UNIVERSITY OF SOUTHAMPTON

EXPOSURE TO INDOOR AIR POLLUTION AND THE RISK OF UPPER AND LOWER RESPIRATORY DISEASE IN ASTHMATIC CHILDREN AND THEIR MOTHERS

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ABSTRACT

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Exposure to indoor air pollution and the risk of upper and lower respiratory disease in asthmatic children and their mothers

by Salah Matti

Clinical evidence from previous epidemiological studies suggests that there is a link between indoor air pollution and the respiratory illness, the following study aimed to test this hypothesis in asthmatic children and their mothers. 84 asthmatic children and their mothers (12 were asthmatic) were followed up for a period of one year. Upper and lower respiratory tract symptoms and peak expiratory flow measurements were recorded daily using diary cards. An experienced paediatrician inspected visually the diary cards and identified the respiratory episodes over the study period. Area under/above the curve (median was used as a baseline) was used to define the severity of the episodes. Four home visits were carried out to measure the levels of indoor air pollutants and co-factors (NO_2; VOCs; Formaldehyde; CO; Cotinine; Particulate matter (respirable:PM_{10}); Der p I; Dampness). Poisson regression and logestic regression analyses were used to study the relationship between the episodes and the indoor environment.

In children, this study demonstrated the following findings:

- Positive association between NO_2 (personal & kitchen mean) and the frequency of LRT episodes, but the episodes were milder in those with high kitchen NO_2.
- Positive association between formaldehyde and the frequency of PEF episodes.
- Exposure to CO, PM_{10} increased the severity of LRT, PEF episodes. There was a positive association between the severity of URT episodes and kitchen peak NO_2.
- Exposure to PM_{10} increased the incidence of LRT and PEF episodes following the occurrence of upper respiratory tract episodes.

Among mothers, this study demonstrated the following findings:

- A positive association between dampness and PEF episodes.
- In the analysis of the severity of the episodes, exposure to PM_{10} and VOCs increased the severity of URT episodes.
- A positive association was demonstrated with PM_{10} and cotinine.
- Mothers with high kitchen peak NO_2 have reported less URT symptoms, and those with high urine cotinine the episodes were milder and less frequent. It also seems there were milder LRT symptoms among mothers with high NO2 levels, and the episodes were shorter in relation to formaldehyde.
  PEF episodes were milder among mothers with high indoor exposure to NO_2 (kitchen) and formaldehyde.

Our study suggests that some of the indoor environmental factors have a detrimental health effects on asthmatic children and their mothers.

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DECLARATION

The work presented in this thesis is substantially the work of the author. Many people were involved in various aspects of the study and their collaboration is acknowledged in the previous section.

Publications:

- **Matti SJ, Chauhan AJ, Jeffs JAR, Clough JB.** Indoor air pollution on trial. Environmental Health Journal 1999;107:188-190.

- **Matti SJ, Clough JB.** Exposure to indoor air pollution and the risk of upper and lower respiratory diseases in asthmatic children and their mothers. Institute for Environmental Health 'annual report' (year 2000).

Abstracts/Presentations

- **Matti SJ, Chauhan AJ, Clough JB, Holgate ST.** Distribution of personal exposure in the home to nitrogen dioxide in 8-12 year old children and their mothers. (Abstract). Am J Respir Crit Care 1999;159 (3):A774.
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- **Matti SJ, Chauhan AJ, Bolt A, Jeffs JAR, Clough JB.** The association between skin test reactivity to indoor allergens and asthma severity. Eur Respir J 1999;14 S30:307s.
  Discussed poster; European Respiratory Society 1999.

- **Matti SJ, Chauhan AJ, Jeffs JAR, Clough JB.** The relationship between atopy, asthma severity and passive smoking on asthmatic children. Eur Respir J 1999;14 S30:483s.
  Discussed poster; European Respiratory Society 1999.

- **Clayson EM, Matti SJ, Rowe DJF.** The relationship between urinary cotinine concentration in mothers and their asthmatic offspring. Thorax 1999; 54 S3:A45
  Discussed poster; British Thoracic Society1999.

- **Matti SJ, Chauhan AJ, Jeffs JAR, Clough JB, Holgate ST.** The effect of nitrogen dioxide and environmental tobacco smoke on peak expiratory flow measurement of healthy non-smoker housewives.
  Am J Respir Crit Care 2000;161 (3):A532
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- **Matti SJ, Chauhan AJ, Clough JB.** Methods, Materials and results of measuring indoor air pollution. **Discussed poster**; Fourth review meeting of joint programme on outdoor and indoor pollution

- **Matti SJ, Chauhan AJ, Jeffs JAR, Frew AJ,Clough JB.** The asthma and the environment: Do environmental factors affects the incidence of lower respiratory diseases in asthmatic children? Eur Respir J 2001;18, S33:186s.
  Oral presentation; European Respiratory Society 2001

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ABBREVIATIONS USED IN THE TEXT

PM_{10}	Particulate Matter
NO_2	Nitrogen dioxide
VOCs	Volatile Organic Compounds
PEF	Peak Expiratory Flow
URT	Upper Respiratory Tract
LRT	Lower Respiratory Tract
CO	Carbon Monoxide
ETS	Environmental Tobacco Smoke

CHAPTER 1

Introduction

1.1 Asthma and the environment

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early in the morning. These episodes are usually associated with wide spread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness (National Heart Lung and Blood Institute, 1995).

A number of respiratory health outcomes have been associated with indoor air exposure to agents such as formaldehyde, volatile organic compounds and different allergens(Karol, 1991). The reported effects include irritation, inflammation, bronchoconstriction and sensitization. The induced responses depend on genetic and other host-specific factors, such as the immunologic status of the host, and also on agent related factors such as the nature of the pollutant, concentration and length of exposure. In addition, exposure to adjuvant risk factors such as tobacco smoke and

other environmental pollutants seem to be of importance and to increase the risk of atopic sensitization and asthma (Lindfors *et al*, 1994).

Some of the most potent agents associated with allergic lung disease are found in indoor environments. The allergenic constituents of indoor air environments are predominantly found in the biologic fraction and include allergens from house dust mites, pet dander, insects ''such as cockroaches'', as well as mould (Karol, 1991). Such allergens have been recognized for many years and are associated with a large proportion of childhood asthma (Karol, 1991). Current knowledge on hypersensitivity and asthmatic reactions after exposure to chemical agents is primarily based on data from high exposures in occupational settings. However, there is evidence that indoor exposure to both mixtures and to single components of volatile compounds can be related to asthmatic symptoms (Harving *et al*, 1991).

It has been generally assumed that air pollution mainly affect the outdoors environment. However, a number of studies have shown that indoor concentrations of some pollutants may be far in excess of the outdoor concentrations (Abramson and Voigt, 1991).

There are considerable differences in the prevalence of allergy within industrialized countries, i.e., between urban and rural areas. As an example, the relative risk for a positive skin prick risk test is 70% higher among 11 yr old children living in a moderately polluted town in northern Sweden than among children living in the neighbouring countryside (Braback *et al*, 1994).

The role of environmental factors in the development of asthma has been supported by the studies of twins. Edfors –Lubs (Edfors-Lubs, 1971) studied 6996 twin pairs in the Swedish twin registry office and found that when one monozygotic twin had asthma,

19% of the other twins also had asthma. Among dizygotic twins, if one twin had asthma, only 4.8% of the other twins had asthma. It was therefore concluded from this study, although there are certainly genetic factors involved, there is clearly an important environmental component to developing asthma.

It is generally agreed that, in recent decades, we have experienced a global increase in asthma prevalence (Haahtela, 1990). Particularly in more economically developed and rapidly developing countries, rising prevalence has been accompanied by unprecedented changes in both life styles and environmental quality. One impact of development has been an upsurge in the proportion of inhabitants living in cities. In consequence an escalating number of the population are exposed to the contaminants of urban air (Lipfert, 1997). Although this has led to concern that outdoor air pollution may be to blame in causing asthma, the evidence of this is weak or contradictory (Brunekreef *et al*, 1995). Consequently, there has been a shift of attention from outdoors to the situation indoors. It seems that changes in indoor air quality may be more important in explaining the rise in asthma cases.

It is estimated that the average individual born today will spend over 95% of their life inside (Platts-Mills *et al*, 1995). This trend has coincided with major changes to the home environment, in part driven by alterations to building design which were hastened by high fuel costs during the 1970s energy crisis (Jones, 1998). Modern homes are much better insulated than was previously the case. Improved insulation has been accompanied by numerous other alterations. Many more houses have central heating and sealed unit double glazing. For example, although only 29% of British homes were centrally heated in 1970, this figure has risen to over 85% by 1995 (ONS, 1996). Fitted carpets have generally replaced loose rugs, while advances in construction

technology have meant a greater use of synthetic building materials (D'Amato *et al*, 1994).

All these transformations have undoubtedly led to more comfortable living conditions. However, they have also resulted in warmer, more humid houses with poorer availability of fresh air. These conditions provide an environment in which airborne contaminants are readily produced and may buildup to much higher concentrations than typically encountered outside (Hyndman *et al*, 1994).

Of course, many other aspects of the internal and external environment have changed in recent years and it is quite possible that this may partially explain the increasing prevalence of asthma. However, given the amount of time that most individuals spend indoors, it seems that the indoor environment may have an important role to play in allergic disorders.

As with all respiratory allergies, asthma is caused by an interaction between genetic and environmental factors (D'Amato *et al*, 1994). A great number of substances found in the environment can induce allergic respiratory sensitization and allergic reaction (Lau S, 1990), while many more can precipitate or aggravate respiratory symptoms by non-allergic mechanisms (Salvaggio, 1991).

Various indoor exposures have been related to asthma, including house dust mites, moulds and fungal spores and nitrogen dioxide from gas cooking (Hasselblad *et al*, 1992). High concentrations of volatile organic compounds and formaldehyde have also been associated with asthma (Wieslander *et al*, 1997), as has particular matter from smoking and bio-fuel combustion.

Domestic air pollution is now seen as a major public health issue and it seems likely that the future research would focus on this particular area.

1.2 Indoor air pollution sources, levels, toxic effects on health and general review of epidemiological studies

1.2.1 Nitrogen dioxide

1.2.1.1 Sources and typical concentration

Gas cooker, pilot lights, unvented kerosene, gas space heaters, gasoline engines, and outside air are the commonest sources of indoor nitrogen dioxide. 25-75 ppb is typical range for homes with gas stoves, while peak values (100 – 500 ppb) are found in the kitchen with gas stoves or kerosene gas heaters. Indoor nitrogen dioxide levels are affected by several factors such as the type of fuel used for heating and cooking, and the outdoor level.

1.2.1.2 Toxicological effect

The formation of nitric and nitrous acids in aqueous solution on the moist surfaces of airspaces is probably of importance for toxicity of nitrogen dioxide(Greenberg SD, 1971). The main mechanisms of pulmonary toxicity of nitrogen dioxide have, however, been suggested to be due to its oxidant capacity and involve lipid peroxidation in cell membranes (Mustafa and Tierney, 1978) (Patel and Block, 1986), as well as various actions of free radicals on structural and functional molecules (Proctor and Reynolds, 1984) (Pryor and Lightsey, 1981;Thomas and Rhoades, 1970). Particularly strong free radicals are formed when nitrogen dioxide oxidizes lecithin in cell membranes or surfactant, and interaction with haem (Rowlands and Gause, 1971). Nitric oxide binding to the iron in haeme-protein complexes may, therefore, be used as a biomarker for exposure to nitric oxide (Maples *et al*, 1991).

1.2.1.3 General review of epidemiological studies

Pubmed search was performed on the relationship between indoor nitrogen dioxide and the respiratory symptoms among children and adults (1970-1998). In this review I listed the relevant epidemiological and human studies which looked at relationship between nitrogen dioxide/gas cooker and the respiratory illnesses. This review demonstrated clear inconsistency in the outcomes of those studies. Methodological limitations of the epidemiological studies can readily explain the lack of the definite data, particularly in terms of misclassification of exposure (for e.g. using the presence of gas cooker as surrogate marker for nitrogen dioxide) and heath outcomes, study design (the risk of recall bias of respiratory symptoms/infections in retrospective cross-sectional studies) and confounding variables.

1.2.1.3.1 General review of epidemiological studies using gas cooking as a measure of nitrogen dioxide exposure.

Mixed results have been found in studies using gas for cooking at home as a measure of nitrogen dioxide, (tables 1.1& 1.2). These studies mainly involved cross-sectional study designs with retrospective parental questionnaires to determine illnesses and respiratory symptoms.

Melia and Florey found a positive relationship between gas cooking at home and respiratory symptoms (Melia *et al*, 1977) (Melia *et al*, 1979) (Florey *et al*, 1979). Melia's earlier study did not control for parental smoking, but this was corrected in later studies. Speizer and colleagues, using physician-diagnosed bronchitis and a history of serious respiratory illness before the age of two years, found a significant association between gas cooking and respiratory illnesses in the under two year age group (Speizer *et al*, 1980). In Dodge's study the prevalence of cough was found to be

significantly higher in homes which used gas cooking (Dodge, 1982). Ekwo et al found a positive association between hospital admissions and gas cooking at home in a group of two year olds. But no such association was found for coughs with colds in children (Ekwo *et al*, 1983).

Houthuijs found an increased prevalence of respiratory symptoms associated with the use of unvented geysers in the kitchen, while Melia found a positive association in certain ethnic groups, namely africocaribbeans and whites (Houthuijs *et al*, 1987).

In contrast to these studies, others have found no such positive association. In a 12 month longitudinal study involving 441 families, Keller and co-workers found gas cooking was not associated with any increase in respiratory illness in either adults or children (Keller *et al*, 1979).

Of particular significance, Ware and colleagues expanded the cohort used in Speizer's study and found no association between respiratory illness before the age of two and gas cooking at home (Ware *et al*, 1984). In another study conducted by Harrington and co-workers, no association was found between gas cooking and respiratory illness (Harrington and Krupnick, 1985). Similarly, Ogston and colleagues found no association between gas cooking at home and hospitalization and illness in the first year of life (Ogston *et al*, 1985).

1.2.1.3.2 General Review of epidemiological studies looking at the association between the levels of indoor nitrogen dioxide and respiratory illness

Mixed results have occurred in the few studies that measured indoor nitrogen dioxide levels and attempted to estimate personal levels of exposure (table 1.3). Florey et al found a positive association of respiratory illness prevalence with nitrogen dioxide exposure (as they have also found with gas cooking) (Florey *et al*, 1979).

Houthuijs and co-workers, in the study previously reported, also found a positive relationship of prevalence of respiratory symptoms with estimated personal exposure levels of nitrogen dioxide (Houthuijs *et al*, 1987).

Berwick and colleagues, using a prospective design found an increase in symptoms of the lower respiratory tract in children aged under seven exposed to more than 0.015ppm of nitrogen dioxide (Berwick *et al*, 1987). However this study included only 121 children, making extrapolation to the population in general difficult. Neas et al using Palmes diffusion tubes to estimate mean annual house hold nitrogen dioxide exposure, found that a 15 ppb increase in the mean exposure level was associated with an increased cumulative incidence of lower respiratory tract symptoms (Neas *et al*, 1991).

Four other studies, however, have found no such positive relationship. Melia and co-workers detected no significant relationship between average measured nitrogen dioxide levels in bedrooms and living rooms and respiratory illness (Melia *et al*, 1982). This result was contrary to their original findings using gas cooking as a measure of exposure. They discounted high humidity or low temperature as being responsible for the discrepancy.

Hoek and co-workers, using Palmes tubes and activity data to determine personal exposure in a case –control study, found no difference in exposure between control and cases reported to suffer from bronchitis, asthma, frequent coughs or colds, and allergy (Hoek *et al*, 1984).

Koo and colleagues used passive diffusion badge-style monitors, worn for 24 hours to measure personal nitrogen dioxide exposure (Koo *et al*, 1990). They reported these monitors as having an accuracy of plus or minus 20 percent when compared to other

recognized forms of monitoring. Monitoring was conducted during one week only for each subjects and no association was found between the children's nitrogen dioxide exposure levels and respiratory symptoms. Dijkstra and colleagues estimated weekly average nitrogen dioxide concentrations at home using Palmes diffusion tubes but no association between nitrogen dioxide home exposure and respiratory symptoms was found(Dijkstra *et al*, 1990).

Table1.1: Gas cooking versus non- gas cooking at home – Studies with positive association with gas cooking

Design / Reference	Symptom measure	Results
Cross Sectional (Melia *et al*, 1977) Children aged 6-11 ys Number =5758	Retrospective questionnaire for symptoms in the previous year. Not adjusted for smoking.	Excess cough, colds going to the chest and bronchitis OR=1.3 (P<0.001)
Cross sectional (N=4827)(Melia *et al*, 1979) Longitudinal (N=2408) Children aged 5-11 ys	Questionnaire as above but smoking was adjusted for.	Relative risk was variable, but mostly an increased risk of one or more symptoms with gas cooking OR=1.25 (P<0.05)
Cross sectional (Florey *et al*, 1979) Children aged 6 –17 ys Number = 808	Symptom questionnaire based on *Medical Research Council* Questionnaire	Positive association between gas cooking and respiratory illness OR=1.5 (95%CI:1.04-2.2)
Cross sectional (Speizer *et al*, 1980) Children aged 6-10 Number=8120	Questionnaire for doctor for diagnosis of bronchitis and history of serious respiratory illness before age 2 and in the previous year	Significant association between gas cooking and respiratory illness before the age of 2 ys OR=1.1(95%CI:1.0-1.26)
Cross sectional (Dodge, 1982) Children aged 8-12 ys Number = 676	Questionnaire for asthma, sputum, cough and wheeze	Prevalence of cough was significantly associated with gas cooking (P<0.05)
Cross sectional (Ekwo *et al*, 1983) Children aged 6 –12 ys Number = 1138	Used a modified American Thoracic Society Questionnaire	Hospitalisation before the age of 2 was associated with gas cooking at home (OR=2.4; 95%CI 2.0-3.1)
Cross sectional (Houthuijs *et al*, 1987) Children aged 6-9 ys Number = 630	World Health Organisation Questionnaire for respiratory symptoms	Gas use at home associated with an increased prevalence of respiratory symptoms OR= 1.4, 1.3 (P<0.05) for cough, and breathlessness
Cross sectional (Melia *et al*, 1988) Children aged 5-11 ys Number = 4815	Retrospective questionnaire for respirtory symptoms in ethnic groups	All respiratory conditions were more prevalent in afrocaribbeans and whites P<0.01
Cross sectional and longitudinal(Garrett *et al*, 1998) Children aged 7-14 ys Number = 148	Questionnaire of respiratory symptoms Adapted from Monash respiratory questionnaire	Significant association between cough, chest tightness and the use of gas cooking at home OR=2.3 (95%CI 1.0-5.0)

Table1.2: Gas cooking versus non- gas cooking at home – Studies where no association was found

Design/Reference	Symptom measure	Results
Longitudinal (Keller *et al*, 1979) Adults and children Number= 176	Bi- weekly phone data from each House hold	No association was found between gas cooking and respiratory in children or adults OR=1.1 (95%CI: 0.7-1.5)
Cross sectional (Schenker *et al*, 1983) Children aged 5 – 14 ys Number = 4070	American Thoracic Society Questionnaire for respiratory symptoms and illness	No association between gas cooking and respiratory illness.
Longitudinal (Harrington and Krupnick, 1985) Children aged up to 12 ys Number =4898	Bi-weekly telephone data for symptoms and illness	Respiratory illness was not associated to gas cooking at home Beta=0.05 (95% CI: -0.09 – 0.01)
Cross sectional (Ware *et al*, 1984) Children aged 6-9 ys Number=10106	Retrospective questionnaire for symptoms and illness	No significant association was found between gas cooking and respiratory illness OR=0.8 (95%CI: 0.7-1.0)
Longitudinal (Ogston *et al*, 1985) Infants in their first year of life Number= 1565	Hospitalisation and recall of respiratory symptoms in the previous year	No significant association was found, but trend did occur RR=1.1 (95%CI: 0.8-1.5)

Table1.3: Association between indoor nitrogen dioxide and respiratory diseases

Design/Reference	Mean NO2 ppm	Symptom measure	Results
Cross sectional (Melia *et al*, 1979) Childrenn aged 6-11ys Number=808	0.018-0.122 Kitchen & Bedrooms	Medical Research Council Questionnaire	Positive association IRR=1.5 (95%CI:1.04-2.24)
Cross sectional (Houthuijs *et al*, 1987) Children aged 6-9ys Number=630	0.103 Personal exposure	World Health Organisation Questionnaire	Positive association
Longitudinal (Berwick *et al*, 1987) Children less than 7 ys Number=121	0.03-0.045	Bi-weekly phone calls for respiratory symptoms	Increased the risk of Lower respiratory infections OR=2.2 (95%CI:1.6-2.7)
Cross sectional (Melia *et al*, 1982) Children aged 5-6ys Number=179	0.005-0.161 in bedrooms 0.009-0.292 living rooms	Questionnaire for respiratory symptoms and illness	No significant association
Case control (Hoek *et al*, 1984) Children aged 6ys Number=231	0.022-0.057	Questionnaire for symptoms and illness occurrence	No significant difference between cases and controls
Cross sectional(Koo *et al*, 1990) Children aged 7-13ys Number=362	13.03-23.11	Medical Research Council and American Thoracic Society Questionnaires	No significant association
Longitudinal and cross sectional (Dijkstra *et al*, 1990) Children aged 6-12ys Number=1051	20-60ug/m^3	Modified World Health Organisation Questionnaire	No significant association OR=0.9 (95%CI 0.4 – 2.3)

1.2.1.4. Human studies, the effects of nitrogen dioxide on healthy people and asthmatics

A considerable number of studies have investigated the lung function response to nitrogen dioxide in healthy subjects, asthmatics and to lesser extent patients with chronic obstructive pulmonary disease. The results have been quite variable over a wide range of concentrations, which leaves us with an incomplete understanding of nitrogen dioxide effects in the lungs.

In healthy subjects, several studies have reported that exposure to 1.5-5 ppm of nitrogen dioxide significantly increases airway resistance (Beil and Ulmer, 1976) (Stresemann and Von Nieding, 1980). However, there have been occasional studies, like that from Linn et al, which were unable to demonstrate any effects on lung function, despite an exposure dose as high as 4ppm for 75 min with intermittent exercise (Linn *et al*, 1985).

There is more controversy concerning the effects of nitrogen dioxide concentrations below 1ppm on lung mechanics. Several studies have failed to demonstrate any significant effects at this low dose (Hackney *et al*, 1978;Kerr *et al*, 1979;Kleinman *et al*, 1983). Bylin et al, in a well designed study, were able to detect elevated airway resistance in healthy subjects exposed to a concentration as low as 0.24ppm without exercise (Bylin *et al*, 1985). However, a higher concentration of 0.51ppm, examined in the study did not cause any effect. It has been suggested that there may be a biphasic response to nitrogen dioxide, with mechanisms eliciting bronchoconstriction at lower and higher concentrations, but bronchorelaxation mechanisms dominating at concentrations around 0.5 ppm. So far, this is only speculative.

