In families that have a member that gets sick when exposed it is natural to avoid pets, resulting in a seemingly "protective" effect of pet-keeping in cross-sectional or cohort studies ("the healthy pet keeping effect"). This effect is obvious in a country like Sweden, with a number of national campaigns, informing everyone about risk factors for allergies (including pets), but not existing in Bulgaria (no campaigns, pets is a real risk factor!). The same selection bias could be found among farmers, and other groups that are used as evidence of the "hygiene hypothesis". In the same field of research we have the protective effect of endotoxin. As endotoxin is strongly associated with pet keeping, we have the same strong selection bias involved. The idea that it is cleaner today (more hygienic) in homes, schools than 50 years ago, is also against common experience. We have a society were most are working outside the home. It is reasonable to assume that homes are dirtier today. For schools, day care centers, offices the development has been the same. There is in most buildings less cleaning today than was usual decades ago, as cleaning is a major cost for building owners (much more important than energy use). More frequent early infections should prevent asthma/allergies, according to the "hygiene hypothesis", but in the Swedish study (DBH), it's the opposite! The more early infections (day care attendance), the more asthma/allergies.

If not the hygiene hypothesis, what environmental change could be responsible for the increase in atopic morbidity? :
Outdoor air, Yes for exacerbations; No for incidence!
Food, in spite of two decades of research, No! (part of the hygiene hypothesis)
Indoor air:

- ETS, Yes!
- Ventilation rate, possibly!
- Dampness, Yes!
- Mould, maybe?
- Phthalates, maybe?
- Other new chemical exposures, possibly

There are most certainly other chemical compounds, new in our environments, which may be as important as phthalates. This is where new science should start.

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