



CME article

## Environmental exposures and respiratory outcomes in children

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### EDUCATIONAL AIMS

- To identify the challenges in relating environmental exposure to asthma causation
- To summarise selected studies published in 2010 and 2011 which illustrate some of the challenges in relating environmental exposure to asthma causation and also underlying mechanisms.
- To synthesise current understanding into advice clinicians can offer to parents and governments about what steps can be taken to prevent childhood asthma

### ARTICLE INFO

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### SUMMARY

Asthma is a complex condition where genetic and environmental interactions occur at critical periods in development. The focus of this review was the role of environmental exposures on asthma causation. Selected studies published in 2010 and 2011 were reviewed to illustrate the challenge in relating environmental exposure(s) on asthma causation and also to focus on some exposures currently thought to be important to asthma pathogenesis. Challenges in understanding how environmental exposures may translate into asthma causation are summarised. Inhaled and ingested exposures are described, including microbial products, swimming pools, diet and antenatal tobacco exposure. A final synthesis summarises what is currently understood about childhood asthma causation and what advice might be given to parents and governments interested in reducing asthma risk.

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### INTRODUCTION

This article is based on a presentation given at the 2011 meeting of the European Respiratory Society in Amsterdam. The presentation shares the same title as this article and was given as part of the "Paediatric Year in Review". The overall aim of this body of work was identify articles in the recent literature which identified associations between environmental exposures and asthma and also highlighted the challenges in studying the association. The relationship between environmental exposure and asthma exacerbation is a large subject all of its own and outside the remit of this article. The specific aims were to (i) describe the challenges in relating environmental exposure to asthma causation, (ii) focus on a relatively small number of studies which give insight into inhaled

and ingested exposures and asthma causation and finally to (iii) synthesise the results into a clinically relevant take home message. There were no conflicts of interest to declare.

### CHALLENGES

#### *Methodological challenges*

In a nutshell, it is hard to relate environmental exposure to asthma causation and [Table 1](#) summarises the obstacles. Arguably the greatest challenge is the lack of a gold standard for asthma, some studies report wheeze or diagnosed asthma as the outcome but these are not necessarily interchangeable terms, especially in young children. The absence of a solid definition of the outcome might rightly be considered as the biggest challenge but not necessarily so; measuring the exposure is not straight forward either since our environment is never constant. For example a child's diet changes on a daily basis so what is "typical" for ingested exposure? A second important issue is that exposures do not occur

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**Table 1**

A summary of the obstacles to relating environmental exposure to asthma causation in children

Lack of gold standard definition for asthma
Environment rarely constant
Can one exposure be considered important in isolation?
The same exposure can have different (sometimes opposite) effects in different individuals
Often several years pass between exposure and onset of symptoms
Cost of following up individuals
Loss to follow up introduces bias to population
Publishing studies which find no association is a challenge
Only intervention studies can demonstrate causation

**Table 2**

Examples of how an apparently simple and single exposure can prove to be a complex exposure some of whose constituents may be “good” and some “bad”

Route	Exposure	Factors within exposure
Inhaled	Household Dust	HDM products, LPS, pet allergen
	Products of tobacco smoke	PM <sub>2.5</sub> , volatile organic compounds (benzene, formaldehyde)
	Traffic fumes	PM <sub>2.5</sub> , SO <sub>2</sub> , oxides of nitrogen
	Pollens	Trees, plants, fungi
Ingested	Swimming pool	Chlorine, humidity, exercise
	Fish	Omega 3 and 6 fatty acids, fat soluble vitamins, allergenic proteins
	Fruit	Water soluble vitamins, allergenic proteins, pesticides
	Dairy products	Vitamin D, allergenic proteins

HDM = house dust mite, LPS = lipopolysaccharide, PM<sub>2.5</sub> = fine particulate matter with a diameter of less than 2.5 microns.

in isolation, for example household dust contains many components including house dust mite and lipopolysaccharide; are both these components “bad”? (Table 2).

### Practical challenges

Moving on from the methodological to the practical challenges of relating environmental exposures to asthma causation, the first issue is the interval between exposure and onset of symptoms. It is generally thought that early exposures, during the first two or perhaps three years of life, are important to asthma causation in children<sup>1</sup> but the diagnosis of asthma can be difficult to make in children aged under five years due to overlap with viral induced wheeze.<sup>2</sup> Following up children in a cohort study requires staff who require a salary and funding can be hard to obtain. A second issue is that follow up is rarely complete and this leads to loss of power and also the characteristic of the cohort changes to reflect those who do not drop out. Typically over time, cohort studies of asthma causation become enriched with children whose parents are non-smokers, are more affluent and are often more likely to have asthma. Bias in follow up leads to the question “how generalisable are the results?”