Beil and Ulmer demonstrated that healthy subjects developed an increase in airway reactivity following 7.5 ppm, but not 5 ppm, nitrogen dioxide for 2 h (Beil and Ulmer,

1976). Subsequent low dose studies with 0.1 ppm (Hazucha *et al*, 1983) and 0.48 ppm (Bylin *et al*, 1985) were unable to demonstrate any effect. Mohsenin and co-workers (Mohsenin, 1987) demonstrated an increased reactivity to methacholine in healthy subjects exposed to 2.0 ppm nitrogen dioxide for 1 h. This was further investigated by Frampton et al (Frampton *et al*, 1991) who found 1.5 ppm for 3 h to increase airway reactivity, whereas three 15 min peaks of 2.0ppm during a 3 h exposure to a basal concentration of 0.05ppm produced no effect.

Studies in asthmatics, Orehek et al (Orehek *et al*, 1976) demonstrated increased bronchial reactivity to carbachol after exposure to 0.1ppm, whereas other two studies conducted by Hazucha et al (Hazucha *et al*, 1983) and Jorres et al (Jorres and Magnussen, 1991) did not show an increase in bronchial reactivity with 0.1ppm and 0.25ppm. Kleinman and co-workers showed increased bronchial reactivity after 0.2ppm (Kleinman *et al*, 1983), as did Bylin and co-workers after 0.29ppm and 0.51 ppm (Bylin *et al*, 1985;Bylin *et al*, 1988).

Bauer et al (Bauer *et al*, 1986) studied the effects of 0.30ppm of nitrogen dioxide on the airway response of asthmatics. Instead of methacholine or histamine challenge, they used exercise and cold air provocation. These authors demonstrated that the nitrogen dioxide exposure caused hyperresponsiveness to these provocations.

Much of the lack of consistency among studies may be explained by the following: differences in measuring lung function, bias due to the readily identifiable smell of nitrogen dioxide, small sample sizes, timing of reactivity measurements (variable between 0-60 min after exposure), differences in the mode of action of bronchoconstrictorstimuli, whether subjects were exercising or resting, and differences in asthma severity (Chauhan *et al*, 1998).

Nitrogen dioxide induced inflammation has long been studied in animals models, using biopsy and bronchoalveolar lavage specimens (Glasgow *et al*, 1987;Gordon *et al*, 1986). The inflammation mainly involves high number of neutrophils and macrophages.

In humans, Helleday et al demonstrated a small, but significant increase in neutrophils in the bronchoalveolar lavage of healthy subjects 24h after exposure to 3.5ppm of nitrogen dioxide (Helleday *et al*, 1994). Similar data was obtained by Becker et al, there was a mild neutrophil response in the bronchoalveolar lavage after 4 h exposure to 2 ppm nitrogen dioxide.

Jorres et al reported that following a 3 h exposure to Ippm of nitrogen dioxide there was no significant changes in cell numbers in bronchoalveolar lavage or bronchial biopsy among healthy subjects (Jorres *et al*, 1995).

The cellular inflammation detected after higher concentrations of nitrogen dioxide over a short period was investigated in a dose-response study by Sandstrom et al (Sandstrom *et al*, 1991). Twenty four hours after 20 minutes exposure to 2.25-5.5ppm of nitrogen dioxide, small dose-dependent increases in mast cells and lymphocytes were found, without shift in CD4/CD8 ratio.

Rubinstein et al studied the effect of repeated exposure to low concentrations of nitrogen dioxide (0.6ppm) for 2 h for four days. No effects on bronchoalveolar lavage cell numbers were seen (Rubinstein *et al*, 1990).

1.2.2 Carbon monoxide

1.2.2.1 Sources and typical concentration

Gas cooker, pilot lights, unvented kerosene, gas space heaters, tobacco smoke, gasoline engines are the commonest sources of indoor carbon monoxide. The indoor range is 2-15 ppm in homes with gas stove.

1.2.2.2 Toxicological effect

Carbon monoxide is an odorless, colourless gas with well characterized effects on oxygen transport. Carbon monoxide interferes with oxygen transport by avidly binding to haemoglobin to form carboxyhaemoglobin and by shifting the oxyhaemoglobin dissociation curve to the left (National Research Council, 1977). It also binds to myoglobin, but the physiologic significance of the formation of carboxymyoglobin has not been established (Coburn, 1979). Tissues with highest oxygen needs, myocardium, brain, and exercising muscle, are most affected by the formation of carboxyhemoglobin.

1.2.2.3 General review of epidemiological studies

Pubmed and embase search was performed (1970-1998) to identify the studies which looked at the relationship between indoor carbon monoxide and the respiratory episodes.

Most evidence on the health effects of low levels of exposure to carbon monoxide, as generally encountered in indoor environments, has been derived from experimental human exposures. This line of investigation has emphasized disease states that increase susceptibility to reductions of oxygen transport: coronary artery disease, peripheral vascular disease, and chronic obstructive pulmonary disease (Aronow, 1983) (Kuller and Radford, 1983) (National Research Council, 1977).

The carboxyhaemoglobin level is only an approximate predictor of the effect of carbon monoxide on the brain. The effects of very high levels of carbon monoxide have well been documented. Significant deterioration of judgment, calculation, and manual dexterity have been detected at levels above 20% and 50% or greater can lead to coma and convulsion or death (Beard, 1982) . Sheps and colleagues demonstrated that exposure to 200ppm of carbon monoxide, produced direct adverse effects on the heart by facilitating ventricular extrasystoles in patients with coronary heart disease (Sheps *et al*, 1990). A multicenter study by Allerd and colleagues suggested that exposure of patients with stable coronary disease to carbon monoxide can induce earlier subjective and objective evidence of myocardial ischemia at carboxyhemoglobin levels as low as 2%-4% (Allred *et al*, 1989).

The relationship between carbon monoxide and cardiovascular disease has been demonstrated in several epidemiological studies. These studies looked at the association between ambient carbon monoxide and mortality and morbidity in the population. A study in Athens found an association between day-to-day fluctuations in carbon monoxide concentrations and mortality (Touloumi *et al*, 1996). The effect was greatest when same day data were used in the comparison and was independent of variables such as temperature, humidity, season, and day of the week. Similarly, studies in Los Angeles have shown that carbon monoxide concentrations are related to deaths from all causes (Shumway *et al*, 1988) and to deaths from cardiovascular diseases (Hexter and Goldsmith, 1971) (Shumway *et al*, 1988), allowing for all other pollutants and air temperature.

In studies of hospital admissions and carbon monoxide, an American study showed that ambient carbon monoxide levels were positively correlated with hospital admissions

for congestive heart failure, adjusting for other pollutants and temperature (Morris *et al*, 1995).

Another American study, in Tucson, Arizona, showed an association between ambient carbon monoxide concentrations and hospital admissions for cardiovascular disease(Schwartz, 1997). In this study an increase of 10ppm would correspond to a rise of 16.8% in admissions.

A study in London found significant relationships between average daily carbon monoxide concentrations and hospital admissions from 1987-1994 (Poloniecki *et al*, 1997). A rise of 10ppm in mean daily carbon monoxide corresponded to 23% more admissions of acute myocardial infarction, 6.9% more heart failure admissions and 23% more admissions for all circulatory diseases.

The above studies suggest that fluctuations in carbon monoxide levels increase the risk of hospital admissions or death due to cardiovascular disease. So far, no studies have looked at the association between indoor carbon monoxide and cardiovascular and respiratory diseases.

1.2.3 Particulate matter (Respirable, PM_{10})

1.2.3.1 Sources and typical concentration

The main indoor sources of particulate matter are tobacco smoke, unvented kerosene heaters, wood and coal stoves, and fire places. The typical indoor concentration of particulate matter is 10-100 $\mu g/m^3$ (1000 $\mu g/m^3$ in homes with fire places). Particles of less than or equal to 10 μm mass median aerodynamic diameter are referred to as respirable particles (PM_{10}).

1.2.3.2 General review of epidemiological studies

Pubmed and embase search was performed (1970-1998) to identify the studies which looked at the relationship between indoor particulate matter (respirable particles) and the respiratory symptoms and pulmonary function among asthmatic and non-asthmatic subjects.

1.2.3.2.1 Respiratory symptoms, pulmonary function test and exposure to particulate matter

Many indoor and outdoor epidemiological studies have demonstrated a negative relationship between the levels of particles and pulmonary function tests, although some did not. Studies in the United States have explored the relationship between wood burning and health. Honicky and co-workers in a survey of 31 children aged 1-7 who lived in homes using wood stoves and 31 children whose homes had no wood stoves found significant increase in the severity of respiratory symptoms was seen in the exposed children. There little difference in the prevalence of asthma between the two groups (Honicky *et al*, 1985), this study has not adjusted for the confounding factors such as dampness, humidity and smoking. Koenig et al demonstrated an association between the decline of pulmonary function in asthmatic children and the increase in

particulate matter (Koenig *et al*, 1993). Anderson et al conducted a cross sectional study and a longitudinal study to assess the effects of woodsmoke pollution on children. 1650 children were enrolled into the study from two communities, one at sea level where wood was not burned and the other in the highland where wood was commonly burned. The two groups did not differ on spirometry testing. The investigator also followed up 112 children with different levels of woodsmoke and did not find a consistent relationship between exposure and respiratory abnormalities during a 30 week surveillance period (Anderson, 1978).

Boezen et al studied the effect of PM10 on subjects with and without airway lability. There was a significant increase in the prevalence of upper and lower respiratory symptoms with increasing level of PM10, NO_2, SO_2. No consistent positive associations between the prevalence of respiratory symptoms and the levels of PM_{10}, NO_2, SO_2 in adults without airway labiality (Boezen *et al*, 1998). Pop and Kanner analyzed repeated FEV_1 measurements in a panel of chronic obstructive pulmonary disease patients who participated in a lung health study. Measurements were taken 10-90 days apart. FEV_1 level was reported to be associated with a 0.2% decrease in FEV_1 for each $10\mu g/m^3$ increase in PM_{10}, 0.2% decline may not be clinically significant but what this study suggests that high exposure to particulate matter would have significant impact on pulmonary function test. In the six cities study (Watertown, Kingston, St Louis, Steubenville, Portage, and Topeka), Neas et al showed no direct association between indoor particulate matter and children's pulmonary function measurements, but found an increase in the cumulative incidence of lower respiratory symptoms (Neas *et al*, 1994).

1.2.3.2.2 Peak flow variability and Particulate matter

Peak flow measurements have been widely used as an indication of acute changes in lung function among asthmatic patients. Pope and co-workers studied the association between daily changes in respiratory health and respirable particulate pollution (PM_{10}) on children. The investigator demonstrated a significant negative association between PM_{10} and peak expiratory flow rate. The was a stronger association between PM_{10} and the incidence of respiratory symptoms (Pope and Dockery, 1992). Similarly in Dutch school children weekly peak flow measurements showed a decline of approximately 0.16% for each $10\mu g/m^3$ increase in PM_{10} (Hoek and Brunekreef, 1993) (Hoek and Brunekreef, 1994).

1.2.4 Formaldehyde

1.2.4.1 Sources and typical concentration

The main indoor sources are consumer products (such as cosmetics, preservatives, furniture, textiles), cigarette smoking and gas cooking. The Environmental Protection Agency estimates average conventional home levels at 0.03 ppm. Formaldehyde may cause irritation to the lower respiratory tract at concentrations of 5 to 30ppm, but animal experiments have indicated that the molecule may not reach the lower respiratory tract in appreciable quantities (Chang *et al*, 1983;Egle, 1972).

1.2.4.2 General review of epidemiological studies

Pubmed and embase search was performed (1970-1998) to identify the studies which had examined the relationship between the respiratory symptoms, sensitization and pulmonary function and formaldehye.

1.2.4.2.1 Formaldehyde and asthma, pulmonary function test and airway hyperresponsiveness

Animal experiments demonstrated that formaldehyde is largely absorbed on the upper respiratory tract and very little reaches the lower respiratory tract (Chang *et al*, 1983;Egle, 1972). Therefore, the state of transient bronchial hyperreactivity demonstrated from exposure nitrogen dioxide in normal and asthmatic subjects appears less likely to occur with formaldehyde (Imbus, 1985). Frigas et al conducted a single blind bronchial provocation study on 13 subjects with asthma symptoms where formaldehyde was presumed to be a major triger or cause. Bronchial provocation with 0.1, 1.0, and 3.0 ppm of formaldehyde and randomly air-placebos were introduced. The investigators in this study was unable to confirm that formaldehyde was either causing or aggravating symptoms in any of the subjects (Frigas *et al*, 1984).

Asthma has been described in association with formaldehyde exposure by a number of investigators (Porter, 1975;Sakula, 1975). A Finnish study revealed positive bronchial provocation tests to formaldehyde in 12 of 230 persons with asthma-like symptoms who had been exposed occupationally to formaldehyde (Nordman *et al*, 1985).

Several studies have looked at the effects of formaldehyde on pulmonary function. A study conducted by Anderson and Molhave 16 subjects exposed to concentration of formaldehyde between 0.2 and 1.7 ppm for up to five hours with no effects on nasal resistance, expiratory vital capacity or tracheobronchial resistance (Anderson and Molhave, 1983). Horvath et al studied 109 workers (workers who were exposed to airborne formaldehyde at its particle-board or molded products operation) and 254 control subjects (workers who worked at food processing factories) to evaluate the effects of formaldehyde on the respiratory tract. The investigators demonstrated that formaldehyde can contribute to short decline in lung function in some industrial settings, but dose-response relationship were weak (Horvath *et al*, 1988). Farhang Akbar-khazadeh et al studied the effect of formaldehyde on the respiratory function of 50 non smoking medical students, compared with a group of physiotherapy students. The investigators found that the variables of respiratory function of both the exposed and the control subjects increased significantly within one hour and from one to three hours after exposure. The increase in respiratory function of the exposed group was significantly less than that of the control group (Akbar-Khanzadeh and Mlynek, 1997).

1.2.4.2.2 Formaldehyde and sensitization

In the past, concern regarding formaldehyde exposure has focussed on its potential as a carcinogen. In recent years the focus of attention has shifted towards the effects of low

level exposure to formaldehyde as a possible cause of immunologically mediated respiratory diseases (Smedley, 1996).

Specific IgE to formaldehyde has only seen in a small proportion of these subjects, who have reported formaldehyde-related symptoms (Kramps *et al*, 1989;Wilhelmsson and Holmstrom, 1987). Kramps et al found no specific antibodies among 28 adults exposed to formaldehyde in domestic and office environments (Kramps *et al*, 1989), But another study has shown that the prevalence of sensitisation increases with increasing exposure intensity (Cullinan *et al*, 1994).

Some investigators have not found any correlation between IgE and the prevalence of the respiratory symptoms (Wantke *et al*, 1996) (Wilhelmsson and Holmstrom, 1987). It would appear that even at relatively high exposure levels, inhaled formaldehyde rarely induces a specific immune response, and the relationship between the response and respiratory symptoms is poor. To date, environmental exposure to formaldehyde has not been proven as an important cause of immunologically mediated respiratory disease in adults (Smedley, 1996). Children may show an increase tendency to develop specific antibodies after exposure to formaldehyde, but their clinical significance is uncertain (Smedley, 1996).

1.2.5 Volatile organic compounds (VOCs)

1.2.5.1 Sources and typical concentration

Volatile organic compounds are a large and diverse group of compounds that volatize into the air at room temperature. VOCs are organic compounds with a boiling point range of 50-100 °C to 240-260 °C. Volatile organic compounds constitute an example of indoor air pollutants that are difficult to consider separately as human health hazards, but they have similar and considerable effects on health as a mixture (WHO, 1989).

The main indoor sources of volatile organic compounds are building materials (such as floor adhesive, floor wax, furniture polish, wood stain), consumer products (such as house hold and cleaning products, gardening and pest control products), and outdoor air penetrating indoor spaces via infiltration or ventilation.

The mean concentration of each VOC in established buildings is generally below 50μg/m^3, with most below 5μg/m^3, whereas total VOC concentrations are substantially higher (often 1100μg/m^3 in dwellings, reflecting the large number of compounds present) (Brown, 1994).

1.2.5.2 General review of epidemiological studies

Pubmed and embase search was performed to examine the relationship between VOCs and the respiratory symptoms (1970-1998).

Exposure to VOCs is associated with a wide variety of symptoms, but most of the health effects associated with these substances are the result of occupational exposure. The symptoms of VOCs exposure range from slight respiratory irritation to death (Ashley *et al*, 1996).

Several epidemiological and controlled studies have examined the relationship between the VOC concentrations encountered in the home environment and the risk of upper

and lower respiratory symptoms. Norback et al found a significant relationship between the concentration of total VOCs and asthmatic symptoms, especially dyspnoea (Norback *et al*, 1995). Bronchial hyperresponsiveness was significantly related to the indoor concentration of limonene and variability in peak expiratory flow to α-pinene and δ-karen. No relation was found between total VOCs and FEV_1% or PEF variability, bronchial hyperresponsiveness.

In a cross-sectional Swedish study of 562 subjects (Wieslander *et al*, 1997), the prevalence of asthma was increased among subjects with domestic exposure to newly painted surfaces (OR=1.5, 95% CI 1.0-2.4), particularly newly painted wood details (OR=2.3, 95% 1.1-4.5). Blood eosinophilia concentration was significantly elevated on subjects living in newly painted dwellings.

In a longitudinal study of personnel from 14 Swedish primary schools, Norback et al assessed the relationship between VOCs and upper airway irritation. They found a relationship between levels of VOCs and persistent upper airway symptoms (Norback *et al*, 1990). Koren et al reported a statistically significant increase in neutrophils in nasal lavage fluid of 14 subjects exposed to a mixture of VOCs (Koren *et al*, 1992). The mixture quality used (VOCs encountered in the home, 25ug/m^3) was thought to be representative of what is found in new homes. In a controlled chamber study, Harving et al studied the effects of 0, 2.5, 25μg/m^3 on non smokers volunters with bronchial hyperreactivity to histamine and bronchial asthma. The concentration of 25ug/m^3 is commonly observed in the occupational environment. At this concentration, a decline in FEV_1 during exposure was observed (Harving *et al*, 1991).

1.2.6 Environmental tobacco smoke

1.2.6.1 Components of Environmental tobacco smoke

The primary components of ETS are side stream smoke (SS) emitted from the smoldering tobacco between puffs, and main stream smoke (MS) exhaled by the smoker. When a cigarette is smoked, roughly one half the generated smoke is SS and the other is MS. However, ETS differs from fresh SS because of dilution and particle deposition on surfaces. The mean particle diameter is about 0.2-0.5μm. More than 2000 compounds have been identified in cigarette smoke, many of which are established carcinogens, irritants.

1.2.6.2 Environmental tobacco smoke, bronchial reactivity and peak flow variability

Pubmed and embase search was performed to identify the studies which have looked at the effect of environmental tobacco smoke on health (1970-1998).

Numerous studies have suggested that exposure to ETS increases the frequency and severity of asthma symptoms. Alteration of non-specific bronchial hyper-responsiveness, is thought to be one of the main effects of ETS on asthmatics.

Fielder et al showed that ETS increases airway variability in children with and without asthma (Fielder *et al*, 1999).Of greater potential importance is whether there are subgroups of children that are particularly susceptible to cigarette smoke. Another study of 40 children aged 10 -11 yrs in Italy reported lower average levels but greater variability in peak expiratory flow in children exposed to ETS. The sample excluded asthmatics and those with respiratory diseases (Casale *et al*, 1992).

A Dutch study on asthmatics reported that circadian variation in peak expiratory flow in asthmatic children was greater in 26 children exposed to ETS in the home than in 29 non- exposed children (Meijer *et al*, 1996).

1.2.6.3 Asthma, Wheezing, Respiratory symptoms and environmental tobacco smoke

Parental smoking is an important risk factor for childhood asthma. In children aged 0-5 yr., maternal smoking was associated with a higher prevalence of asthma (OR=2.1), increased use of medication (OR= 4.6), and an earlier onset of asthma (OR= 2.6) than was observed in children of non-smoking mothers (Weitzman *et al*, 1990).

McConnochie and Roghmann assessed predictors of wheeze in a retrospective cohort study of children who had mild bronchiolitis in infancy and of control children without illness. At mean age of 8.3 yr., current exposure to tobacco smoke at home was significant predictor of wheeze (OR=1.9, P=0.05) (McConnochie and Roghmann, 1985).

In the study of children of Tecumseh, Michigan, parental smoking was associated with a higher prevalence of asthma at the initial examination and with a doubling of the risk for developing asthma during the 15 year follow up period (Burchfiel *et al*, 1986).

In a cross sectional study of 650 children in Massachusetts, the prevalence of persistent wheeze increased significantly with the number of smoking parents, but was unrelated to smoking by the children themselves (Weiss *et al*, 1980).

Cogswell and colleagues found that 62% of the children of smokers developed wheeze by the age of five, compared with 37% of children of non-smokers (Cogswell *et al*, 1993). In a case- control study, Ehrlich et al studied passive smoking and childhood asthma. Acute and non-acute asthmatic children had similar prevalence of passive

smoking at home. Acute asthmatic subjects showed higher mean cotinine /creatinine ratio than non-acute cases, but this was not significant (Ehrlich *et al*, 1992). In comparing all asthmatics children to control, smoking by the maternal caregiver was more prevalent among asthmatic children (OR= 2.0, 95% CI 1.1-3.4).

This finding was confirmed by cotinine creatinine ratio (OR= 1.9, 95% CI 1.04-3.35) and the difference in mean CCR 943.6 versus 25.8 ng/mg, P =0.06)

Palmieri et al examined the relationship between parental smoking and asthma in childhood. 302 white children between 1 and 12 years of age with a history of at least three asthma attacks in the past year, compared with a control group of 433 matched children (Palmieri *et al*, 1990). All asthmatic children underwent skin prick testing to define their atopic status. The number of heavy parental smokers was statistically higher in the skin prick test negative group. This study concluded that parental smoking is the main risk factor for skin prick test negative asthmatics.

Goren and hellman (Goren and Hellman, 1995) examined links between self reported exposure to tobacco smoke and respiratory conditions in school children in Israel. Over 8000 second and fifth grade student's parents were surveyed, with a 91% response rate over all. Prevalence of most respiratory symptoms including cough and wheezing, was found to be higher among children whose fathers or mothers were smokers than children with non smoking parents. The study also found statistically more reports of asthma among children exposed to paternal or maternal smoke than those of non-smokers. This prevalence was greatest among children who had two parents smoked, demonstrating a dose- response effect.

1.2.6.4 Pulmonary function test and environmental tobacco smoke

Many epidemiological studies have demonstrated the adverse effect of parental smoking in children's lung function, lung growth and development. Evidence that passive smoking has a significant effect on lung function has come from the Harvard longitudinal study of childhood risk factors for the development of adult chronic obstructive airway disease. In a seven-year prospective study of 1156 children from this cohort there was a significant association between maternal smoking and lower FEV_1 and forced mid expiratory flow rate, maternal smoking lowered the expected increase of FEV_1 by 7-10 % over this period, even after correction for confounding factors (Tager *et al*, 1983).

Burchfiel examined the effects of parental smoking on 15 year lung function change of subjects in the Tecumseh study (Burchfiel *et al*, 1986). In the female subjects who remained non smokers across the follow up period, parental smoking was not associated with lung function change. In non-smokers males, parental smoking reduced the growth of FEV_1, FVC and $Vmax_{50}$ (flow at 50% of the vital capacity). For the FEV_1 in males, the analysis estimated 7.4% and 9.4% reductions in 15 year growth associated with 1 or 2 smoking parents (the increase of FEV_1 with age), respectively.

Murry and Morrison (Murray and Morrison, 1988) compared the lung function of 247 children of mothers whose smoking habits were recorded by questionnaire. Lung function as measured by FEV_1 was found to be significantly lower and bronchial reactivity was significantly higher with histamine concentration producing a 20 % fall in lung function being related to the amount of admitted maternal smoking.

David Strachan et al studied the effect of passive smoking on pulmonary function and the respiratory symptoms on 770 children (mean age 7yrs), using cotinine as a

biomarker of exposure (Strachan *et al*, 1990). After adjustment for sex, height and housing tenure, all baseline spirometric indices except FVC were inversely associated with salivary cotinine. Only FEF_{75-85} and FEF_{75} were significantly reduced. These changes may be evidence of small airways damage, which could later progress to more severe respiratory impairment.

In a British study Rona and Chinn examined the relationship between lung function and passive smoking on 2756 children aged 6.5- 11.9 year (Rona and Chinn, 1993). Samples represented Scottish, English, inner city and ethnic minority children. Maternal smoking, but not paternal smoking, was associated with reduced FEF_{25-75} (forced expiratory flow rate) and FEF_{75-85} in boys. No significant association was found between pulmonary function test and passive smoking among girls in this study.

1.2.7 Dampness and asthma

Recently, with the increasing prevalence of asthma reported in several countries, there have been a number of community surveys which have looked either at the effect of housing conditions on health in general or, more specifically, at the relationship between respiratory symptoms/asthma and damp housing and mould. Children are particularly suitable for assessment of the influence of environmental factors on respiratory disease because active smoking and occupational variables are excluded.

Martin et al on a questionnaire study in Edinburgh, found children living in damp houses, especially where fungal mould was present, had higher rates of respiratory symptoms, which were unrelated to smoking in the house hold. In this study no conclusive effects of damp on the health of adults were identified (Martin *et al*, 1987).

On a Swedish study parents of children aged 6months – 16 years living in rural areas in Sweden , were sent a questionnaire regarding respiratory symptoms reflecting bronchial hyperreactivity and allergic asthma (Andrae *et al*, 1988),. There was a significant association between dampness and allergic asthma, chronic cough, exercise induced asthma and allergic rhinitis. The most noticeable effects were found in children having a family history of asthma.

Platt and co-workers found children living in damp and mouldy dwellings had a greater prevalence of respiratory symptoms, headaches and fever compared with those living in dry dwellings (Platt *et al*, 1989). The mean number of symptoms was higher and positively correlated with increasing severity of dampness and mould. Adults lived in a damp house reported more symptoms including blocked nose, breathlessness, nausea and vomiting, backach and fainting.

On a population – based Canadian study in the town of Humbolldt, Saskatchewan, Canada, it was found that damp housing is a risk factor for reported chronic wheeze, recent asthma and wheeze with shortness of breath in women but not in men (Rennie *et al*, 1994). This study included 1998 subjects 18-74 years of age.

Andriessen and co-workers found a positive relationship between peak expiratory flow variability, the prevalence of cough and upper respiratory symptoms and dampness (Andriessen *et al*, 1998).

Mohamed and co-workers conducted a case –control study in Nairobi, including 77 school children with asthma and 77 children age and gender matched control (Mohamed *et al*, 1995). There was a strong association between asthma and dampness and other home environmental factor (air pollution: the type of fuel used for cooking and heating).

On another case – control study carried out by Williamson and co-workers (Williamson *et al*, 1997), asthmatic patients aged 5- 44 yrs attending Glasgow chest clinic were age and sex matched to controls. All subjects were interviewed for health, social and behavioural information, and dampness was measured by independent surveyor. Dampness was found higher in asthmatic's homes as compared to control's homes. The association between asthma and dampness persisted after controlling for socioeconomic and other confounding factors such as smoking and pets. The severity of asthma was found to correlate statistically with measures of total dampness and mould growth.

Nicolai et al (Nicolai *et al*, 1998) of the university children's clinic in Munich has demonstrated a positive relationship between nocturnal wheezing, and dyspnoea and

dampness among asthmatic children (OR=16). This relationship has remained significant even after adjusting for the level of house dust mite (OR=5.8).

Recently, a literature review was performed by Bornehag et al to evaluate the association between dampness and the respiratory symptoms (Bornehag *et al*, 2001). 61 studies have been the foundation of this review. This review has concluded that there is a causal relationship between dampness and the respiratory symptoms. One of the possible mechanisms is that dampness increases sensitization to mites.

1.3 Methods of indoor air pollution exposure assessment

1.3.1 Direct methods of exposure assessment

1.3.1.1 Personal monitoring

Personal monitoring samplers are of two types, personal passive samplers and personal exposure monitors. Both methods have the advantage of providing direct and detailed personal exposure to air pollution. The disadvantage of passive sampling devices is that all short exposure information is left, and for the personal exposure monitoring is the cost and the amount of work needed for calibration (Jantunen *et al*).

1.3.1.2 Biomarkers

The use of selected and well validated biomarkers may be useful in assessing the exposure to air pollution. Several biomarkers are relevant for typical indoor air pollutants, for example urinary cotinine is used for exposure to environmental tobacco smoke. Using biomarkers in research is costly and also to collect a biological material from the volunteers may influence the feasibility of the study (Jantunen *et al*).

1.3.2 Indirect methods of exposure assessment

1.3.2.1 Microenvironment monitoring

The average concentrations of the pollutants of interest in microenvironments visited by the subjects can be determined by microenvironmental monitors located in all or selected microenvironments relevant to the study. If continuous microenvironmental monitoring and time-activity are used, the difference between such a study and a study based on personal exposure monitoring may be quite small.

1.3.2.2 Questionnaire and time activity diaries

Time – activity diaries and survey questionnaires can be very helpful in relating sources and concentrations to exposure. Time – activity diaries is usually address the activities

of individuals, whereas survey questionnaires are generally focused on the household characteristics (Jantunen *et al*).

1.4 Assessment of respiratory illnesses in relation to air pollution exposure

Research on air pollution and respiratory diseases has focused largely on infants and younger children. Children, particularly infants have been considered susceptible to inhaled pollutants because their lungs are maturing and rates of respiratory infections in this age group are the highest of any (Monto and Ultman, 1974). The occurrence of respiratory illness can be monitored using subject report of illnesses or by using inpatient or outpatient clinical records.

Retrospective information using questionnaire about respiratory illnesses, can be collected readily but recall bias is likely (Samet *et al*, 1983). With prospective studies the bias risk is less, but it requires an elaborate system to ascertain the occurrence of the respiratory illness. Surveillance approaches using calendar diaries for recording symptoms have been applied successfully in community based studies on respiratory illnesses (Johnston *et al*, 1995).

Bias due to misclassification of health outcomes has been highlighted as a major limitation of epidemiological studies investigating the health effects of air pollutants (Committee of the Environment and Occupational Health Assembly of the American Thoracic Society, 1996b). Retrospective questionnaires have been used to assess respiratory illness in several studies, and are believed to be particularly prone to misclassification, which may explain in part the inconsistencies in the findings of epidemiological studies

In an attempt to overcome this problem, an increasing number of investigators have used daily diary cards to assess prospectively the frequency and severity of respiratory

illness (Mukala *et al*, 1996;Samet *et al*, 1993). By recording the respiratory health of each subject on a daily basis over time, diaries provide a sensitive means of detecting short term changes in an individual's health. These can then be related to fluctuations in concentrations of pollutants to which the individual has been exposed.

Diary symptom-recording has also proved to be a more sensitive means of monitoring asthma than the more commonly used objective measurement of peak expiratory flow (Clough and Sly, 1995).

Recently several epidemiological studies used diary cards to demonstrate the incidence of peak expiratory flow and URT and LRT episodes (Johnston et al 1995; Clough et al 1991; De Bildering: DM thesis; C H Linker: PhD thesis). Several approaches were used to define the episodes, the method of computer defined episode was used by Johnston and co-workers (Johnston et al, 1995) and Clough and co-workers (Clough et al, 1995). In the first study a significant episode of lower and upper respiratory symptoms was defined as a period of at least two days during which the relevant symptom score rose above the individual child's median score for the study duration, preceded by one day and followed by two days at or below the median. In the second study, a symptom event was defined as a period during which the lower respiratory symptoms equaled at least three symptom units within three consecutive days, followed by at least two symptom – free days. Different methods were taken in the study conducted by Linker and co-workers, since the computer-defined episodes were thought to have produced too many episodes. In Linker's study, different types of computer- defined episodes were used; all were thought to have over-estimated the incidence of the episodes. Therefore it was decided that a clinician-defined episode

was probably the most accurate one. The same approach was considered in the study conducted by De Bildering and co-workers (unpublished DM).

One complication arising from the use of diary studies is the variability (heterogeneity) among individuals in their rating of symptoms. An individual's threshold for recording symptoms may be influenced by factors such as illness history-subjects with chronic symptoms may underestimate and consequently underreport episodes of illness (Clough and Sly, 1995). It may also depend upon who fills out the diary cards on a particular day (i.e. parent or child). Researchers have observed a tendency for individuals to record more symptoms in the early weeks of diary keeping, whereas towards the end of the study, participants may tire of the procedure, and be inclined to maintain less accurate records of their health status (Hammer *et al*, 1974).

Another method of assessing the occurrence of respiratory illnesses is by using the inpatient and outpatient medical records. However, the frequency of the respiratory tract infections could be underestimated by using this method, as the severity of the respiratory episodes and the access feasibility to the health care providers may be the determining factors of the health visits(Samet and Speizer, 1993).

1.5 Air pollution, aeroallergens and asthma and allergic diseases

The presence of aeroallergens in the atmosphere has been shown to be associated both with occasional outbreaks of asthma involving large increase in morbidity and day to day variation in symptom severity among asthmatics and individuals with allergen-related conditions such as hay fever.

The presence of air pollutants could exacerbate the severity of symptoms response to a given level of allergen exposure in atopic individuals. Peat et al study showed that an increase in the prevalence of hay fever and asthma was not associated with an increase in the prevalence of atopy. Therefore, Peat et al suggested that there may be some association between the two diseases (asthma & hay fever) and air pollution (Peat *et al*, 1994).

Pollutants such as Ozone and sulpher dioxide are known to react chemically both with individual amino acids, and with proteins, and may cause changes in the allergenicity of allergens. The potential for such effects has been demonstrated by Ruffin et al (Ruffin *et al*, 1986), in this study pollen of oak, fescue and elm were exposed to sulpher dioxide , nitrogen dioxide and carbon monoxide, individually or in combination. They were able to demonstrate in most cases an increase in free amino acid content, which they suggested was of significance because those species having pollen with a high allergenic potential tend to have a high free amino acid content. There was also evidence of effects on low molecular weight proteins.

In a study with cell wall extracts of red oak pollen, pollutant exposure was shown to affect both levels of histamine release in human leukocyte suspensions and the patterns of antibody formation after injection into rabbits (Ruffin *et al*, 1984).

Concern about the spatial and temporal association between the prevalence of allergic rhinitis and the numbers of motor vehicles in Japan has led to a number of studies with diesel exhaust particles (Ishizaki *et al*, 1987). These Japanese studies with mice have demonstrated that diesel particles can act as an adjuvant and increase production of IgE. This has been demonstrated by intraperitoneal injection of a mixture of diesel particles and ovalbumin (Muranaka *et al*, 1986) or of a combination of diesel particles and ceden pollen, and by intranasal administration of combinations of particles and ovalbumin (Takafuji *et al*, 1989).

Effects of ozone in increasing the response to antigen challenge were also reported in dogs by Yanai et al at a concentration of 3000 ppb, this response was only observed in sensitized animals (Yanai *et al*, 1990).

Studies on dogs, short term exposures to ozone (1ppm for 5 minutes) have demonstrated an attenuation of the response to allergen administrated up to 24 hours later (Kleeberger *et al*, 1989;Turner *et al*, 1989).

In the case of sulpher dioxide exposure to a relatively low concentration (100ppb for 8 hours on consecutive days) facilitated allergic sensitization to ovalbumin in four out of six guinea pigs, with increased antibody concentrations being found in bronchoalveolar lavage (Riedel *et al*, 1988).

These animal studies provide some evidence of pollutant/allergen interactions, but most of these studies have used very high pollutant concentrations.

Several human studies have looked at the effects of allergen challenge post exposure to a single and mixture of pollutants. Devalia et al investigated the interaction between two pollutants (sulpher dioxide and nitrogen dioxide) and an allergen (Devalia *et al*, 1994). Eight subjects were exposed for six hours to room air, 400 ppb nitrogen dioxide

alone, 200ppb sulpher dioxide, and 400 ppb nitrogen dioxide and 200 ppb sulpher dioxide. After each treatment the response of the subjects FEV_1 to allergen inhalation was determined. The four pollutant treatments were given on four separate occasions, each at least a week apart with the order being randomized among the subjects unaware of the order. In this study no significant effects of any pollutant treatments alone was found on FEV_1 or FVC. The inhaled allergen dose estimated to produce 20% fall in FEV1 (PD20 FEV_1) was significantly reduced, by approximately 60% by the nitrogen dioxide and sulpher dioxide treatment compared with the control treatment. The PD20 FEV_1 values were also reduced by 41% by nitrogen dioxide alone, and by 32% by sulpher dioxide alone, but these effects were not statistically significant.

Tunnicliffe et al investigated the effects of nitrogen dioxide on both early and late asthma response using two concentrations (100 ppb and 400ppb) (Tunnicliffe *et al*, 1994) . It was demonstrated that exposure to nitrogen dioxide at a concentration of 400 ppb, was associated with a significant change in the early and late asthmatic response. Exposure to a concentration of 100 ppb nitrogen dioxide showed no effects on the early or late asthmatic response.

Several epidemiological studies demonstrated several outbreaks of asthma in relation to specific meteorological conditions. A major example in England was the outbreak associated with thunderstorms in June 1994 (Murray *et al*, 1994). On the night of June 24/25 of 1994 the Accident and Emergency departments of many London hospitals were overloaded with large numbers of cases presenting with asthma/wheeze. Department of Health suggested that four of eight Regional Health Authorities had been particularly affected; these were Anglia and Oxford, North Thames, South Thames, and the Trent. The majority of the patients were adults and many of the

patients had not been known asthmatics previously. The timing and geographical distribution of cases suggested that there was an association with a thunderstorm that passed over London during the evening of June (Campbell-Hewson *et al*, 1994;Murray *et al*, 1994;Sutherland and Hall, 1994). The concentrations of air pollutants in the London area during that week had been highest on June 24, probably because of the calm, still conditions that preceded the storm. The highest hourly average concentrations of ozone, nitrogen dioxide and sulpher dioxide were 44, 126 and 48 ppb respectively, none of these levels exceeded the WHO air quality 1-hour guidelines. In this episode, the daily average grass pollen count reached 258 grains/m^3, this was the highest daily count recorded since 1987 at the monitoring site. There was also a massive rise in the fungal spores (Campbell-Hewson *et al*, 1994).

Linkage of asthma epidemics to thunderstorms occurring at Birmingham, England and Melbourne, Australia had been demonstrated in two previous studies (Bellomo *et al*, 1992;Packe and Ayres, 1985). In these two episodes the levels of fungal spores (Packe and Ayres, 1985;Packe and Ayres, 1986) and grass pollen had been raised at the time of epidemics (Bellomo *et al*, 1992;Knox, 1993).

In general, most analyses of the effects of air pollution episodes on the severity of the symptoms of allergic disease have considered only air pollution levels, and not those of aeroallergens. Similarly, panel studies (cohort studies) of asthmatics have generally only considered air pollution or aeroallergen levels separately, and not investigated in any formal statistical manner the possible interactions of these two factors. Therefore, it is possible that these outbreaks of asthma in these episodes were as a combination /interaction of air pollution and aeroallergens.

CHAPTER 2

Methods and Materials

2.1 Hypothesis

We hypothesized that exposure to indoor air pollutants increases the incidence, severity and duration of lower respiratory tract, upper respiratory tract and peak expiratory flow episodes in asthmatic children and their mothers.

2.2 Objectives

The objectives of this study are:

1. to test whether the incidence, severity and duration of upper and lower respiratory tract symptoms and episodes of reduced peak expiratory flow are related to exposure to nitrogen dioxide, environmental tobacco smoke, volatile organic compounds, formaldehyde, carbon monoxide, allergen and dampness among asthmatic children and their mothers.
2. to determine whether, among these individuals at times of upper respiratory tract symptoms, exposure to these indoor environmental factors increases the risk of
    a. Lower respiratory tract symptoms
    b. Episodes of reduced expiratory peak flow

2.3 Study design

Asthmatic children and their mothers were followed up for one year. Upper and lower respiratory tract symptoms and peak flow measurements were recorded daily using diary cards.

2.4 Study population

The inclusion criteria for the asthmatic children:

1. Asthmatic children aged 7-14y
2. Regular use of inhaled corticosteroid (100 – 400ug per day)

Children with other respiratory conditions and cardiac diseases were excluded from the study. All mothers were enrolled in the study, we enrolled all the mothers in the study to enhance the compliance of the children as well as to study the effect of indoor air pollution on adults.

2.5 Power and sample size calculation

The study hypothesis suggests that with increasing pollutant levels the frequency, severity and duration of respiratory symptoms are expected to increase. We used the rule of thumb to calculate the sample size for regression analysis. The rule of thumb relates the number of parameters (P= the number of variables; i.e the indoor air pollutants and co-factors like dampness) to be fitted in the multivariate analysis, to the number of subjects (N) to be included in the study. The rule of thumb recommended by Altman DG (Head of Medical Statistics Laboratory; Imperial Cancer Research Fund; London) is P= N/10. In this study we planned to fit 11 variables in the multivariate linear regression; therefore according to the above equation 110 subjects should be recruited for our study.

For the second objective of the study (to test whether exposure to indoor air pollutants increases the risk of developing lower respiratory symptoms and peak expiratory flow episodes following an upper respiratory tract episode), we proposed to use multiple logistic regression. The sample size of 110 subjects provides an odd ratio (OR) of 1.67- 2.50 at 5% level with 80% power. Previous epidemiological study (De

Bilderling G; unpublished DM thesis on the relationship between indoor air pollution and adult asthmatics in Southampton City) was used to calculate the sample size of this study. A formal approval was obtained from Dr De Bilderling and the supervisors (Dr J Clough & Professor S T Holgate) to use the data in calculating the sample size of this study. The same statistician was involved in the analysis of the two studies. The data of indoor pollutants were divided in two groups (high and low: Binary outcome), and therefore the power calculation depends on the proportion of successes expected in the lower group versus the higher group. Table 2.1 demonstrates the detected OR with different LRT:URT ratios.

Table 2.1: Odd ratio detection of a sample size of 110 subjects at 5% level with power of 80%.

Population according to levels of indoor air pollutants	Different Ratios of LRT: URT episodes				
Population with low indoor air pollution levels	0.10	0.20	0.30	0.40	0.50
Population with high indoor air pollution levels	0.21	0.33	0.43	0.53	0.62
Odd Ratio	2.5	1.9	1.8	1.7	1.6

2.6 Selection of general practitioners

Thirty primary care Health centers were written to, asking their permission to use their lists of asthmatic subjects, previously used in other studies at Southampton University (Appendix 1).

It was clearly highlighted in the letter that this study would not involve any extra work load for them and also that only subjects who have not been involved in a previous epidemiological (1997-1998) studies would be recruited for this study (to avoid involving children into several studies at the same time which might has an impact on their daily normal activities, therefore precise checking of the database was performed before writing to the subjects).

Twenty out of the thirty primary care health centers responded positively. Six health centers have permitted us to use a room in the health center for recruitment, entry visit and follow up of the enrolled population. These health centers were

- Alma Road Health center
- Tottan Health center
- Bitterne Health center
- Lordshill Health center
- Hythe Health center
- Hedge End Health center

2.7 Recruitment of volunteers

We wrote to the families with asthmatic children, using GP letter head, inviting them to take part in the air pollution study (appendix 2). An information sheet about the study was enclosed with the letter, explaining the objectives of the study, and also an information sheet was provided about the indoor pollutants we were intended to

measure (appendix 3). Families, who agreed to participate in the study and fulfilled the inclusion criteria, were invited for the entry visit at Southampton General Hospital or at one of the allocated Primary Care Health Center.

2.8 Preliminary meeting with volunteers

The introductory visit took place at either Southampton General Hospital or at one of the primary care Health Centers. On average four families were screened per day. In this visit general information about indoor air pollution and its potential detrimental effect on health, was discussed. The methods of measuring indoor air pollutants were demonstrated. We asked each family to sign a consent form at this visit (Appendix 4). The family doctor was informed (written letter) about the enrolled family (Appendix 5)

2.8.1 Spirometry measurement and general information about measuring peak expiratory flow

At the entry visit spirometry was measured, using vitalograph (BS1 Q5640, Vitalograph Ltd, Buckingham, UK). The best out of three spirometry measurements was used in the analysis. The technique of measuring peak expiratory flow was checked with each subject. All subjects were supplied with peak flow meter.

2.8.2 Skin prick test

Skin prick test was performed at the entry visit on mothers and children. We tested for the following aero-allergens: Dog, cat, dermatophagoides pteronyssinus, alternaria tenvis, aspergillus fumigatus, tree mix, feather mix, grass mix (Bayer Corporation Pharmaceutical Division). A positive reaction was considered to be a wheal $\geq$ 2mm. Skin prick test was read by one researcher.

2.9 Respiratory symptoms scoring and peak expiratory flow measurement

Diary cards (appendix 6) were used to record:

1. Daily symptoms of upper and lower respiratory tracts infections.
2. Morning and evening peak expiratory flow measurements.

The upper respiratory tract symptoms listed in the diary cards were runny nose or sneezing, blocked or stuffy nose, sore throat or hoarse voice, headache, aches or pains and chills or fever. The lower respiratory tract symptoms listed in the diary cards were cough, wheezing during the day or on waking, shortness of breath during the day and any night symptoms (cough, wheezing and shortness of breath).

Scoring system was used to characterize the severity of each symptom (Score 1-3), Score 1 meant ' mild' symptom, score 2 and 3 were used to represent moderate and severe symptoms, respectively. The space was left blank if the subject had no respiratory symptoms to report. The total score for each day was documented in the space provided in the diary cards. Each diary card lasts for two weeks.