### Final hurdles

Once the challenges of measuring the environmental exposure, agreeing on the asthma outcome and ensuring that minimal drop out occurs in a cohort study have been navigated there are still a few final hurdles. First, if no evidence of association is found it is less likely that you will get your findings published; publication bias means that studies which find associations are more likely to be published even if they are underpowered (see later for example of this). Second, any association may merely be just an association and may not truly reflect causation; reverse causation and confounders are the problem here. A good example of reverse causation is where parents who have asthma modify their child's

environment in an attempt to reduce the chance of the child developing asthma too. Confounders can be considered third parties which truly explain an apparent association between exposure and outcome; the archetypal confounder is socioeconomic status. Children with a “poor” diet may be at increased risk for asthma but children from a less affluent community are at increased risk for exposure to second hand smoke and this may be the more important exposure. An example of socioeconomic confounding will be presented later.

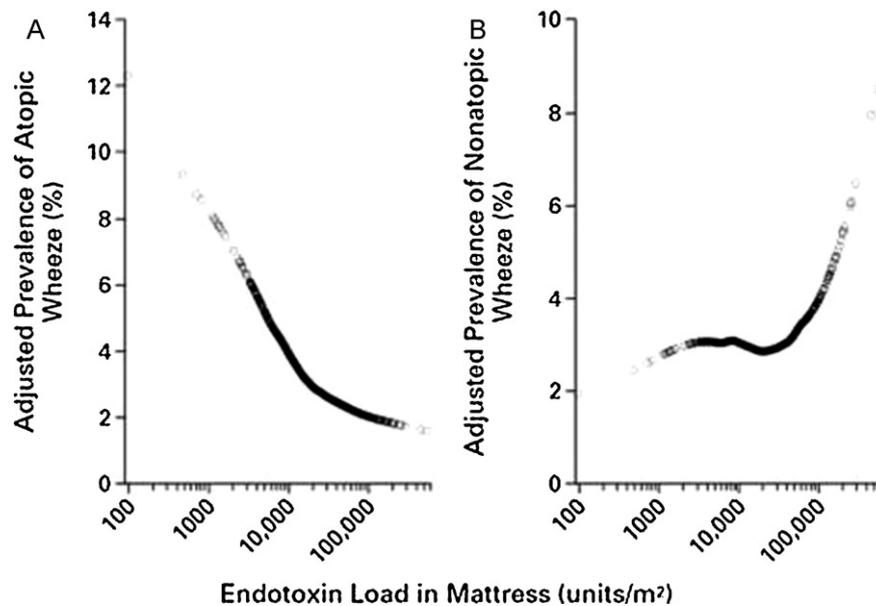
### What are “good” and “bad” environmental exposures?

With the exception of second hand smoke exposure which is “bad”, the concept of “good” and “bad” environmental exposures is simplistic and this has been highlighted by at least two studies in the past. One intervention study demonstrated that exposing infants to an environment where house dust mite exposure was effectively zero lead to reduced airway resistance (“good”) but increased house dust mite sensitisation (“bad”); here the intervention may have also removed lipopolysaccharide (LPS) from the environment.<sup>3</sup> In a second study, the prevalence of wheeze was linked to LPS exposure in the mattress in five year olds.<sup>4</sup> In children with atopic wheeze, increasing exposure was associated with an apparent protective effect (“good”) but in those with non-atopic wheeze, LPS was associated with increased risk (“bad”), Figure 1. Had the authors simply related LPS exposure to wheeze then no relationship would have been apparent.