The best out of three recorded evening and morning peak expiratory flow measurements was documented in the diary cards. An information sheet about the method of filling the diary cards was given to each family (appendix 7). A code was given to each family to document in the diary card (e.g. the first family in the study was asked to put number one as an identity for the family). The code (01) was used for the mother and (02) for the child, as an identity to put in the diary card (for example the child in the first family in the study used the code 01/ 02, and the mother used 01/01). For those families with two children in the study, letter (a) was used by the child's code to represent the older one, and letter (b) to represent the younger one. Screening visits were carried out between August 1998-September 1998.

2.10 Air pollutant measurements and data collection

Four home visits were carried out to measure indoor air pollutant levels (First visit: October- November, Second visit :February –March, Third visit: April-May, Fourth visit: June-July). The availability of the families was an important issue in this study, therefore practically we felt we should perform the visits during the months which coincide with the summer/half term holidays.

This schedule of measurement of pollutants was chosen to establish whether the level of the pollutants are different in different seasons.

Table 2.2 demonstrates the schedule of air pollutant measurement. Measurements were made using active samplers for carbon monoxide, particulate matter and passive samplers for nitrogen dioxide, formaldehyde, and VOCs (volatile organic compounds) (appendix 8). All samples were analysed at GMSS Ltd (Greater Manchester for Scientific Services). Urine cotinine was measured to reflect the exposure to environmental tobacco smoke.

All the tubes and the devices used for pollutant measurements were delivered by a researcher to the families. Passive samplers were placed at 6ft height in the kitchen and the lounge, PM_{10} and carbon monoxide devices were placed at 6ft height and 4ft distance from the cooker.

Table2.2: Frequency, location, and duration of measurements of indoor air pollution

pollutants	type	period	Visit 1	Visit 2	Visit 3	Visit 4
Nitrogen dioxide	personal mother	7 days	+		+	
	personal child	7 days	+		+	
	Kitchen Peak	7 days	+		+	
	Kitchen mean	7 days	+		+	
Particulate Matter	Kitchen	24 hours	+			
Carbon monoxide	Kitchen	24 hours	+			
Tota VOCs	Lounge	28 days		+		+
Formaldehyde	Lounge	7 days		+		
Derp 1	Lounge	stat		+		
	Bedrooms	stat		+		
Dampness	Lounge	stat	+		+	
	Bedrooms	stat	+		+	
Environmental tobacco-smoke (cotinine)	Urine(mother)	stat	+		+	
	Urine(child)	stat	+		+	

2.10.1 Nitrogen dioxide

Two types of nitrogen dioxide measurements were performed:

1. Personal nitrogen dioxide: Both the child and the mother were asked to wear a sampler (Palmes tube; Manchester, UK) for seven days. The sampler was worn indoor only, at night the tube was left un-capped in the bedroom.

2. Kitchen nitrogen dioxide: Continuous as well as peak nitrogen dioxide levels in the kitchen were measured using passive samplers (Palmes tube; Manchester, UK). The sampler of continuous kitchen nitrogen dioxide was left opened for seven days, whilst the sampler for peak nitrogen dioxide was uncapped during cooking only; diary cards were supplied for this purpose to record the time of uncapping and capping the tubes. Written instructions were given to the families about the use of the samplers.

Personal and kitchen nitrogen dioxide measurements were repeated twice (summer measurement: April- May & winter measurement: October- November) during the study. Written and verbal instructions were provided. The samplers were colour coded (Red: child personal nitrogen dioxide; Blue: mother personal nitrogen dioxide; Green: kitchen continuous nitrogen dioxide; Orange: kitchen peak nitrogen dioxide).

Palmes tube sampler consists of a polycarbonate tube sealed at one end with a time – dependant coloured polythene cap which contains two steel mesh discs impregnated with triethanolamine (nitrogen absorping agent). The other end of the tube is sealed with a white cap which is removed during sampling.

2.10.2 Carbon monoxide

The exposure to carbon monoxide in the kitchen was measured using an electro-chemical device (Manufactured at Medical Physics and Bioengineering Department: Southampton University). Exposure to carbon monoxide was measured over 8h period

(Sampling was carried out between 12-8 pm, a timer was used for this purpose). This was performed during the winter season only.

The CO sensor is an electro-chemical cell. Carbon monoxide diffusing into the cell is oxidised thereby producing a small electric current in an external circuit. The size of this current is proportional to the concentration of gas present outside the sensor and therefore gives a direct measure of the toxic gas present.

2.10.3 Total respirable particles

Particulate matter was measured using an active sampler (Casella BMS-2, flow rate 2.2 L/min; GMSS Ltd, Bedfordshire, UK). Sampling was carried out over 24h. Air is sampled for a fixed time (24 hours) and particles are captured onto a filter paper. The filter is weighed before and after sampling, the difference between the two measurements represents the total respirable particles.

2.10.4 Volatile organic compounds and formaldehyde

Both were measured using passive samplers (VOCs passive diffusion tube: Perkin Elmer Thermal desorption tube; Formaldehyde diffusion badge/3M; Perkin Ltd, Pittsburgh, USA). Formaldehyde was measured in the summer only (May-September), whilst VOCs was measured twice (summer measurement: May-September, winter measurements: October-January) in the study.

Volatile organic compounds migrates down the passive sampler by diffusion and are adsorbed onto a polymeric material, then the adsorbed solvents are desorbed from the polymer and analysed by capillary gas chromatography.

Formaldehyde is adsorbed onto a polypropylene sampler, Capillary gas chromatography is used to analyse formaldehyde concentration.

2.11 Cofactors measurements and data collection

2.11.1 Dampness

Dampness was measured twice in the study, using dampmeter (Protimeter PLC; Marlow, UK). Measurements were carried out above the skirting board on each wall of the two bed rooms and the lounge.

2.11.2 Cotinine (environmental tobacco smoke)

Cotinine was measured twice in the study. Urine analysis was performed at Department of Chemical Pathology (Southampton General Hospital) using radio-immuno assay.

2.11.3 House dust mite (der pI)

Dust was collected from the two bedrooms and the lounge by hoovering the carpet for 5 minutes in each room. Dust sample was extracted in phosphate buffered saline (Ph.7.2) containing 0.5% (v/v) Tween 20 and 0.2% (w/v) bovine serum albumin (BSA). The buffer was added at 1:10 (weight of dust to volume) and filtered the following day with 0.2 μm pore size syringe filters (Whatman,UK). Enzyme linked immunosorbant assay (ELISA) methodology was used to measure der pI (Indoor Biotechnologies, Chester, UK).

2.12 Statistical analysis

For the first objective of the study, two analyses were performed:

1. Univariate Poisson regression analysis was performed to study the frequency, duration and severity of the respiratory episodes versus each pollutant.
2. Multivariate regression analysis; in this model the following variables were included in the analysis: nitrogen dioxide, der pI, atopy, formaldehyde, volatile organic compounds, cotinine, gender and age. Carbon monoxide and particulate matter was not entered in this analysis as there was significant data missing.
3. Coefficient of repeatability (Bland Altman Method) was used to assess the repeatability between the summer and winter measurements of air pollutants. This method gives the ratio and absolute difference.

Regression coefficient (beta) and incidence rate ratio (IRR) were estimated from the above analyses. Incidence rate ratio estimates the rate of change in the frequency of the episodes per each unit increase in the measured air pollutant, it is considered a significant finding when confidence interval does not include one in the range. Beta is the estimated regression coefficient and it represents logged IRR, the size of beta gives the change in severity and duration per unit change in the measured pollutant. Beta is considered as significant when the confidence interval does not include zero in the range.

For the second objective of the study, logistic regression was performed. A continuous variable model was used, odd ratio quoted for the outcome variables is for a one unit rise in the continuous variables (indoor air pollutants). The data of nitrogen dioxide, formaldehyde, volatile organic compounds, cotinine, particulate matter, carbon

monoxide, and der pI were logged, to produce normal distribution. The mean of the two measurements of nitrogen dioxide, volatile organic compounds was used in the analysis. The duration and severity data were both logged.

2.13 Collection of samplers and diary cards

Nitrogen dioxide, volatile organic compounds, and formaldehyde samplers were posted to the laboratory, using prepaid self-addressed envelopes. A regular checking was carried out on the received samplers. Families were contacted about the return of the samplers. An attempt was made to repeat the measurements in certain homes with missing data.

Carbon monoxide and particulate matter samplers and urine sample for cotinine were collected by the investigator.

Diary cards were either posted back to us, or collected from the families during the home visits.

2.14 Identification of LRT, URT, PEF episodes, and the definition of duration and severity of the episodes

2.14.1 Definition of the URT, LRT and PEF episodes

Recently several epidemiological studies used diary cards to demonstrate the incidence of peak expiratory flow and URT and LRT episodes (Johnston et al 1995; Clough et al 1991; De Bildering: DM thesis; C H Linker: PhD thesis). Several approaches were used to define the episodes, the method of computer defined episode was used by Johnston and co-workers (Johnston et al, 1995) and Clough and co-workers (Clough et al, 1995). In the first study a significant episode of lower and upper respiratory symptoms was defined as a period of at least two days during which the relevant symptom score rose above the individual child's median score for the study duration, preceded by one day and followed by two days at or below the median. In the second study, a symptom event was defined as a period during which the lower respiratory symptoms equaled at least three symptom units within three consecutive days, followed by at least two symptom – free days. In Linker's study, different types of computer-defined episodes were used (including the methods have been used in Clough's and Johnston's studies at Southampton General Hospital) and found inconsistency in the number of the identified episodes. Therefore it was decided that a clinician-defined episode was probably the most accurate one. The same approach was considered in the study conducted by De Bildering and co-workers (unpublished DM). In our study, we used a clinician- defined episodes to define LRT, URT and PEF episodes. The data of the diary cards were entered in SPSS and graphs were produced to represent symptoms score over the study period (e.g. of LRT, URT and PEF episodes: appendix 9). These

graphs were inspected visually by an experienced paediatrician (Dr J Clough), and the episodes were identified.

In a previous study (De Bilderling; unpublished DM), two experienced paediatricians inspected the graphs and the episode was accepted if it was marked definite by both, or definite by one and possible by the other. The episode was not accepted in the analysis if was marked as possible by one or both, or definite by one only. The agreement between the two paediatricians for the definition of the episodes was assessed, and it was concluded that the agreement was good (Kappa=0.68 for LRT episodes, Kappa = 0.69 for URT episodes, Kappa=0.60 for PEF episodes). Therefore, one paediatrician was asked to identify the respiratory episodes in our study.

2.14.2 Definition of duration and severity of the episodes

The definition of the duration of the episode is merely the number of days of the episode.

The severity of the episode was defined as the area under the curve for each of the LRT and URT episodes (the median score for each subject over the study period was used as a baseline). The severity of PEF episode was defined as the area above the curve for the episode (the median score for each subject over the study period was used as a baseline), and expressed as a percentage of the median.

2.15 Compliance

Different methods were used to maintain families' interest throughout the study. Regular phone calls were made to each family to ensure that the samplers for indoor air pollutants were sent, and also to take the opportunity in answering the questions they have about the study. Birthday cards were sent to the children and mothers during the

study period. Halfway through the study, the families were invited for a day out at Paulton Park.

2.16 Data entry and checking

The data of the indoor air pollutants, co-factors and demographic data were entered on SPSS (SPSS statistical package 1988). Data from the diary cards were checked and coded by a member of the research team (doctor/research nurse) prior to entering twice in computer. During the checking process, it was not always clear whether the absence of a score for URT/LRT symptoms indicated a genuinely symptom-free day (children were asked to leave the spaces for symptoms blank if they had not experienced symptoms that particular day), or rather that the child forgot to score symptoms. Since the children were requested to score URT/LRT symptoms at the end of the day, it was decided that in such instances, the URT/LRT symptoms score should be classified as missing if the evening PEF measurement was also not recorded on the diary card for that particular day. Missing PEF measurements were given the value 999, and missing URT/LRT symptoms score were given the value 99. Validation checks were also performed prior to statistical analyses.

CHAPTER 3

The summary results of response results, children & mothers characteristics and respiratory episodes.

3.1 Response rate

651 families with asthmatic children were written to about the study. 181 families replied agreeing to participate in the study. No reply was received from 154 families. 316 families did not want to take part in the study.

130 families of those who were interested to take part in the study, fulfilled the inclusion criteria. 122 families were screened at the preliminary visit, 8 (6%) families decided not to take part in the study before the screening visit. 10 (7%) families out of those who were screened dropped out at the first visit (no reason was given), and three (2%) families moved out of Southampton. After the first visit and before the second one, 14 (10%) families dropped out; neither diary cards nor air pollution samplers were returned from those families. After six months of the study, 13 (10%) families have decided not to continue in the study, the majority of those families had not completed nor returned the diary cards. 82 families have continued the 12 months prospective study (82 families with one asthmatic child and two families with two asthmatic children). This study was underpowered due to the drop out of the enrolled subjects over the study period.

3.2 Asthmatic children characteristics

There were 48 (57.2%) males and 36 (42.8%) females in the study. Children aged 7-14 y (median=10). The mean height was 139.4cm (SD=11.3), and the mean weight

was 36.3 kg (SD=11.5). FEV_1 ranged from 1.6- 2.1 (median=1.8), FEV_1% of predicted ranged from 81-95 (median = 81).

63 children (75.9%) had a positive skin prick test to at least one allergen. Table 3.1 demonstrates the frequency of positive skin prick test. Six children (7.1%) had a history of hay fever.

Table 3.1: The frequency (percentage) of allergens

Allergen	Frequency (%)
Der pI	52
Cat	37
Grass	46
Tree	21
Alternaria	16
Dog	12
Feather	3
Aspergillus	3

3.3 Results of URT, LRT and PEF episodes (asthmatic children)

3.3.1 Results of the analysis of diary cards

Each subject in the study was asked to record daily UTR, LRT symptoms and twice daily PEF flow rate for a period of one year. The daily recorded symptoms in the diary cards (filled-in diary cards over the study period) ranged from 290 – 392 days (median = 308 days) for URT, LRT symptoms and PEF measurements (table 3.2). The missing data was more among those subjects who participated longer in the study. The percentage of the missing data ranged from 0 – 10.5% (median = 3.7%) for URT and LRT symptoms, and from 0 – 20.7% (median = 11.5 %) for PEF measurements (table 3.2).

Table 3.2: Range, median of the daily recorded and missing data of URT, LRT and PEF rate (asthmatic children)

Filled in diary cards	URT symptoms	LRT symptoms	PEF rate
Minimum recorded symptoms	290	290	290
Maximum recorded symptoms	392	392	392
Median of daily recorded symptoms	308	308	308
Missing data (%) Minimum	0.00	0.00	0.00
Missing data (%) Maximum	10.5	10.5	20.7
Median of Missing data (%)	3.7	3.7	11.5

3.3.2 Number and frequency of URT, LRT and PEF episodes

The number of physician's defined URT, LRT and PEF episodes were 151, 151, 159 episodes, respectively. The identification of the episodes was done by one physician, who had inspected the graphs of URT, LRT, and PEF episodes individually (was

blinded to the demographic, atopic and environmental factors data). The frequency of the episodes was described in tables 3.3, 3.4, 3.5. The majority of the subjects had 1-2 episodes during the study period. 12 children did not have any LRT episodes during the study. 90.5 % of the asthmatic children had three or less of LRT episodes during the study period.

Nineteen subjects (22.6%) did not have URT episodes during the study. Eighty asthmatic children (95.2 %) had four or less of URT episodes.

Nineteen asthmatic subjects (22.6%) did not have PEF episodes over the study period. Six subjects (7.2%) had five or more of PEF episodes in the study period. The majority of the cohort had 1- 4 episodes over the study period.

Table3.3: Number and frequency of LRT episodes

Number of episodes	Number of subjects	Percentage	Cumulative percentage
0	12	14.3	14.3
1	28	33.3	47.6
2	24	28.6	76.2
3	12	14.3	90.5
4	5	6.00	96.4
5	1	1.2	97.6
7	2	2.4	100
Total	84	100	

Table3.4: Number and frequency of URT episodes

Number of episodes	Number of subjects	Percentage	Cumulative percentage
0	19	22.6	22.6
1	20	23.8	46.4
2	20	23.8	70.2
3	14	16.7	86.9
4	7	8.3	95.2
5	3	3.6	98.8
6	1	1.2	100
Total	84	100	

Table 3.5: Number and frequency of PEF episodes

Number of episodes	Number of subjects	Percentage	Cumulative percentage
0	19	22.6	22.6
1	16	19	41.7
2	22	26.2	67.9
3	11	13.1	81
4	10	11.9	92.9
5	4	4.8	97.6
7	1	1.2	98.8
9	1	1.2	100
Total	84	100	

3.3.3 Duration of URT, LRT and PEF episodes

The duration of LRT episodes ranged from 2 – 78 days (median = 9) .The majority of the LRT episodes (137 episodes; 90.7%) lasted less than 20 days. Three LRT episodes have lasted longer than 40 days (table 3.6).

The duration of URT episodes ranged from 3 – 42 days (median =8). The majority of subjects had URT episodes of 10 days or less, and only two subjects had URT episodes of 30 days or more (table 3.7).

The duration of PEF episodes ranged from 3 – 87 days (median =11). The total PEF episodes were 169 episodes. 84.6% of PEF episodes were of 20 days duration or less and 4.8% of the total episodes lasted for 30 days or more (table 3.8).

Some of the asthmatic children had suffered from a rather prolonged respiratory episodes. One of the possible explanations is that those subjects who suffered rather prolonged respiratory episodes, had more severe disease. The other explanation for this is that there might been a difference in the treatment strategy among asthmatic children (i.e. some of the children have increased the dose of inhaled corticostroid during the respiratory episodes whilst the others did not).

Table 3.6: Frequency of the duration of LRT episodes

Duration of episodes	Frequency	Percentage	Cumulative percentage
0 -10	98	64.9	64.9
11 - 20	39	25.8	90.7
21 – 30	11	7.3	98
31- 40	0	0	98
41 – 50	1	0.7	98.7
51- 60	0	0	98.7
61 - 70	1	0.7	99.3
71 - 80	1	0.7	100
Total	151	100	

Table 3.7: Frequency of the duration of URT episodes

Duration of episodes	Frequency	Percentage	Cumulative percentage
0 -10	106	70.2	70.2
11 - 20	40	26.5	96.7
21 - 30	3	2	98.7
31 - 40	1	0.7	98.7
41 - 50	1	0.7	99.3
Total	151	100	100

Table3.8: Frequency of the duration of PEF episodes

Duration of episodes	Frequency	Percentage	Cumulative percentage
0 -10	74	43.8	43.8
11 - 20	69	40.8	84.6
21 - 30	18	10.7	95.3
31 - 40	6	3.6	98.8
41 – 50	1	0.6	99.4
51 –60	0	0	99.4
61 –70	0	0	99.4
71 - 80	0	0	99.4
81 - 90	1	0.6	100
Total	169	100	

3.3.4 Severity of URT, LRT and PEF episodes

The severity of the URT/LRT episode was defined as area under the curve for each episode (the median score for each subject over the study period was used as a baseline). The severity of PEF episode was defined as the area above the curve for each episode (the median score for each subject over the study period was used as a baseline), this was expressed as a percentage of the median.

The majority of the asthmatic subjects had a median score of zero for the lower respiratory symptoms (60 subjects; 71.4%) (table 3.9). The severity score of LRT episodes ranged from 1 – 15 (median = 3.5). The frequency and percentage of LRT severity score is demonstrated in table 3.10 . One hundred and thirty (86.1 %) episodes had a severity score of 6 or less, and only 21(13.9 %) episodes had a severity score of more than 6.

The distribution of the median of URT symptoms score is demonstrated in table 3.11. Fifty subjects had a median of zero for the URT symptoms score. Only one asthmatic child had a median of 4 for the URT symptoms score. The majority of the asthmatic children had a median of zero for the URT symptoms score; only four subjects had a median of three or more.

The severity score of URT episodes ranged from 1 – 5 (median =2). 140(92.7%) episodes were of severity score of six or less; only eleven episodes (7.3 %) had a severity score of 7 or more (table 3.12).

The median of PEF measurements for all asthmatic children ranged from 100 - 500 L/min (median= 310) (table 3.13). The severity score of the episodes ranged from –1% - -35% (median= -7.8%) (table 3.14).

Table 3.9: The frequency of the median of LRT symptoms score over the study period

Median of LRT episodes	Frequency	Percentage	Cumulative percentage
0	60	71.4	71.4
1	9	10.7	82.1
2	9	10.7	92.9
3	2	2.4	95.2
4	1	1.2	96.4
5	2	2.4	98.8
6	1	1.2	100
total	84	100	

Table 3.10: LRT episodes severity score

Severity score	Frequency	Percentage	Cumulative percentage
0 - 2	18	11.9	11.9
3 - 4	72	47.6	59.5
5 - 6	40	26.5	86.1
7 - 8	15	9.9	96
9 – 10	3	2	98
11 – 12	1	0.7	98.7
13 - 14	1	0.7	99.3
15 – 16	1	0.7	100
total	151	100	

Table 3.11: The frequency of the median of URT symptoms score over the study period

Median of URT episodes	Frequency	Percentage	Cumulative percentage
0	55	65.5	65.5
0.5	1	1.2	66.7
1	11	13.1	79.8
2	13	15.5	95.2
3	3	3.6	98.8
4	1	1.2	100
total	84	100	

Table 3.12: Frequency and percentage of URT episodes severity score

Severity score	Frequency	Percentage	Cumulative percentage
0 - 2	29	19.2	19.2
3 - 4	82	54.3	73.5
5 - 6	29	19.2	92.7
7 - 8	9	6	98.7
9 – 10	2	1.3	100
total	151	100	

Table3.13: The range and percentiles of PEF score

Range/ Percentiles	PEF score
Minimum	100
Maximum	500
Percentiles	
10	215
20	250
30	275
40	300
50	310
60	330
70	340
80	350
90	395

Table 3.14: The range and percentiles of PEF severity score

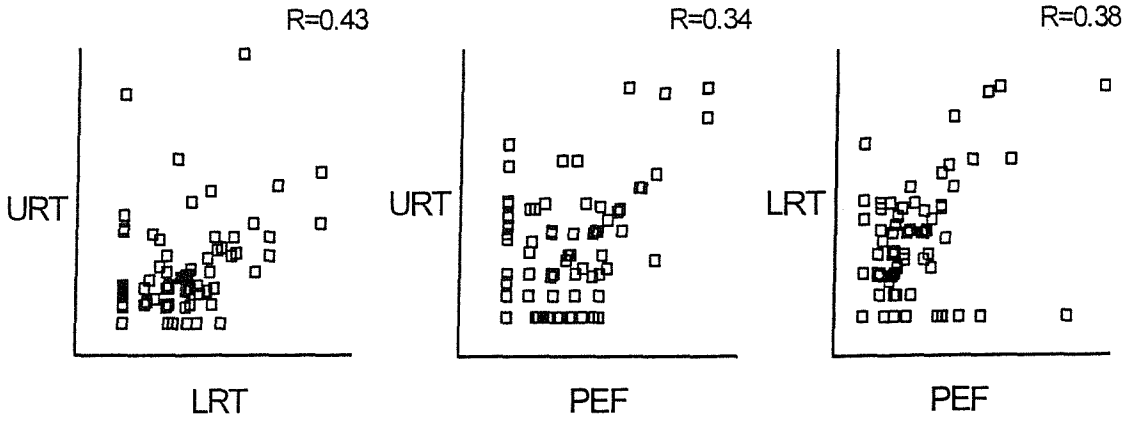
Range/ Percentiles	PEF episodes Severity score
Minimum	- 1
Maximum	- 35
Percentiles	
10	- 2.59
20	- 3.66
30	- 4.85
40	- 6.36
50	- 7.86
60	- 9.29
70	- 11
80	- 14.5
90	- 19.7

3.3.5 The association between URT, LRT and PEF episodes

3.3.5.1 The association between the frequency of the episodes

There is a moderate association between the frequency of LRT and URT episodes (r = 0.43; P=0.000), and a weak significant relationship between the frequency of URT/ LRT and PEF episodes (r=0.34, P=0.000; r=0.38, P=0.000, respectively). Fig 3.1 demonstrates the relationship between the frequencies of the episodes.

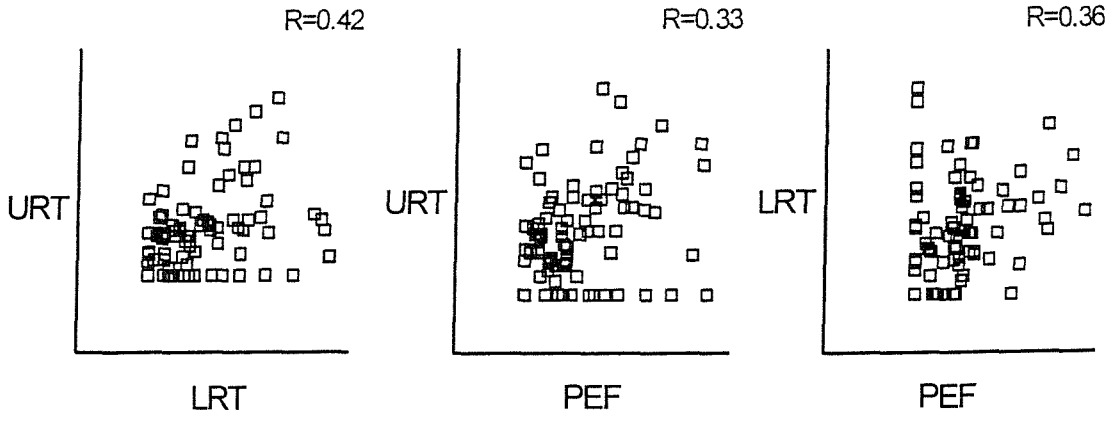
Fig 3.1: The association between the frequency of URT, LRT and PEF episodes



3.3.5.2 The association between the duration of URT, LRT and PEF episodes

Since the URT, LRT and PEF episodes do not necessarily occur at the time, therefore the mean of the duration of all the episodes for each subject was used in the analysis. There is a moderate association between the duration of URT and LRT episodes (r=0.42; p=0.000), and a statistically significant weak association between URT, LRT and PEF episodes (r=0.33, P=0.002; r=0.36, P0.001, respectively). Fig 3.2 demonstrates the relationship between the duration of the episodes.

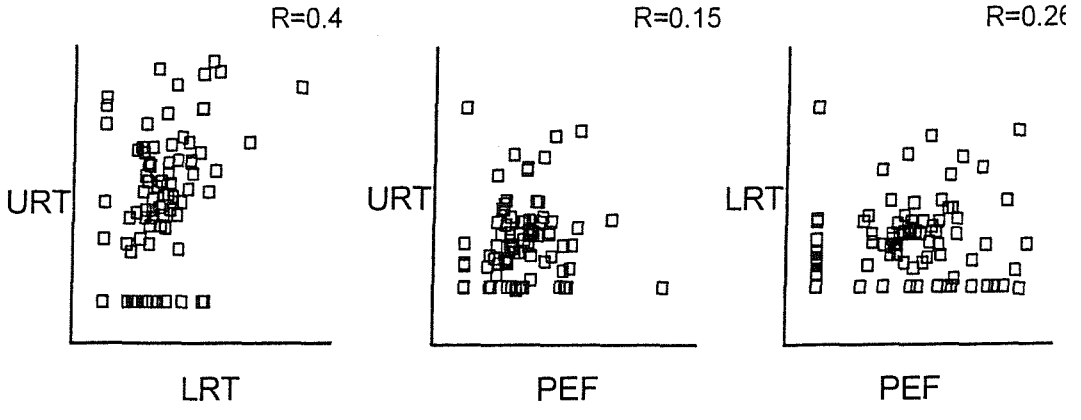
Fig 3.2: The association between the duration of URT, LRT and PEF episodes



3.3.5.3 The association between the severity score of URT, LRT and PEF episodes

Since URT, LRT and PEF episodes do not occur at the same time, it was therefore the mean of the severity score of URT, LRT and PEF episodes for each subject which was used in the analysis. There is a moderate association between the severity score of the URT and LRT episodes (r=0.4, P=0.000), and only a trend towards a positive association between the severity score of LRT,URT and PEF episodes (r=0.26, P=0.14, r=0.15, P=0.17, respectively), but this did not reach statistical significance. Fig 3.3 demonstrates the severity score relationship between URT, LRT and PEF episodes.

Fig 3.3: The severity score association between URT, LRT and PEF episodes



3.4 Characteristics of the mothers

The mothers aged 28-52 y (median=39). The mean height 163.2cm (SD=6.6) and mean weight 71.3 (SD=19.2). FEV1 ranged from 2.5-3.1 (median=2.8) and FVC ranged from 3.1-3.9 (median =3.5). 42 mothers had a positive skin prick test; table 3.15 demonstrates the frequency of skin prick test among mothers. 12 (14.4%) mothers were asthmatics on salbutamol inhaler only.

Table 3.15: The frequency (percentage) of allergens among mothers

Allergen	Frequency (percentage)
Der pI	27
Cat	12
Grass	25
Tree	8
Alternaria	2
Dog	1
Feather	2
Aspergillus	3

3.5 The results of URT, LRT and PEF episodes (mothers' data)

3.5.1 The results of the diary cards (recorded and missing data)

Each subject in the study was asked to record daily URT, LRT symptoms and twice daily PEF rate for a period of one year. We are not aware of any previous epidemiological studies looked at the effect of indoor air pollution on peak expiratory flow measurements among healthy subjects, we therefore proposed to study this area in

our study. We would not expect the effect if any from indoor air pollution would be the same between the asthmatic and healthy subjects. The daily recorded symptoms in the diary cards over the study period ranged from 263 – 387 days (median = 297 days) for URT, LRT symptoms and PEF measurements (table 3.16). Some of the subjects filled in the diary cards for more than one year period; only the data of the first twelve months were entered in the analysis. The missing data of the daily reported URT and LRT symptoms in the returned diary cards ranged from 0- 24% (median =5.7%), and ranged from 0-34% (median =10%) for the PEF measurements (table 3.16).

Table 3.16: Range and median of the duration of daily recorded and missing data of URT, LRT and PEF rate

Filled in diary cards	URT symptoms	LRT symptoms	PEF rate
Returned diary cards			
Minimum	263	263	263
Maximum	387	387	387
Median	297	297	297
Missing data (%)			
Minimum	0	0	0
Maximum	24	24	34
Median	5.7	5.7	10

3.5.2 The number of URT, LRT and PEF episodes

82 mothers were participated in the study. The number of physician-defined URT, LRT and PEF episodes were 138, 76, 103 respectively. The graphs of the URT, LRT and PEF episodes were inspected separately by one physician, who was blinded to the dermographic, atopy and environmental factors data. Among asthmatic mothers the number of the URT, LRT AND PEF episodes were 38, 22 and 40, respectively. The frequencies of the episodes were described in tables (3.17, 3.18, 3.19). The majority of the subjects had 1-2 episodes during the study period.

In the analysis of the LRT episodes, thirty-eight subjects (46.3%) did not have LRT episodes during the study period, all were not asthmatics. 43 subjects (52.4%) had between 1 and 3 LRT episodes, and only one subject had four episodes over the study period.

No URT episodes were identified in 22 subjects during the participating period in the study, only one was asthmatic. 57 (69%) subjects had between 1 and 5 URT episodes, and only five mothers (6%) had URT episodes which ranged from 5-7 episodes.

Twenty-nine (35.4%) mothers did not have PEF episodes, all were not asthmatics; the rest had 1 - 4 episodes over the study period.

Table 3.17: Number and frequency of LRT episodes

Number of episodes	Frequency	Percentage	Cumulative percentage
0	38	46.3	46.3
1	23	28	74.4
2	8	9.8	84.1
3	12	14.6	98.8
4	1	1.2	100
Total	82	100	

Table 3.18: Number and frequency of URT episodes

Number of episodes	Frequency	Percentage	Cumulative percentage
0	22	26.8	26.8
1	24	29.3	56.1
2	16	19.5	75.6
3	8	9.8	85.4
4	7	8.5	93.9
5	2	2.4	96.3
6	1	1.2	97.6
7	2	2.4	100
Total	82	100	

Table 3.19: Number and frequency of PEF episodes

Number of episodes	Frequency	Percentage	Cumulative percentage
0	29	35.4	35.4
1	22	26.8	62.2
2	15	18.3	80.5
3	13	15.9	96.3
4	3	3.7	100
Total	82	100	

3.5.3 Duration of URT, LRT and PEF episodes

The duration of LRT episodes ranged from 3 – 34 days (median = 10). The majority of the LRT episodes lasted less than 20 days (table 3.20). Seven (8.9%) LRT episodes lasted between 21 - 30 days, and only one (1.3%) episode lasted more than 30 days.

The duration of the URT episodes ranged from 3- 26 days (median =9). The duration of URT episodes ranged from 3 – 26 days (median 9). The majority of URT episodes lasted for 20 days or less, only four (2.9%) URT episodes were of more than 20 days (table 3.21).

The duration of PEF episodes ranged from 3 – 30 days (median =11). The total PEF episodes were 103 episodes. 87.4% of PEF episodes were of 20 days duration or less, thirteen episodes (12.6%) of the total episodes lasted for more than 20 days (table 3.22).

It seems that the duration of some of the respiratory episodes were rather long, this may reflect the fact that those individuals were left with residual symptoms following the respiratory episode. One of the problems arising from the use of the diary cards in the epidemiological studies is the variability (heterogeneity) among individuals in their rating of symptoms, this of course might have an impact on the duration of the episodes. It is also possible that some of the recorded symptoms during the episodes were chronic rather an acute ones, particularly among smokers.

Table 3.20: Frequency of the duration of LRT episodes

Duration	Frequency	Percentage	Cumulative percentage
0 -10	42	53.2	53.2
11 - 20	29	36.7	89.9
21 - 30	7	8.9	98.7
31 - 40	1	1.3	100
Total	79	100	

Table 3.21: Frequency of the duration of URT episodes

Duration of episodes	Frequency	Percentage	Cumulative percentage
0 -10	91	65.9	65.9
11 - 20	43	31.2	97.1
21 - 30	4	2.9	100
Total	138	100	

Table3.22: Frequency of the duration of PEF episodes

Duration of episodes	Frequency	Percentage	Cumulative percentage
0 -10	50	48.5	48.5
11 - 20	40	38.8	87.4
21 - 30	13	12.6	100
Total	103	100	

3.5.4 Severity of URT, LRT and PEF episodes

The severity of the LRT/URT episode was defined as area under the curve for each episode (the median of the respiratory symptoms was used as a base line). The severity of PEF episode was defined as the area above the curve for the episode (the median score for each subject over the study period, was used as a baseline). The severity of PEF episodes was expressed as a percentage of the median.

The frequency of the median of URT symptoms score is demonstrated in table 3.23. The median score of URT was zero in 61(74.4%) subjects, one (19.5%) in 16 subjects, and only 5 (6.1%) subjects had a median URT symptoms score ranged 2 – 4. The severity score of URT episodes ranged from 0.6 – 12.2 (median =3). The majority of the URT episodes had a severity score of less than six, only ten episodes were of severity score more than six (table 3.24).

The majority of the mothers had a median of zero for the LRT symptoms score; only five (6.1%) subjects had a median of two or more (table 3.25). The severity score of LRT episodes ranged from 1 – 9.2 (median = 2.4). Sixty-four episodes (93.7 %) had a severity score fall in the range 0 – 6, and only 5 (6.4 %) episodes had a severity score more than six (table 3.26).

The measurements of PEF rate ranged from 210- 540 (median = 420). The severity of PEF episodes ranged from – 10.9% - - 40% (median = - 6.0%). Table 3.27 demonstrates the range, median and percentiles of PEF episodes.

Table 3.23: The frequency of the median of URT symptoms score over the study period

Median of URT episodes	Frequency	Percentage	Cumulative percentage
0	61	74.4	74.4
1	16	19.5	93.9
2	3	3.7	97.6
3	1	1.2	98.8
4	1	1.2	100
total	82	100	

Table3.24: Frequency and percentage of URT episodes severity score

Severity score	Frequency	Percentage	Cumulative percentage
0.6 - 2	26	18.8	18.8
3 - 4	81	58.7	77.5
5 - 6	21	15.2	92.8
7 - 8	6	4.3	97.1
9 – 10	3	2.2	99.3
11 - 14	1	0.7	100
total	151	100	

Table3.25: The frequency of the median of LRT symptoms score over the study period

Median of LRT episodes	Frequency	Percentage	Cumulative percentage
0	67	81.7	81.7
1	10	12.2	93.9
2	3	3.7	97.6
4	1	1.2	98.8
6	1	1.2	100
total	82	100	

Table 3.26: Frequency and percentage of LRT episodes severity score

Severity score	Frequency	Percentage	Cumulative percentage
1 - 2	20	25.3	25.3
3 - 4	42	53.2	78.5
5 - 6	12	15.2	93.7
7 - 8	4	5.1	98.7
9 – 10	1	1.3	100
total	79	100	

Table 3.27: The range and percentiles of PEF score

Range/ Percentiles	PEF score
Minimum	210
Maximum	540
Percentiles	
10	350
20	380
30	400
40	400
50	420
60	430
70	450
80	460
90	497

Table 3.28: The range and percentiles of PEF severity score

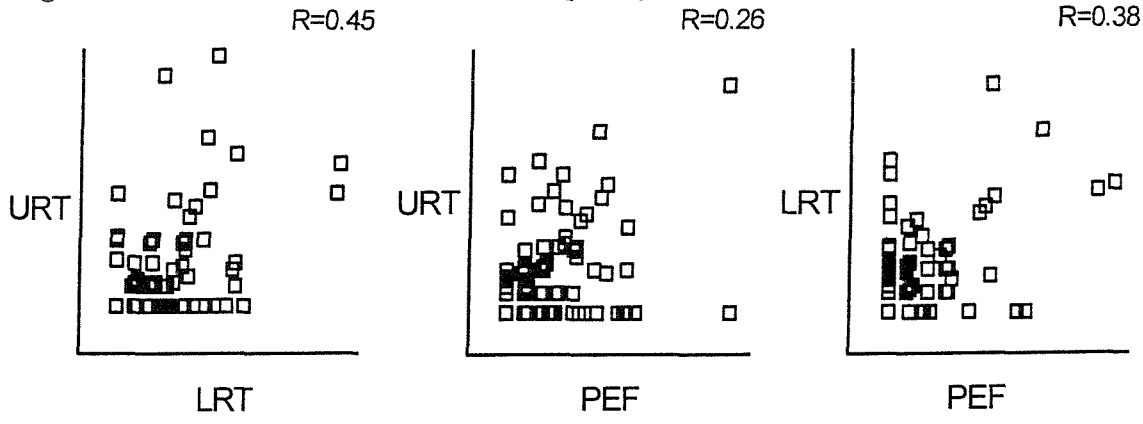
Range/ Percentiles	PEF episodes Severity score
Minimum	- 10.9
Maximum	- 40.0
Percentiles	
10	- 16.6
20	- 10.0
30	- 8.1
40	- 6.8
50	- 6.0
60	- 4.9
70	- 4.0
80	- 2.7
90	- 1.5

3.5.5 The association between URT, LRT and PEF episodes

3.5.5.1 The association between the frequency of the episodes

There was a moderate association between the frequency of LRT and URT episodes (r = 0.45; P=0.000), and a weak relationship between the frequency of URT, LRT and PEF episodes (r=0.26, P=0.01; r=0.38, P=0.000, respectively). Fig 3.4 demonstrates the relationship between the frequencies of the episodes.

Fig 3.4: The association between the frequency of URT, LRT and PEF episodes

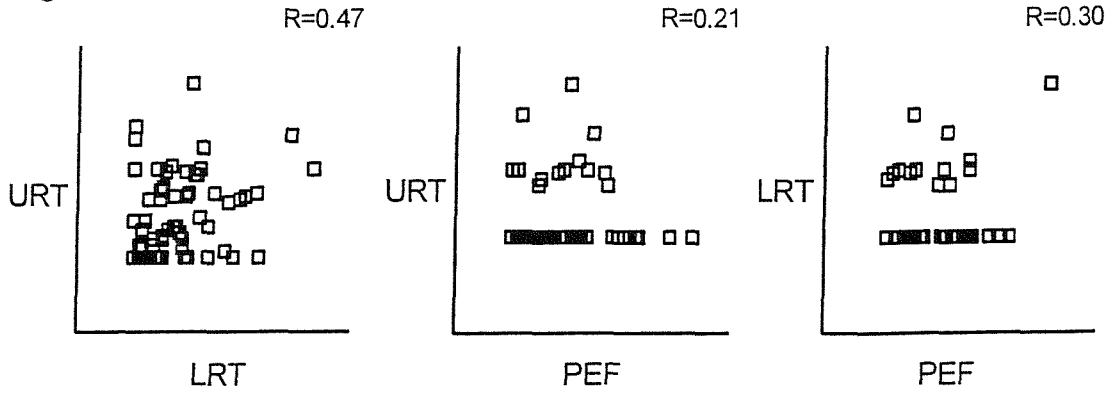


3.5.5.2 The association between the duration of URT,LRT and PEF episodes

Since URT, LRT and PEF episodes do not necessarily occur at the same time, therefore the mean of the duration of all the episodes for each subject was used in the analysis.

There was a moderate association between the duration of URT and LRT episodes (r=0.47;p=0.000), and a statistically significant weak association between URT, LRT and PEF episodes (r=0.21, P=0.05; r=0.30, P=0.006). Fig 3.5 demonstrates the relationship between the duration of the episodes.

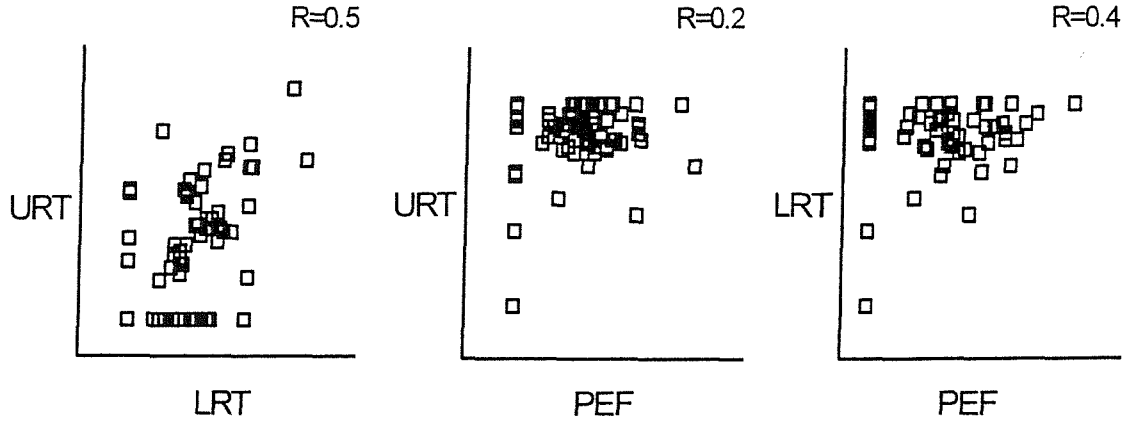
Fig 3.5: The association between the duration of URT, LRT and PEF episodes



3.5.5.3 The association between the severity score of URT, LRT and PEF episodes

Since URT, LRT and PEF episodes do not necessarily occur at the same time, it was therefore the mean of the severity score of URT, LRT and PEF episodes for each subject which was used in the analysis. There was a moderate association between the severity score of the URT and LRT episodes (r=0.5, P=0.000), and a moderate association between the severity score of LRT and PEF episodes (r=0.4,P=0.000). Our study demonstrated a trend towards a weak positive association between the severity score of URT and PEF episodes (r=0.2, P=0.04), but this did not reach statistical significance. Fig 3.6 demonstrates the severity score relationship between URT, LRT and PEF episodes.

Fig 3.6: The severity score association between URT, LRT and PEF episodes



CHAPTER 4

The summary results of indoor air pollutants

4.1 Repeatability of the indoor air pollutant measurements (summer & winter)

Bland – Altman statistical method was used to estimate (Bland & Altman 1986):

- The range of the differences between the summer and winter measurements of indoor air pollution
- The mean and 95% confidence interval of the difference between the two seasonal measurements (when zero falls in the range of confidence interval, this suggests that the difference is not significant).
- The range, mean and 95% confidence interval of the summer:winter ratio of indoor air pollution (when zero falls in the range of the confidence interval, this suggests that there is no significant difference between the two measurements).

In our study there were missing data among indoor air pollutant measurements, it was therefore felt that it is essential to establish whether there was a significant seasonal difference, before we use the houses/subjects with one measurement in the analysis. The seasonal difference was assessed in the following air pollutants and co-factors:

- Nitrogen dioxide
- Volatile organic compounds
- Dampness
- Cotinine

4.1.1 Kitchen mean nitrogen dioxide

The winter/summer ratio of kitchen mean nitrogen dioxide ranged from 0.08 – 17.3μgm^{-3} (1.14, 95% CI 0.8- 1.6), and the difference between the two seasons ranged from –1.1 – 1.2μgm^{-3} (mean=0.05, 95%CI –0.09-0.2). This suggests that there is no significant difference between the two seasonal measurements. There were three houses with very high summer measurements and one house with high winter measurements.

4.1.2 Kitchen peak nitrogen dioxide

The difference in kitchen peak nitrogen dioxide between the summer and winter seasons ranged from –1.4-1.2μgm^{-3} (mean=-0.09, 95%CI –0.2-0.07). The seasonal ratio of kitchen peak nitrogen dioxide ranged from 0.39 – 16.1 μgm^{-3} (mean = 0.8μgm^{-3} ; 95%CI 0.5-1.1). This data suggests that there is no significant seasonal difference in the kitchen peak nitrogen dioxide measurements. There were two houses with high summer measurements, and two with high winter measurements.