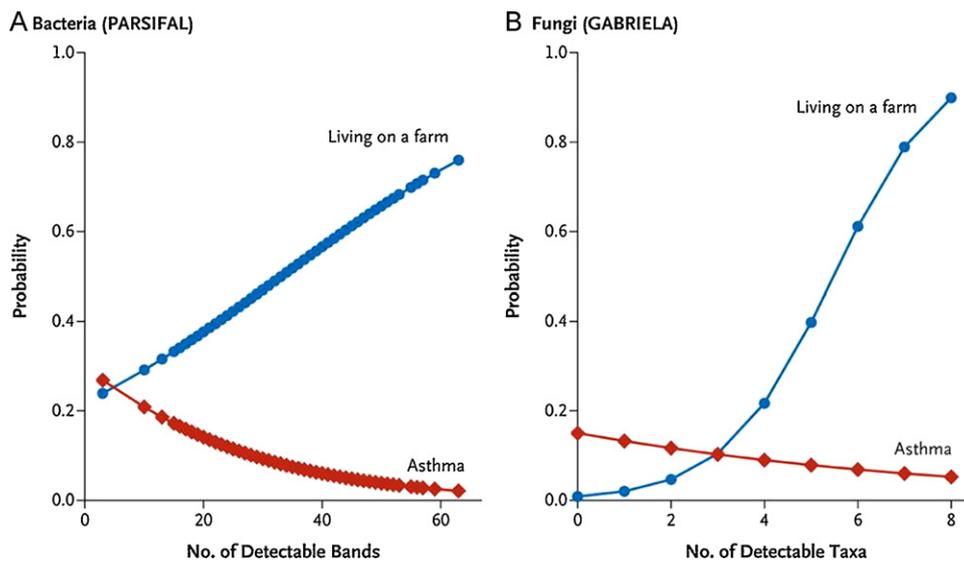
Despite these rather daunting challenges, there have been many reports published in 2010–2011 relating environmental exposures to childhood asthma causation. The following studies are not an exhaustive summary of the literature but were chosen to illustrate current thinking.

### Quantity of exposure or quality?

One study combined the results from two cross sectional studies undertaken in central Europe to answer the question does diversity in the microbial exposure alter risk for asthma?<sup>5</sup> This work extends previous work showing the complicated relationship between quantity of microbial exposure (i.e. LPS) and wheeze.<sup>4</sup> In the first study, PARISFAL, dust was sampled from the mattresses of 489 Bavarian children of whom approximately 50% lived on a farm; here dust was analysed for number of different bacteria. In the second study, GABRIELA, airborne dust was captured from the bedrooms of 444 children of whom 16% lived on farms; here, dust was analysed for the number of different fungal species. In both studies, increasing numbers of different species was associated with a greater probability of living on a farm and reduced probability of having asthma (Figure 2). The authors concluded that microbial diversity explains the apparent protective effect of living on farm and developing childhood asthma, but not eczema, hayfever or skin prick reactivity. These findings are also consistent with the paradigm that the summation of exposures (the “soup”) is important rather than the individual exposure. What this cross sectional study was not able to do was to describe the timing of this exposure, nor was it able to consider the relevance of genetic factors/modifiers. In another publication by the same group,<sup>6</sup> gene-environment interactions for exposure to farm and childhood asthma were described in 1708 children who were participants in the GABRIEL study and included 850 children with asthma. Here the authors categorised individuals as exposed or not exposed to a farm and having asthma or not. In a genome-wide association study, half a million single nucleotide polymorphisms (SNPs) were studied across the four groups. Somewhat unexpectedly, given the perceived importance of genetic factors to asthma causation, there was no convincing evidence for gene-environment interactions



**Figure 1.** Smoothed Plots of the Prevalence of Atopic Wheeze (Panel A) and Nonatopic Wheeze (Panel B) in Relation to the Log-Transformed Endotoxin-Load Values. From Braun-Fahrlander et al.<sup>4</sup>. Permission granted from NEJM.



**Figure 2.** Relationship between Microbial Exposure and the Probability of Asthma. From Eeg et al.<sup>5</sup>. Permission granted from NEJM.

despite this study being adequately powered for common SNPs. The study, despite its considerable size, was not powered for less common SNPs and these may be important to gene environment interactions but an even larger study will be required to test this hypothesis; by definition, these SNPs are not common and therefore not likely to be important at a whole-population level.

What do these two studies<sup>5,6</sup> add? The first study provides proof-of-concept that the *quality* of environmental exposure is important to asthma development, but not to eczema, hayfever or skin prick positivity. The second study demonstrates that some environmental factors may act independently of genetic factors, albeit in farming populations where microbial exposures may be very high relative to non-farming populations. These studies cannot determine at what age exposure to a farming environment is important.