4.1.3 Personal nitrogen dioxide (mothers and children)

The seasonal ratio of mother and child personal nitrogen dioxide differences ranged from 0.06 – 21.7μgm^{-3} (mean=1.5, 95% CI 0.7- 1.7), and 0.07- 22.0μgm^{-3} (mean=1.2, 95% CI 0.8-1.8), respectively. The difference between the two seasons measurements among mothers and children ranged from –1.2–1.3μgm^{-3} (mean=0.06,95%CI –0.1-0.2) and from –1.1-1.3μgm^{-3} (mean=0.09, 95%CI-0.06—0.2), respectively. This finding suggests that there is no significant seasonal difference in the personal measurements of nitrogen dioxide. Two high summer and one winter mother nitrogen dioxide were observed in three subjects. No extreme seasonal measurements were observed in child personal nitrogen dioxide.

4.1.4 Volatile organic compounds

There was one home with very high summer VOC measurement, and another one with very high winter. The ratio of the winter/summer of lounge total VOC ranged from 0.3- 5.2 μgm^{-3}, and a mean of 1.36 (95%CI 1.14- 1.64). There was a significant difference between the two measurements; the difference ranged from 0.45-0.7μgm^{-3} (mean=0.1, 95%CI 0.05-0.2). Different in the use of building materials (for e.g: furniture polish) and consumer products (cleaning and gardening products is a possible explanation to the difference between the two seasonal measurements. Outdoor air penetrating indoor spaces via ventilation is potentially another factor which could have accounted for the difference of two VOCs measurements. The difference between the two measurements was small, therefore it is possible that impact of VOCs on the prevalence of the respiratory episodes may not be significantly different between the different seasons.

4.1.5 Urine cotinine

The winter/summer ratio of urine cotinine ranged from 0.2-8.2 (mean = 1.48; 95%CI 1.1-1.8), and from 0.17 – 23.2 (mean =2.0; 95%CI 1.42-2.88), in children and their mothers, respectively. The difference in cotinine measurements between the two seasons ranged from –1.3-2.1μg/L (mean=0.3,95%CI 0.1-0.6) among children, and ranged from –1.7-3.1μg/L (mean=0.7, 95%CI 0.3-1.0) in mothers. This observation suggests that there is a significant seasonal difference between the summer and winter urine cotinine measurements, among children and their mothers.

There was one child with very high urine cotinine level in the summer and another one with very high winter urine cotinine. There were two mothers with high winter urine cotinine measurement as compared to the summer ones.

Clearly our findings suggest that cotinine levels are higher in the winter, this is probably explained by the fact that during the winter that subjects (particularly kids) spend more time indoor. Ventilation is probably a second contributory factor to the discrepancy between the two measurements. Interindividual differences in the metabolism of cotinine might have had some impact on the difference between the two measurements we observed in this study.

4.1.6 Dampness

There were four homes with high summer dampness measurements in the bedrooms and the lounge as compared to the winter season, and one home with high winter dampness measurement. The seasonal difference of dampness in child bedroom, mother bedroom and the lounge ranged from – 3.7 – 3.77 (mean = 0.038; 95% CI – 0.373 – 0.448), -3.5 - 3.2 (mean = 0.164; 95% CI – 0.531 – 0.204), -5.2 – 4 (mean = -0.586; 95% CI – 1.09 – 0.079), respectively. Dampness was high in the child bedroom during the summer in four homes, and one high winter bedroom dampness. Similarly there were four homes with high dampness in the mother's bedroom, and three lounges with high summer dampness as compared to the winter measurements. Our data suggests that there was no significant seasonal in dampness, in the homes of our cohort. Dampness has been considered as one of the important factors which could influence the indoor level of mites and moulds, therefore the observation of no difference between the two seasons in the measurements of dampness would suggest that there had been no variable impact from the dampness point view on mites and moulds.

4.2 Summary of the results of indoor air pollutants, dampness and Der pI measurements

4.2.1 Kitchen mean nitrogen dioxide

82 homes have had at least one nitrogen dioxide measurement during the study period. 73 homes had winter nitrogen dioxide measurements, and 68 homes had the summer measurements. The summer and the winter kitchen mean nitrogen dioxide were highly skewed. Logarithmic transformation normalized it (Fig 4.1 &4.2). The winter and summer measurements of kitchen mean nitrogen dioxide ranged from 1.92 – 1244.23 μgm^{-3} (median = 34.62μgm^{-3}; mean= 96.15μgm^{-3}), and ranged from 5.77 – 1353 (median=30.77μgm^{-3};mean=69.29μgm^{-3}) respectively (table 4.1). The mean of the two measurements ranged from 5.77 – 1244μgm^{-3} (median=33.25μgm^{-3};mean=77.45μgm^{-3}) (table 4.1).

Table 4.1: Mean, Median, range and percentiles of kitchen mean nitrogen dioxide

Nitrogen dioxide	Winter Nitrogen dioxide	Summer Nitrogen dioxide	Mean of summer + winter Nitrogen dioxide
Number	73	68	59
Missing	9	14	23
Mean	96.15	68.29	77.45
SD	184	193.26	165.51
Minimum	1.92	5.77	5.77
Maximum	1244.23	1353.85	1244.23
Percentiles			
5	7.69	7.69	7.69
25	17.31	19.23	17.31
50	34.62	30.77	33.25
75	85.58	45.19	58
95	497.31	168.85	453

Fig 4.1: Log transformed kitchen mean (winter)

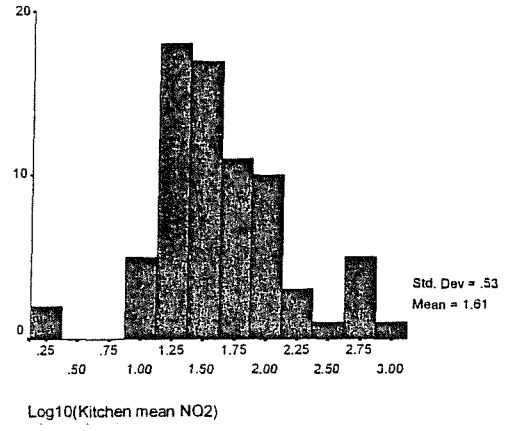
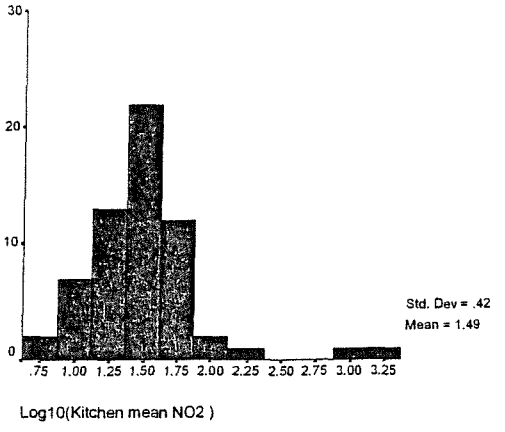


Fig 4.2: Log transformed kitchen mean (summer)



4.2.2 Kitchen peak nitrogen dioxide

Each home had at least one measurement of the kitchen peak nitrogen dioxide. 74 homes had the winter measurements and 67 homes had the summer measurements. Data was logged to normalize the skewed distribution (Fig 4.3 & 4.4). The mean, median and the mean of the summer and the winter measurements of nitrogen dioxide are described in table 4.2. The summer measurements of nitrogen dioxide ranged from 5.77 – 4213.46μgm^{-3} (median = 218.27μgm^{-3};mean=437μgm^{-3}). Kitchen peak nitrogen dioxide during the winter ranged from 13.47 – 9805μgm^{-3} (median = 210.58μgm^{-3};mean=775.31μgm^{-3}), and the mean of the summer and winter measurements ranged from 13.46 – 9805.77μgm^{-3} (median = 245.33 μgm^{-3} ;mean=651μgm^{-3}).

Table 4.2: Mean, Median, range and percentiles of kitchen peak nitrogen dioxide (μgm^{-3})

Nitrogen dioxide	Winter Nitrogen dioxide	Summer Nitrogen dioxide	Mean of summer + winter Nitrogen dioxide
Number	74	67	59
Missing	8	15	23
Mean	775	437	651.56
SD	1658	635.93	1493.56
Minimum	13.46	5.77	13.46
Maximum	9805.77	4213.46	9805.77
Percentiles			
5	20.67	36.54	32.47
25	95.67	133.77	116.82
50	210.58	218.27	245.33
75	562.5	439.42	547.54
95	4150.38	1678.54	8159.62

Fig 4.3: Distribution of log transformed Kitchen peak NO2 (winter)

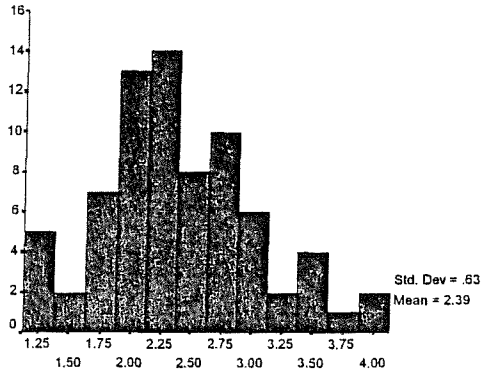
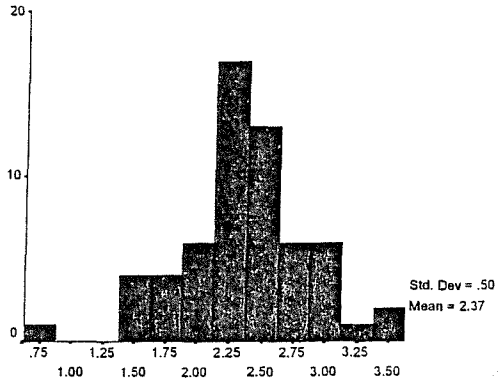


Fig 4.4: Distribution of log transformed Kitchen peak NO2 (summer)



4.2.3 Child personal nitrogen dioxide

All asthmatic children had at least one nitrogen dioxide measurement over the study period; 78 children have had the winter measurements and 69 have had the summer one. Logged data of personal nitrogen dioxide for the two seasons are demonstrated in Figures 4.5 & 4.6. The summer and winter personal nitrogen dioxide ranged from 3.85 – 175μgm^{-3} (median =21.15; mean=35.58), 1.92 – 555.77 (median=21.15;mean=66.36) respectively, and the mean of the two measurements of child personal nitrogen dioxide ranged from 3.33 – 555.77μgm^{-3} (median=24.70;mean=48.76).

Table 4.3: Mean, Median, range and percentiles of child personal nitrogen dioxide (μgm^{-3})

Nitrogen dioxide	Winter Nitrogen dioxide	Summer Nitrogen dioxide	Mean of summer + winter Nitrogen dioxide
Number	78	69	63
Missing	6	15	21
Mean	66.36	35.58	48.76
SD	100.29	39.59	75
Minimum	1.92	3.85	3.33
Maximum	555.77	175	555.77
Percentiles			
5	5.77	3.85	5.77
25	13.46	11.54	14.39
50	21.15	21.15	24.70
75	99	39.42	47.51
95	297.88	136	282.69

Fig 4.5: Distribution of log transformed personal NO2 (winter)

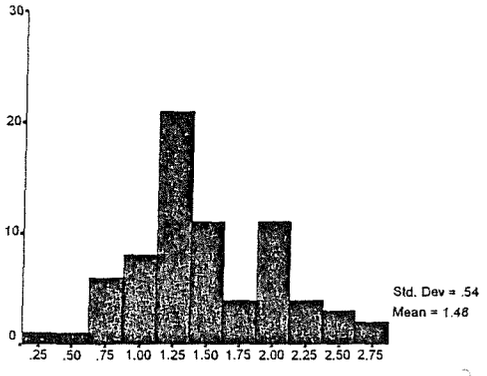
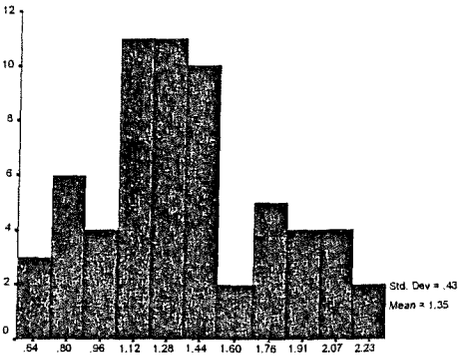


Fig 4.6: Distribution of log transformed personal NO2 (summer)



4.2.4 Mother personal nitrogen dioxide

Each mother had at least one nitrogen dioxide; 77 mothers have had the winter measurements and 67 have had the summer one. The distribution of the logged data of personal nitrogen dioxide for the two seasons is demonstrated in Figures 4.7 & 4.8; this appears normally distributed. The summer and winter personal nitrogen dioxide ranged from 1.92 – 328.85μgm^{-3}(median =19.23; mean=31.22), 1.92 – 238.46 (median=18.27; mean=45.86) respectively. The mean of the two measurements of mother personal nitrogen dioxide ranged from 3.33 – 194.23μgm^{-3} (median=19.61;mean=32.73) (table 4.4). There was a strong relationship between the mothers and children personal nitrogen dioxide (summer: r= 0.6, winter: r=0.7).

Table4.4: Mean, Median, range and percentiles of mother personal nitrogen dioxide(μgm^{-3})

Nitrogen dioxide	Winter Nitrogen dioxide	Summer Nitrogen dioxide	Mean of summer + winter Nitrogen dioxide
Number	77	67	62
Missing	5	15	20
Mean	45.86	31.22	32.73
SD	63.87	45.72	36.22
Minimum	1.92	1.92	3.33
Maximum	238.46	328.85	194.23
Percentiles			
5	5.77	5.77	5.77
25	11.54	9.62	13.46
50	18.27	19.23	19.61
75	33.65	30.77	36.54
95	209	89.81	121.15

Fig 4.7: Distribution of log transformed personal NO2 (winter)

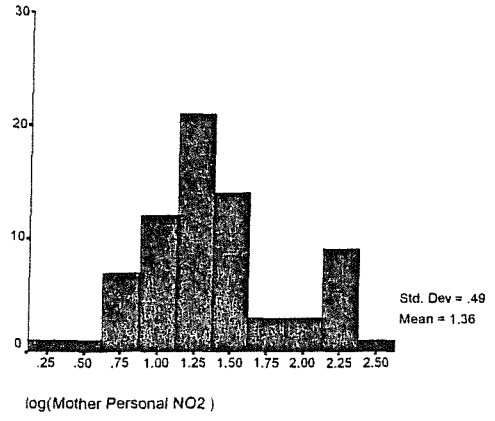
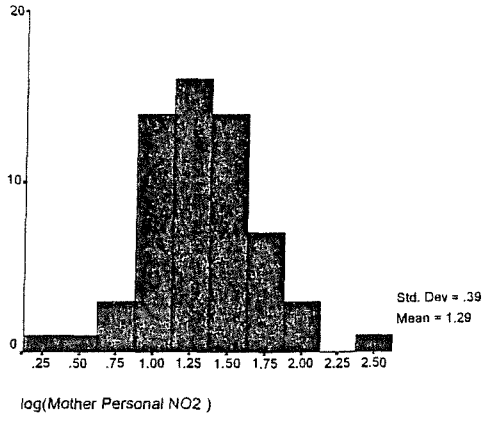


Fig 4.8: Distribution of log transformed personal NO2 (summer)



4.2.5 Kitchen particulate matter & carbon monoxide

Particulate matter was measured in the kitchen of 65 homes. Particulate matter in the kitchen ranged from 3 – 397μgm^{-3} (median =22;mean=47.88) (table 4.5). Fig 4.9 demonstrates the distribution of the particulate matter. The exposure to carbon monoxide over 8hrs was measured in 60 homes. The distribution of the carbon monoxide is demonstrated in Fig 4.10, ranged from 0.3–6.19 ppm (median=0,76;mean=1.11)(table 4.6). There were a considerable missing data in particulate matter and carbon monoxide; this was due to the fact that some families did not tolerate the noise of the devices. Furthermore, it was reported by some families that some of the sampling process have been interrupted several times by their children.

Table 4.5: Mean, Median, range and percentiles of kitchen particulate matter (μgm^{-3})

Range, Median, Mean and Percentiles	Particulate Matter
Number	65
Missing	17
Mean	47.88
SD	77.24
Minimum	3
Maximum	379
Percentiles	7.11
5	13.50
25	22
50	40
75	279.6
95	365.15

Table 4.6: Mean, Median, range and percentiles of kitchen carbon monoxide (ppm)

Range, Median, Mean and Percentiles	Carbon monoxide
Number	60
Missing	12
Mean	1.11
SD	0.99
Minimum	0.3
Maximum	6.19
Percentiles	0.34
5	0.52
25	0.76
50	1.22
75	3.22
95	4.33

Figure 4.9: The distribution of kitchen particulates.

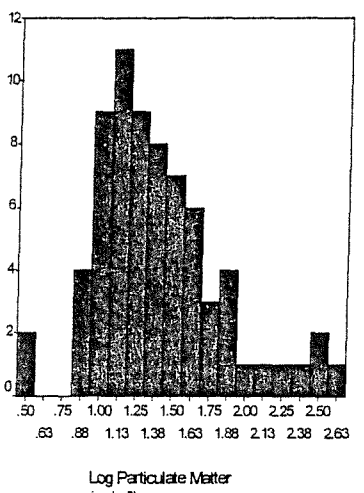
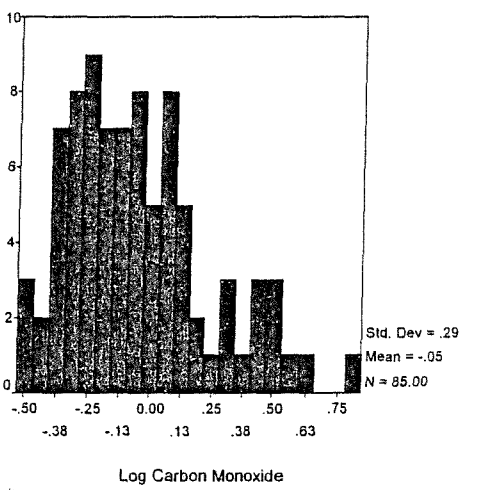


Figure 4.10: The distribution of kitchen carbon monoxide



4.2.6 Total volatile organic compounds and formaldehyde

At least one measurement of the total volatile organic compounds was carried out in each home during the study period. 69 homes have had the winter measurements and 76 homes have had the summer ones. The distribution of the total volatile compounds is demonstrated in figures 4.11 & 4.12. The summer and winter measurements of total VOCs ranged from 96 – 1197μgm^{-3} (median=189;mean=267), 72–3881μgm^{-3} (median=238;mean=393.42), respectively (table 4.7).

The mean of the two seasonal measurements ranged from 72 – 3881μgm^{-3} (median= 230.68;mean=341).

Formaldehyde levels in the lounge ranged from 0.49 – 43.68 μgm^{-3} (median= 8.89 ;mean=10.42) (table 4.8). Formaldehyde was measured in all homes. The distribution of the formaldehyde measurements is demonstrated in fig 4.13.

Table 4.7: Mean, Median, range and percentiles of total volatile organic compounds

	Winter	Summer	Mean of the two measurements
Number	69	76	64
Missing	12	6	18
Mean	393.42	267.29	341.99
Standard deviation	471.90	205.57	448.18
Minimum	72.00	96.00	72.00
Maximum	3881.00	1197.00	3881.00
Percentiles			
5	137.00	106.40	146.27
25	205.50	144.75	191.46
50	283.00	189.00	230.68
75	450.00	330.00	376.54
95	749.00	726.10	658.01

Fig 4.11: Distribution of log VOCs (winter)

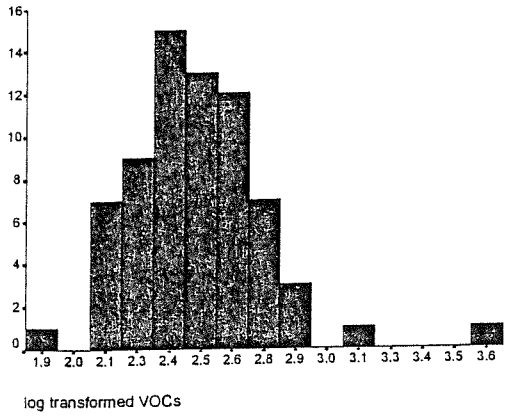


Fig4.12: Distribution of Log VOCs (summer)

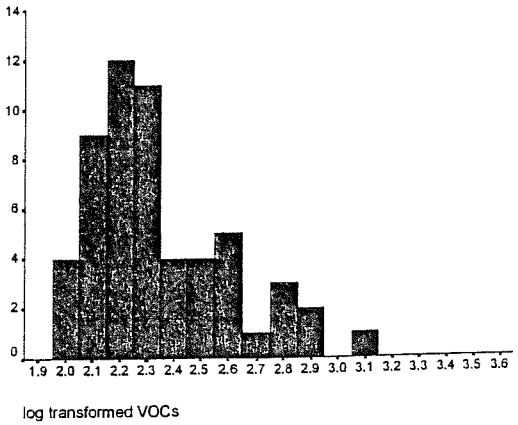
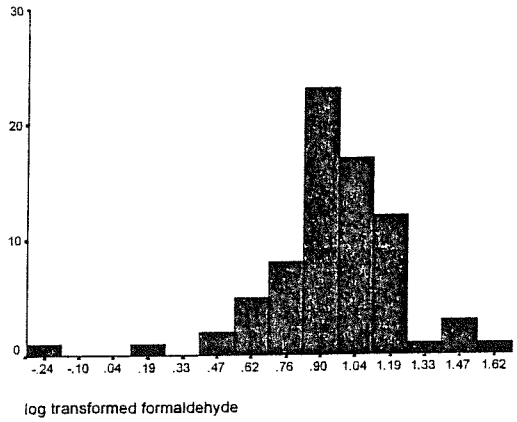


Table 4.8: Mean, Median, range and percentile of formaldehyde

	Formaldehyde
Number	82
Missing	0
Mean	10.42
Standard deviation	6.65
Minimum	.49
Maximum	43.68
Percentiles	
5	3.19
25	7.14
50	8.89
75	12.39
95	26.90

Fig 4.13 Distribution of logged Formaldehyde



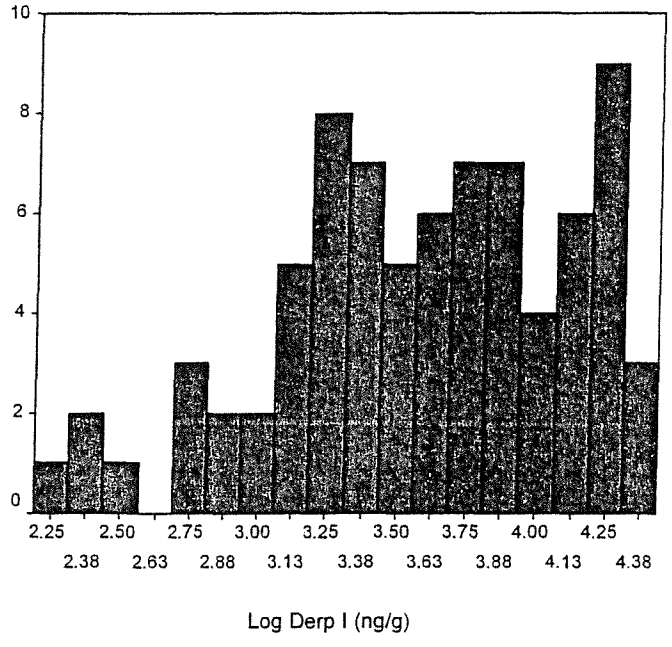
4.2.7 Der pI

The level of der pI was measured in all homes. The median, mean, range and percentiles of der pI are summarized in table 4.9. der pI ranged from 180 – 25515ng/g (median=4323;mean=6746.55). The distribution of der pI is demonstrated in Fig 4.14.

Table 4.9: Mean, Median, range and percentile of Der pI

	Der pI
Number	82
Missing	0
Mean	6746.55
Standard deviation	6471.79
Minimum	180.00
Maximum	25515.00
Percentiles	
5	342.10
25	1604.00
50	4323.50
75	10930.25
95	20071.90

Fig 4.14: Distribution of Der pI (ng/g)



4.2.8 Urine cotinine

The summer urine cotinine of the mothers and the children ranged from 2.80 – 5170 μg/L (median=17.50;mean=244.47), 6 – 139μg/L. (median=20;mean=28.24), respectively (table 4.10) The winter mother and child urine cotinine ranged from 2.25 – 9309μg/L (median=32.8; mean=465.8), 3.4 – 291 (median=28.6;mean38.06), respectively (table 4.11). The mean of the two measurements of the child and mother urine cotinine ranged from 3.40–291(median=23.43; mean= 31.67), 2.25–5740.55 (median=25.22;mean =381.59), respectively.

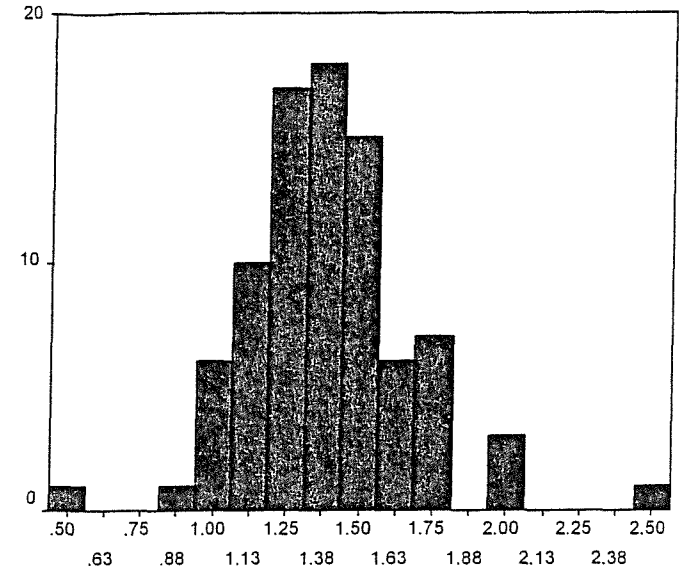
Table 4.10: Range, Median and Mean of Child urine cotinine

		Urine Cotinine Winter	Urine cotinine Summer	Mean
Number		84	84	84
Missing		0	0	0
Mean		38	28.2	31.6
SD		40.2	25.9	34.7
Min		3.4	6	3.4
Max		291	139	291
Percentiles	5	10.2	8.5	9.5
	25	17.1	12.5	16.6
	50	28.6	20	23.4
	75	41	35.4	33
	95	86.7	91.8	88

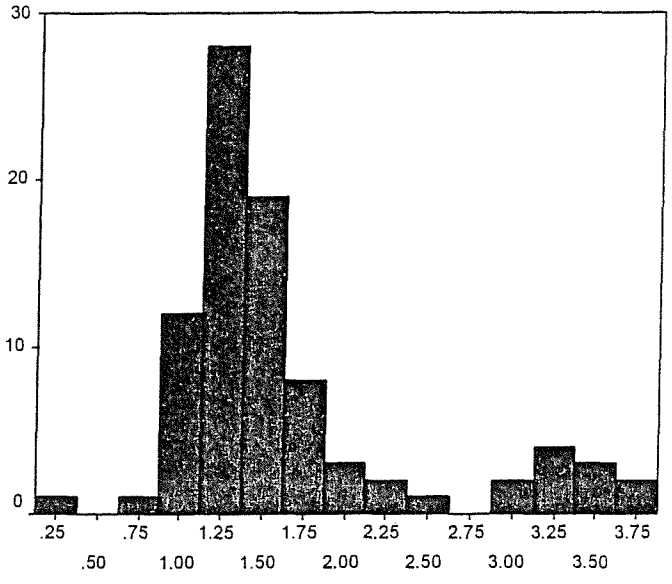
Table 4.11: Range, Median and Mean of Mother urine cotinine

		Urine Cotinine Winter	Urine cotinine Summer	Mean
Number		82	82	82
Missing		0	0	0
Mean		465.8	244.4	381.5
SD		1400	914.4	1088.3
Min		2.2	2.8	2.2
Max		9309	5170	5740.5
Percentiles	5	7.9	3.4	8.7
	25	18.7	10.0	17.1
	50	32.8	17.5	25.2
	75	71.6	27.6	59.6
	95	4028.8	2698.5	4018

Fig 4.15: Distribution of urine cotinine



Log Mean of Child Urine Cotinine



Log Mean of Mother Urine Cotinine

4.2.8 Dampness

Child bedroom dampness was measured in 76 homes in the summer and 81 homes in the winter. The distribution of dampness is demonstrated in Figures 4.15 & 4.16. The summer measurements of child bedroom dampness ranged from 6 – 16.90 (Median=9.9;Mean=10.17), the dampness measurements in the winter ranged from 4.8 – 16.7(Median=9.8;Mean=9.88)

Mother bedroom dampness was measured in 77 homes during the summer, and 81 homes during the winter. The summer and winter measurements of mother bedroom dampness ranged from 7.1- 16.8 (Median=10.2;Mean=10.70), 6.3 – 20.4 (Median=10.3;Mean=10.76), respectively.

The dampness in the lounge was measured in 81 homes. The summer dampness measurements ranged from 6.5 – 15.4 (Median=10.1;Mean=10.4). During the winter season the dampness in the lounge ranged from 7 – 21.8(Median=10.5;Mean=11).

There is a strong/moderate relationship between the summer and winter measurements in the child bedroom, the mother bedroom and the lounge (Pearson Correlation Coefficients; R=0.64, P<0.01;R=0.63, P<0.01; R=0.44, P<0.01,respectively). There was a weak relationship between the mother bedroom and the child bedroom dampness (R=0.22;P<0.05 (winter); R=0.37;P<0.01 (summer). There was a weak relationship between the lounge and the child bedroom dampness (R=0.3, P<0.01). The dampness in the lounge was moderately correlated with dampness in the mother bedroom (R=0.5;P<0.01).

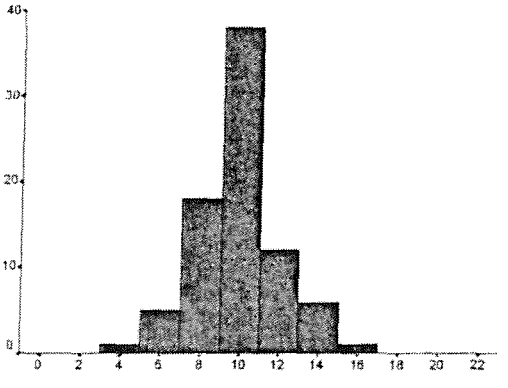
Table 4.12: Dampness (%) in the winter

	Mother's Bedroom	Child's bedroom	Lounge
Number	82	84	82
Missing	0	0	0
Mean	10.76	9.88	10.40
Standard deviation	2.23	1.98	1.88
Minimum	6.30	4.80	6.50
Maximum	20.40	16.70	15.40
Percentiles			
5	8.40	6.53	7.25
25	9.40	8.75	9.30
50	10.30	9.80	10.10
75	11.45	10.70	11.40
95	15.10	13.50	14.00

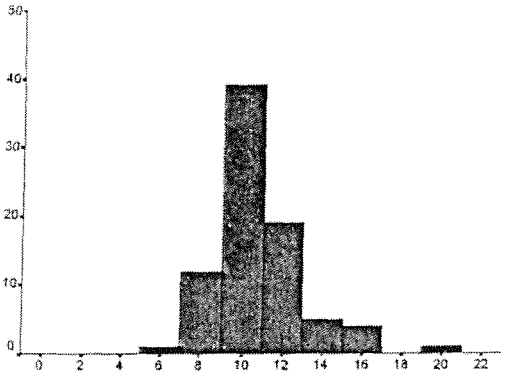
Table 4.13: Dampness (%) in summer

	Mother's Bedroom	Child's bedroom	Lounge
Number	82	84	82
Missing	0	0	0
Mean	10.70	10.17	11.05
Standard deviation	2.09	2.06	2.32
Minimum	7.10	6.00	7.00
Maximum	16.80	16.90	21.80
Percentiles			
5	7.94	7.70	8.00
25	9.00	8.73	9.50
50	10.20	9.90	10.50
75	12.00	11.00	12.23
95	15.00	14.30	14.17

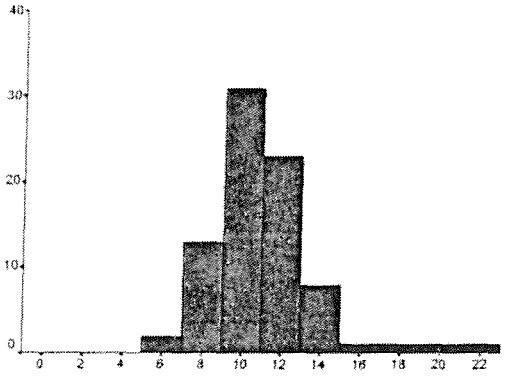
Figures 4.16: Dampness in the child's bedroom, mother's bedroom, and lounge (winter)



Child Bedroom dampness (%) winter

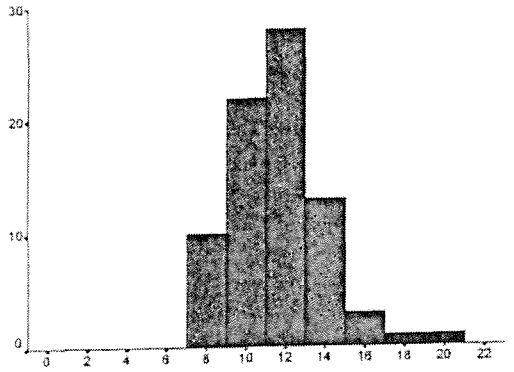


Mother bedroom dampness (%) winter

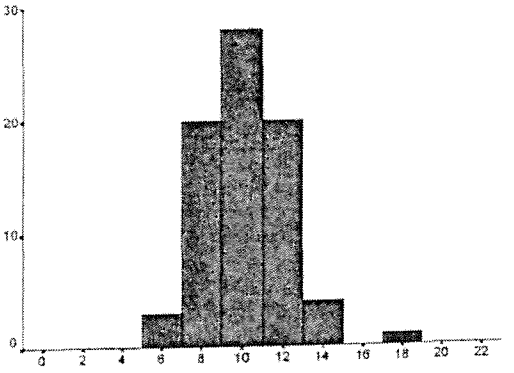


Lounge dampness (%) winter

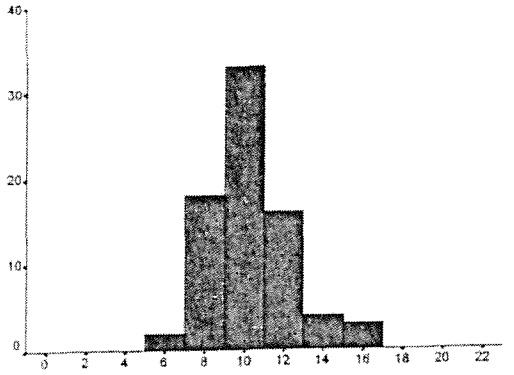
Figures 4.17: Dampness in the child's bedroom, mother's bedroom, and lounge (Summer)



Lounge dampness (%) summer



mother bedroom dampness (%)



Child bedroom dampness (%) summer

4.3 Summary

Our study found no significant seasonal differences in the levels of indoor nitrogen dioxide, nor in the degree of dampness.

We did not demonstrate a significant difference in the degree of dampness between the two seasons, this may be due to the fact that there was not a significant change in temperature between the months when dampness was measured.

As regard nitrogen dioxide measurements, we have shown no significant seasonal difference in the measurements of nitrogen dioxide. One of the main sources of nitrogen dioxide in the homes is the gas appliance such as gas cooker and outside air. Therefore, it is possible the ventilation was similar during the months when nitrogen dioxide was measured, which could have led to stabilize the indoor level of nitrogen dioxide. Furthermore, there might been no significant difference in the outdoor level of nitrogen dioxide, which could have attributed to our findings in this study.

However, it appears that the level of total volatile organic compounds is higher in the winter season as opposed to the summer one. Different in the use of building materials (for e.g: furniture polish) and consumer products (cleaning and gardening products is a possible explanation to the difference between the two seasonal measurements. Outdoor air penetrating indoor spaces via ventilation is potentially another factor which could have accounted for the difference of two VOCs measurements. The difference between the two measurements was small, therefore it is possible that impact of VOCs on the prevalence of the respiratory episodes may not be significantly different between the different seasons. Similar observation was noted in urine cotinine level, probably the rate of ventilation, the time spent indoor during the winter and the variability in the

metabolism of cotinine were the contributory factors to the difference between the two seasonal measurements.

Most of the previous epidemiological studies which examined the relationship between exposure to indoor air pollution and the incidence, duration and severity of the respiratory episodes, have used the average exposure to the indoor air pollutant over a period of time (1-6 weeks). One of the criticisms for using one measurement may not be a valid reflect of what subjects encounter on daily basis, particularly given the fact that the indoor level of any particular air polltutant is influenced by several factors such as the outdoor level of the air pollution, temperature, and humidity.

Therefore in our study it was felt that we ought to address the above issue by carring out two measurements to determine whether there is a seasonal difference or not, it was also felt that by including the mean of the two measurements it would probably give more accurate estimate of the average exposure to indoor air pollution over the study period. However, in our study the data of the subjects and fixed places with only one recorded air pollutant measurement over the study period was also included, to avoid loosing the power of the study.

CHAPTER 5

The association between the respiratory episodes and the indoor environment

5.1 Results of the frequency, duration and severity of URT, LRT and PEF episodes (asthmatic children) in relation to indoor air pollution

Univariate and multivariate linear regression analyses were carried out to study the relationship between the frequency, duration and severity of the URT, LRT and PEF episodes and indoor exposure to air pollutants. In the multivariate analysis, we entered the following variables: nitrogen dioxide, formaldehyde, volatile organic compounds, der pI, dampness, age, atopy, and gender.

Incidence of rate ratio (IRR) represents the increase/decrease of the incidence of the episodes for each one unit increase in the air pollutant, it is significant when one does not fall in the range of the 95%CI. Beta is logged IRR, it is significant when zero does not fall in the range of 95%CI..

5.1.1 Frequency of the URT, LRT and PEF episodes and the indoor environment

The respiratory episodes were identified by an experienced paediatrician, who inspected visually all the diary cards (the data of diary cards was transformed to a graph using SPSS). Tables 5.1 & 5.2 summarize the association between the frequency of the respiratory episodes and the indoor environment.

Our study suggests that exposure to nitrogen dioxide (kitchen mean & personal) has a significant impact on the frequency of lower respiratory tract episodes, and there was a trend only towards a positive association between kitchen peak nitrogen dioxide and the frequency of lower respiratory tract episodes.

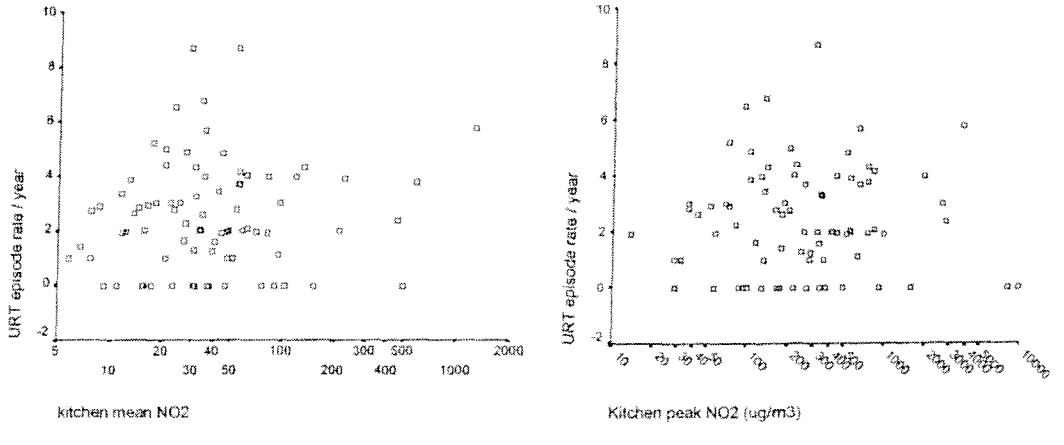
We also demonstrated that there was a positive relationship between indoor formaldehyde and the frequency of peak flow episodes.

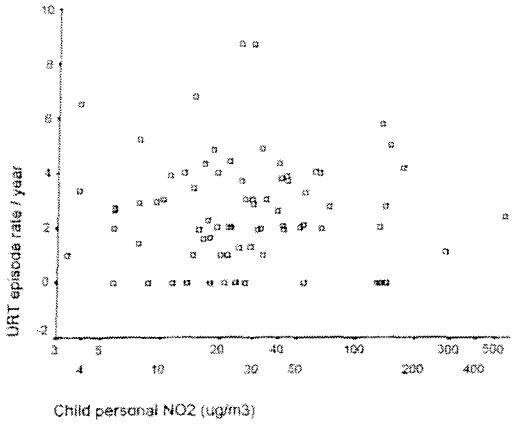
The above findings would probably been stronger had we have a bigger sample size, our study was under powered due to subjects' drop-out over the study period.

5.1.1.1 Frequency of the URT, LRT and PEF episodes and indoor exposure to nitrogen dioxide

No significant association was found between kitchen peak and personal nitrogen dioxide and the frequency of URT episodes among asthmatic children (IRR=1.0, 95%CI: 0.8-1.3; IRR=0.9, 95%CI: 0.6-1.4, respectively)(table 5.1,Fig 5.1). There was a trend towards an increase in the frequency of URT episodes, in relation to kitchen mean nitrogen dioxide, but this did not reach statistical significant (IRR=1.1, 95%CI: 0.8-1.5).

Fig 5.1: The association between nitrogen dioxide and the frequency of URT episodes



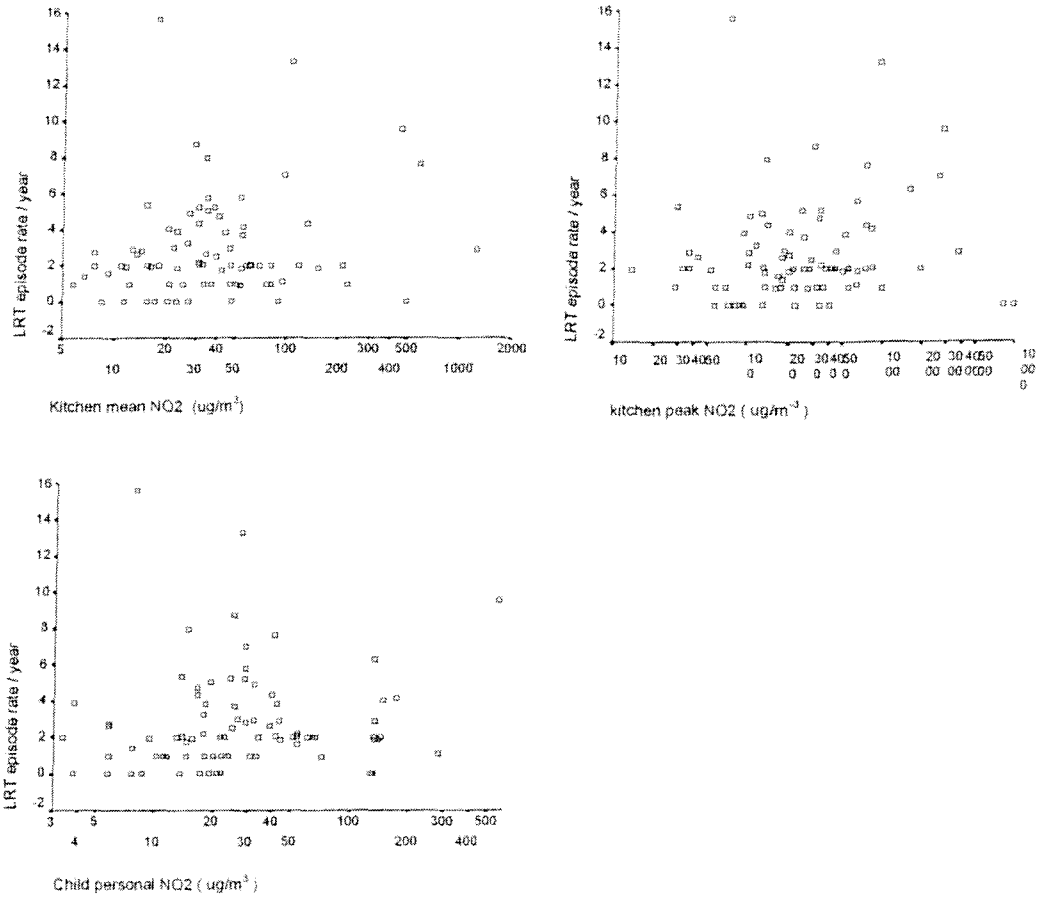


After adjusting for atopy, gender and other indoor air pollutants, there was a trend towards a positive relationship between the episodes and kitchen mean, kitchen peak and personal nitrogen dioxide, but this did not reach statistical significance (IRR=1.1, 95% CI: 0.8-1.6; IRR=1.1, 95% CI: 0.8-1.4; IRR=1.1, 95% CI: 0.7-1.6, respectively)(table 5.2).

Kitchen mean & peak and personal nitrogen dioxide have not influenced the frequency of LRT episodes in the univariate analysis (IRR=1.3, 95%CI: 0.9-2.0; IRR=1.3, 95%CI: 0.9-2.2; IRR=1.3, 95%CI: 0.8-1.9, respectively) (table 5.1, fig 5.2).