#### Dietary exposures

The association between dietary exposures and childhood asthma was studied in 50,004 children aged 8–12 years as part of

the International Asthma and Allergy Study in Children (ISAAC, phase II).<sup>7</sup> Data were collected from 20 countries, exposure to eight food items was captured and the outcome was wheeze in the last year. Most of the associations reported were of borderline significance. Among affluent countries, wheeze was associated with increased consumption of burgers and reduced intake of fruit and fish. In contrast, burger consumption was associated with an apparent protective effect on wheeze; this may be reverse causation where in developing countries burger consumption is an index of affluence and therefore reduced risk for asthma. In non-affluent countries, wheeze was also associated with reduced intake of cooked vegetables, fruit and fruit juice. These dietary exposures were associated with a minor change in wheeze risk of approximately 15–20%. The authors of the ISAAC report then combined foods together and categorised each child's diet on a scale of "Mediterranean-ness" ranging between –16 and +16; the rationale was to extend previous reports which have linked a Mediterranean diet to reduced asthma risk.<sup>8</sup> There was a 3% reduction for risk of wheeze for each unit increase on the

“Mediterranean-ness” score. There was no association between eczema or hayfever and dietary exposure.

So what does this study add? Well, this gives insight into the complexity of assessing dietary exposures, demonstrates that socioeconomic factors may confound associations on an international scale and also indicates that different factors may be important to asthma and other “allergic” conditions. What this cross sectional study cannot do is to determine when the important environmental exposures occur.

#### Swimming pool exposures

Two studies gave different insight into the relationship between early exposure to a swimming pool and later asthma symptoms. In the first study, parents of 839 five-year-old children were asked to complete a questionnaire which asked them to recall whether their child had more than 20 hours exposure to a swimming pool during infancy and whether they had ever had bronchiolitis or asthma.<sup>9</sup> Among the 430 respondents, swimming pool exposure was associated with an approximate doubling of bronchiolitis (56 bronchiolitics not exposed and 71 exposed). Although there was no association with asthma *per se*, individuals exposed to swimming pools and who had bronchiolitis were at increased risk for asthma. This study does give an insight into the timing of early environmental exposures and suggests the possibility of an interaction between early respiratory infection and exposure to swimming pool resulting in later asthma, but there are some potential problems with this study including recall bias, publication bias, reverse causation and lack of power. What is really required to address this potentially important issue is a prospective study with longer follow up of a larger population. A study matching these criteria was also published recently and arrived at a very different conclusion. The Avon Longitudinal Study of Parents and Children reported on 5738 ten-year-old children studied in detail since birth.<sup>10</sup> The authors were able to demonstrate that exposure to a swimming pool was confounded by many factors. Swimming was less likely in children who watched a lot of television, were thin, had older siblings and were exposed to second hand smoke. In contrast, swimming was more likely in children of more affluent parents whose mothers had a higher educational qualification. Once all these confounders were considered, exposure to a swimming pool at any age was associated with a 50% reduction in asthma. What these two studies demonstrate is that different methods of evaluating early environmental exposure can yield very different answers, however the take home message is that swimming is “good”. A very recent study where asymptomatic elite young adult swimmers exposed to chlorinated pools underwent airway biopsy found evidence of airway changes consistent with “mild asthma” suggesting that very prolonged and repeated exposure to the swimming pool environment may have a minor potentially adverse effect on the airways.<sup>11</sup> What is not clear is exactly which exposure during swimming is important, eg humid air, chlorine, exercise, and whether there is an optimum duration of exposure which yields apparent protection.

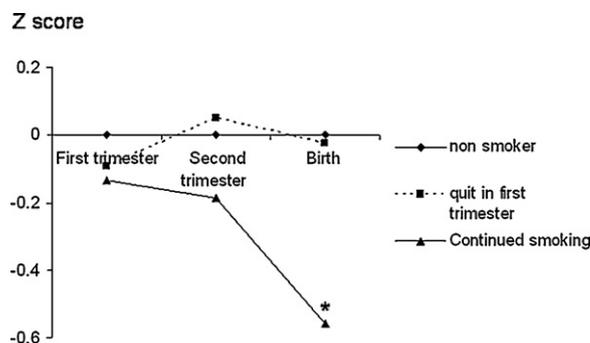
#### Fetal exposures

Reduced birth weight is associated with increased risk for asthma in children and adults and this suggests that environmental exposures before birth may be important to asthma causation. Two recent publications from the author’s group have related antenatal exposure to maternal smoking and plasma alpha tocopherol (vitamin E) to fetal growth and asthma outcomes at age five years. The rationale underlying this work is that whilst there is no index of fetal lung function, fetal size will be correlated with

fetal lung function in the same way that a child’s height is predictive of spirometry. The first study<sup>12</sup> asked the question “does fetal growth explain the previously described association between increased maternal plasma alpha tocopherol in early pregnancy and reduced childhood asthma<sup>13</sup> ?” There was a positive relationship between plasma alpha tocopherol and fetal size at ten weeks gestation and also between reduced fetal size and asthma outcomes.<sup>12</sup> When both factors were considered, the effect of maternal alpha tocopherol on asthma outcomes was subsumed by fetal size, i.e. maternal alpha tocopherol was apparently a determinant of fetal growth which in turn was an apparent determinant of asthma outcome. The second paper<sup>14</sup> asked the question “at what gestation does maternal smoking affect fetal growth? (and by inference affect fetal lung development)” Here outcomes in fetus and child were compared across groups categorised by maternal smoking habits during pregnancy. Second, but not first, trimester growth was associated with maternal smoking. As might be anticipated, mothers who carried on smoking beyond the first trimester delivered lighter infants who were at increased risk for requiring asthma medication and also had reduced lung function as five-year-olds (Figure 3). In contrast, individuals whose mothers reported quitting during the first trimester were of normal birth weight and were not at increased risk for any adverse respiratory outcome at five years (Figure 3). This suggests that smoking cessation after during first trimester may be sufficient to prevent the fetus from harmful effects of maternal smoking. In summary these two studies suggest that antenatal environmental exposures may influence the development of childhood asthma and that crucial exposures may occur at different stages of pregnancy as windows of opportunity open and close throughout gestation.

*So what do we know about how environmental exposures might cause asthma in 2012?*

1. Asthma causation is complex and involves a number of environmental factors each of modest effect interacting with a number of genetic factors and that these interactions occur at different stages of development. At the time of writing, the nature of the mechanism for the “asthma epidemic”<sup>15</sup> is still not known and this complex mechanism is unlikely to be ever fully understood due to the challenges outlined at the start of this article, i.e. a whole population study where all exposures are captured from conception to grave is simply not feasible.
2. What we can infer from the present literature is that some factors are definitely harmful, e.g. second hand smoke exposure, and others are definitely not harmful, e.g. swimming, and for many factors we are not sure. Certain exposures may reduce



**Figure 3.** A line chart comparing mean fetal size in the first trimester (crown rump length), second trimester (femur length) and birth in individuals whose mothers had never smoked, who smoked but quit in the first trimester and whose mothers smoked throughout pregnancy. \* $p < 0.001$  compared with non-smoker group.

asthma risk for some individuals and increase risk for others. Intervention studies have taught us that complex interventions in early development are more likely to reduce asthma risk whereas single intervention studies often do not affect asthma outcome and may even increase risk for atopy.

3. What we also know is that the greatest drivers for asthma risk are not modifiable, ie genes, socioeconomic status, gender and age.

*So what do we tell parents and legislators?*

We should seek to change what can be changed and that is air quality, diet and possibly the level of activity, eg swimming. Since the seeds of asthma are sewn at an early stage of development, environmental changes should be effected during pregnancy and the first two–to–three years of life. Most intervention studies aimed at reducing asthma have failed to show a benefit. What is evident is that the few studies which have effected a reduction in asthma prevalence have applied multiple interventions in very early life<sup>16,17</sup> (reduced pet/dust mite exposure, prolonged breast feeding, delayed weaning). The current evidence is therefore that making one intervention is not likely to be effective. Indeed allergen reduction<sup>3</sup> and prolonged breast feeding<sup>18</sup> in isolation may not prevent asthma but have been associated with increased allergic sensitisation.

The heterogeneity of the population means that advice to parents of the individual child cannot be specific (see “what are “good” and “bad” environmental exposures) but for the whole population there are more clear pointers which can be presented to governments:

1. Parents. We can tell parents that at present there is no strong and consistent evidence base upon which to give specific advice for an individual child with the exception of preventing exposure to products of tobacco smoke. However, parents of unborn and young children can be assured that standard public health advice about maternal lifestyle during pregnancy (balanced diet, not smoking, regular exercise), infant feeding and weaning, early childhood diet and promoting regular activity are important for the overall wellbeing of the child, may also reduce asthma risk but will not increase asthma risk.
2. Governments. There are some exposures where evidence of causation is strong, weak or simply unknown. Exposure to tobacco smoke is a consistent factor associated with childhood asthma and governments can address this with legislation (e.g. brand-free packaging, advertising bans and taxation. Indoor air quality can be improved by changing parental smoking habits<sup>19</sup> and we must do all we can to help parents who smoke to quit; at the very least, parents who smoke should agree to establish smoke free homes and cars. Most children with asthma do not have parents who smoke and other indoor air exposures may be important in disease pathogenesis, for example allergen and virus infection. Improving ventilation of home and nurseries might reduce some exposures but evidence for this is lacking. Outdoor air quality is a determinant of indoor air quality and a recent article has described a “road map” to clean outdoor air;<sup>20</sup> with 2013 being the European Year of Air there should be awareness in governments in Europe of the need to set more clinically and stringent standards for air quality. Antenatal maternal diet<sup>21</sup> and early infant feeding/weaning may also impact on childhood asthma causation but at present the evidence for providing clear advice is lacking and more research is needed given that early dietary exposures are one of relatively few modifiable environmental exposures which may impact on childhood asthma.

## PRACTICE POINTS

- The imprecise nature of “asthma” and “the environment” mean that it is likely the association between the two will never be fully understood.
- Across the whole population, single environmental exposures have a small-moderate effect on asthma causation (ie odds ratio 2–4) although for susceptible individuals, a single exposure may have a greater influence on outcome.
- Whilst there is insufficient evidence to tailor advice as to how an individual’s asthma risk may be modified, there is sufficient evidence to point towards environmental exposures during antenatal and early post natal life being important.

## RESEARCH DIRECTIONS

- Better understanding of the relationship between early indoor/outdoor air pollution and asthma
- Better understanding of the relationship between early dietary exposures and asthma
- Better understanding of the relationship between early respiratory virus infection and asthma
- Intervention studies where several environmental modifications are made during pregnancy and during infancy eg smoking cessation, normalising maternal diet where key nutrients are deficient, promoting breast feeding, delayed introduction of solids in at-risk infants. Ideally, interventions have to be feasible and deliverable within the context of current healthcare systems.

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These are best-of-five questions, a format which suits this "grey" topic well. The statements are in alphabetical order.

1. Select only one answer which you feel is most correct. Childhood asthma is best defined as:
  - a. The presence of bronchial airway mucosal eosinophilia
  - b. The presence of bronchial hyperreactivity to inhaled methacholine
  - c. The presence of doctor diagnosed asthma
  - d. The presence of peak flow variability measured over one month
  - e. The presence of parent-reported wheeze
2. With regard to methodological issues in relating environmental exposure to asthma causation, which one of the following statements is most correct?
  - a. Most exposures occur in isolation from others associated with asthma and are usually easily quantified.
  - b. Most exposures occur constantly for a given individual over 24 hours and intrasubject variability is low.
  - c. Most exposures are similar between individuals over 24 hours and intersubject variability is low.
  - d. Some exposures are associated with increased asthma risk for some individuals and reduced risk for others
  - e. The methodology to measure many exposures does not yet exist
3. With regard to practical issues in relating environmental factors to asthma causation, which one of the following statements is most correct?
  - a. Bias in recruitment and follow up usually mean that the final population is not representative of the general population
  - b. Cohort studies are the best way to establish association and are not expensive to run
  - c. Cohort studies which find association between exposure and asthma risk provide proof of causation
  - d. Loss to follow up often has no implications for the power of a cohort study
  - e. Studies which find no association between exposure and outcome are usually published although with some difficulty
4. Which one of the following statements is most correct?
  - a. Exposure to products of tobacco smoke during pregnancy and infancy causes asthma
  - b. Exposure to prolonged breast feeding causes asthma
  - c. House dust mite exposure reduction in infancy prevents asthma
  - d. House dust mite exposure reduction, late introduction of solids and prolonged breast feeding prevents asthma.
  - e. Late introduction of solids prevents asthma
5. What is the best single piece of advice we can give to governments who wish to reduce the prevalence of childhood asthma in their population?
  - a. Interventions which alter dietary and inhaled exposures are most likely to reduce asthma risk.
  - b. Providing fresh fruit to young children in nurseries will reduce asthma prevalence by 10% after ten years
  - c. Providing free swimming lessons to young children will reduce asthma prevalence by 10% after ten years
  - d. There is nothing you can do, the mechanisms are too complicated.
  - e. The same public health advice which reduces atopy will also reduce asthma prevalence.