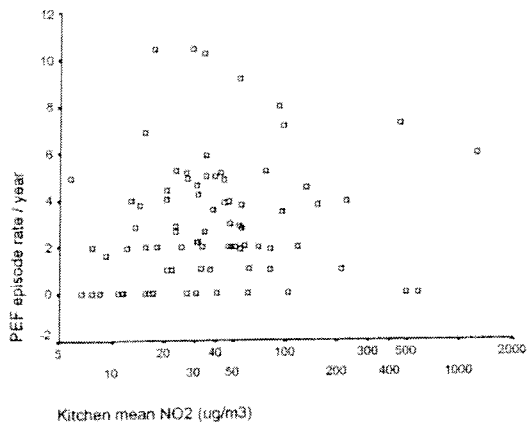
A positive association was demonstrated between the frequency of LRT episodes and kitchen mean and personal nitrogen dioxide in the multivariate analysis (IRR=1.4, 95%CI: 1.0-2.1; IRR=1.4, 95%CI: 1.0-2.0, respectively), and only a trend towards a positive relationship between URT episodes and kitchen peak nitrogen dioxide (IRR=1.4, 95%CI: 0.9-2.2) (table 5.2).

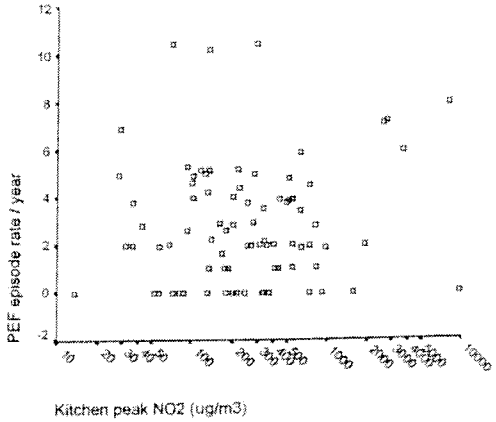
Fig 5.2: The association between nitrogen dioxide and the frequency of LRT episodes

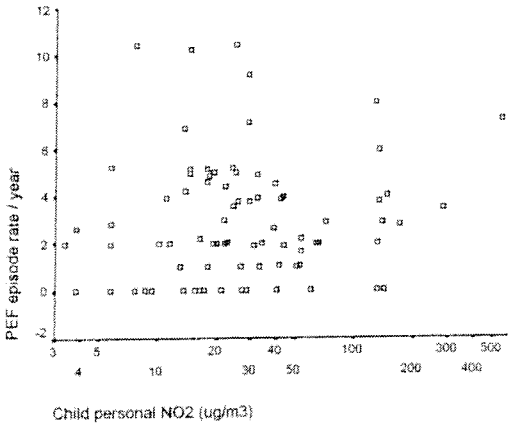


Neither kitchen (mean & peak nitrogen dioxide) nor personal nitrogen dioxide were associated with an increase in the rate of PEF episodes among asthmatic children (IRR=1.3, 95%CI: 0.9-1.9; IRR=1.1, 95%CI: 0.7-1.6; IRR=1.1, 95%CI: 0.8-1.5, respectively) (table 5.1, fig 5.3). The relationship between the PEF episodes and kitchen (mean& peak) and personal nitrogen dioxide has remained statistically insignificant in the multivariate analysis (IRR=1.2, 95%CI: 0.7-1.9; IRR=1.0, 95%CI: 0.7-1.5; IRR=1.3, 95%CI: 0.9-1.3, respectively)(table 5.2).

Fig 5.3: The association between nitrogen dioxide and the frequency of PEF episodes



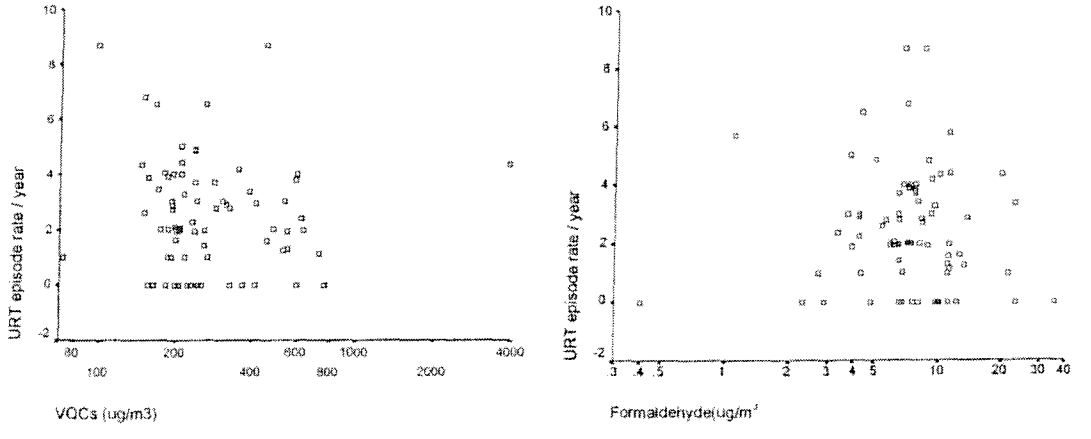




5.1.1.2 Frequency of URT, LRT and PEF episodes and indoor exposure to VOCs and formaldehyde

Exposure to indoor volatile organic compounds and formaldehyde was not associated with any increase in the frequency of URT episodes (IRR=0.7, 95%CI: 0.3-1.5; IRR=0.5, 95%CI: 0.2-1.1, respectively) (table 5.1, fig 5.4). After adjusting for gender, atopy, der pI and other indoor air pollutants, this association remained insignificant (IRR=0.6, 95%CI: 0.3-1.4; IRR=0.5, 95%CI: 0.2-1.3, respectively)(table 5.2).

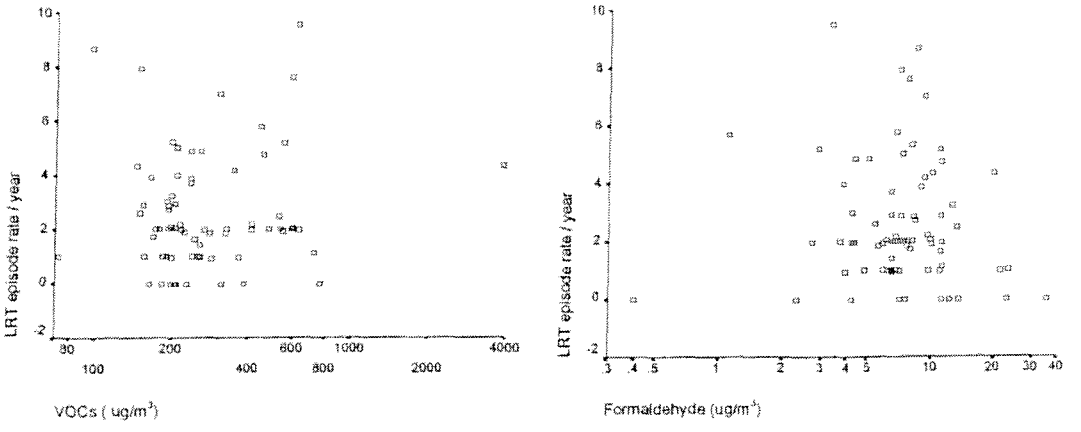
Fig 5.4: The association between Formaldehyde, VOCs and the frequency of URT episodes



There was no increase in the frequency of LRT episodes in relation to indoor formaldehyde and VOCs exposure (IRR=0.4, 95%CI: 0.6-2.6; IRR=0.5, 95%CI: 0.2-1.1, respectively) (table 5.1,fig 5.5).

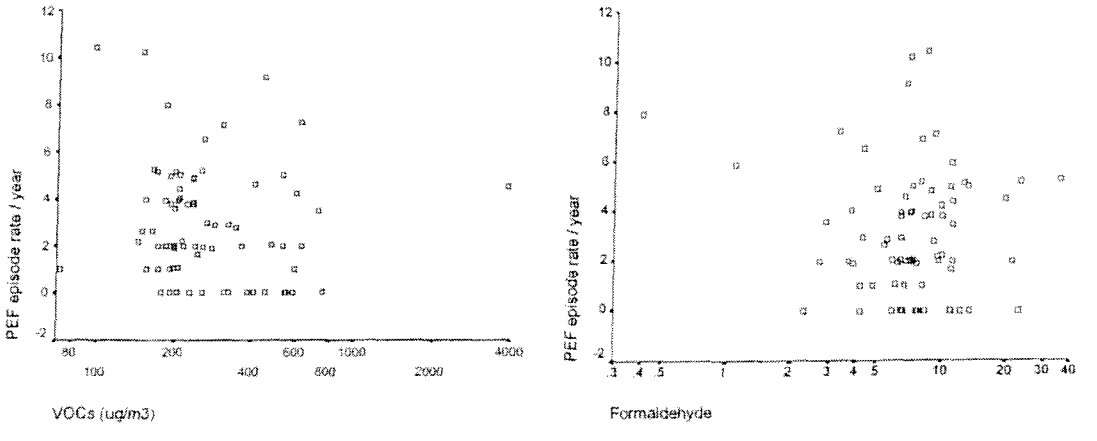
In the multivariate analysis this relationship remained insignificant for both (VOCs: IRR = 1.3; 95%CI: 0.5-3.1, and formaldehyde: IRR=0.4; 95% 0.2-1.0).

Fig 5.5: The association between Formaldehyde, VOCs and the frequency of LRT episodes



There was a positive association between the frequency of PEF episodes and indoor formaldehyde, after adjusting for other indoor air pollutants (IRR=1.8; 95%CI 1.0-3.4)(table 5.2, fig 5.6), but not with VOCs before and after adjustment for other variables (IRR=0.6, 95%CI: 0.2-1.6; IRR=0.5, 95%CI: 0.2-1.3, respectively) (tables 5.1 & 5.6, fig 5.6).

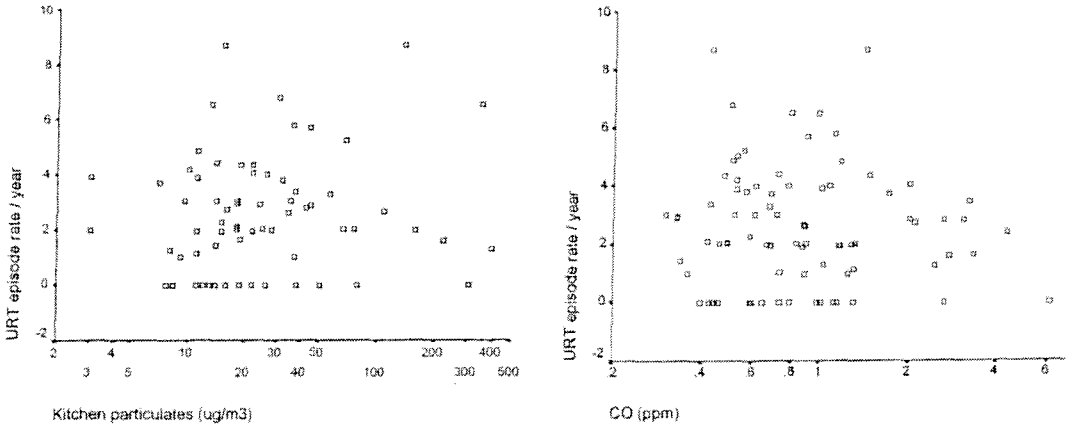
Fig 5.6: The association between Formaldehyde, VOCs and the frequency of PEF episodes



5.1.1.3 Frequency of URT, LRT and PEF episodes and indoor exposure to particulate matter and carbon monoxide

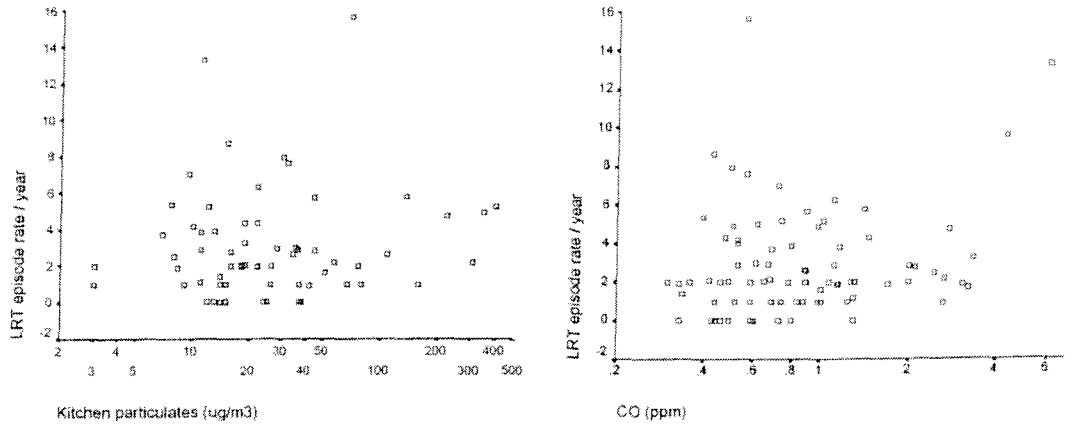
In the analysis of the relationship between particulate matter, carbon monoxide and the frequency of URT episodes, no significant association was found (IRR=1.0, 95%CI: 0.6-1.5; IRR=0.8, 95%CI: 0.5-1.4, respectively)(table 5.1, Fig 5.7).

Fig 5.7: The association between carbon monoxide, particulate matter and the frequency of URT episodes



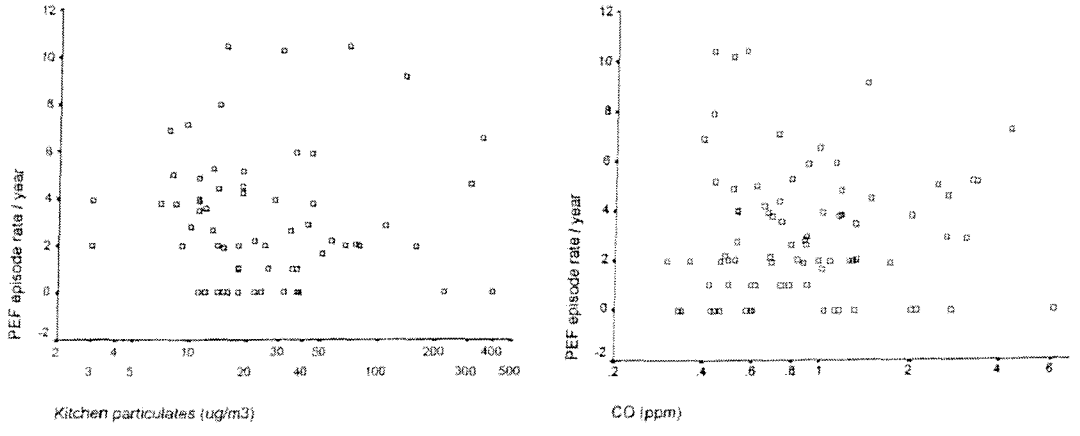
Similarly, the frequency of the LRT episodes did not seem to have been influenced by exposure to indoor particulate matter (IRR=1.1; 95%CI: 0.8-1.7) nor by exposure to carbon monoxide (IRR=1.3;95%CI: 0.7-2.5).

Fig 5.8: The association between carbon monoxide, particulate matter and the frequency of LRT episodes



The frequency of acute asthma attacks (PEF episodes) was not influenced by the exposure to carbon monoxide and particulate matter (IRR=0.8, 95%CI: 0.5-1.3; IRR=1.4, 95%CI: 0.7-2.5, respectively)(table 5.1, fig 5.9).

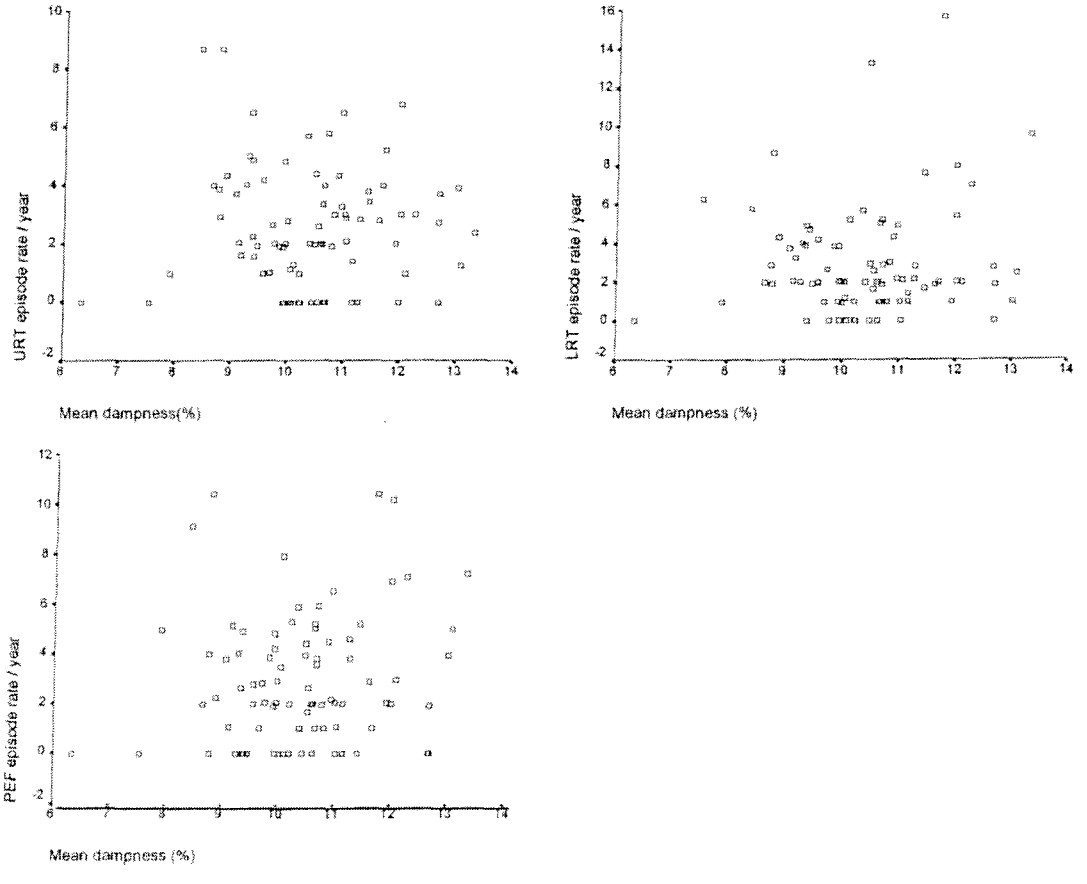
Fig 5.9: The association between carbon monoxide, particulate matter and the frequency of PEF episodes



5.1.1.4 Dampness and the frequency of the episodes

Dampness did not seem to have any influence on the frequency of URT episodes (IRR=0.9; 95% CI: 0.8-1.1), LRT episodes (IRR=1.0;95%CI: 0.9-1.2) and PEF episodes (IRR=1.1; 95% CI: 0.9-1.3) (table 5.1, fig 5.10). This association remained statistically insignificant after adjusting for atopy, gender, der pI and other indoor air pollutants (IRR=1.0, 95%CI: 0.8-1.1; IRR=1.0, 95%CI: 0.8-1.2; IRR=1.1, 95%CI: 0.9-1.3, respectively)(table 5.2).

Fig 5.10: The association between dampness and the frequency of URT, LRT and PEF episodes

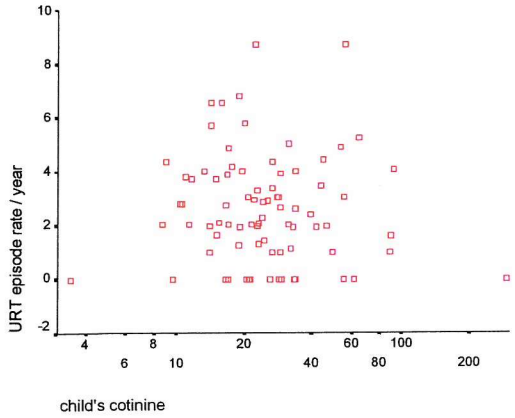


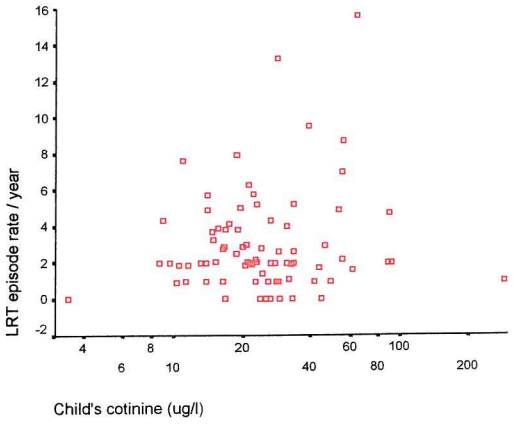
5.1.1.5 Environmental tobacco smoke and the frequency of URT, LRT and PEF episodes

Exposure to environmental tobacco smoke as measured by urine cotinine was not associated with any increase in the frequency of URT, before and after adjusting for other variables (IRR=0.6, 95%CI: 0.3-1.2; IRR=0.7, 95%CI: 0.3-1.2, respectively).

There was a trend towards a positive association between cotinine and the frequency of lower respiratory tract and peak expiratory flow episodes and urine cotinine (IRR=1.1, 95%CI: 0.6-2.1; IRR=1.1, 95%CI: 0.6-1.9, respectively) (table 5.1, fig 5.11). In the multivariate analysis, this association has remained statistically insignificant (IRR=1.2 95%CI: 0.6-2.3; IRR=1.2, 95%CI: 0.9-2.5, respectively) (table 5.2). As I mentioned before that this study was underpowered, therefore the trend we have shown on the relationship between cotinine and the frequency of the episodes would probably been different had we have a larger sample size.

Fig 5.11: The association between environmental tobacco smoke and the frequency of URT, LRT and PEF episodes





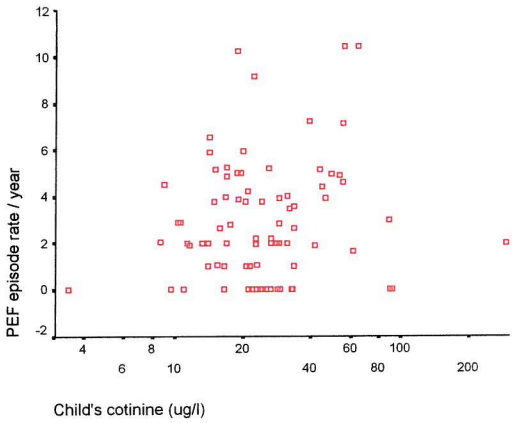


Table 5.1: The association between the frequency of URT, LRT, PEF episodes and *indoor air pollutants: univariate analysis*

Air Pollutant	URT(IRR; 95%CI) P	LRT(IRR; 95%CI) P	PEF (IRR; 95%) P
Kitchen Mean NO2	1.1; 0.8-1.5 P=0.43	1.3; 0.9-2.0 P=0.1	1.3;0.9-1.9 P=0.1
Kitchen Peak NO2	1.0; 0.8-1.3 P=0.8	1.3; 0.9-2.2 P=0.1	1.1; 0.7-1.6 P=0.4
Child Personal NO2	0.9; 0.6-1.4 P=0.9	1.3; 0.8-1.9 P=0.1	1.1;0.8-1.5 P=0.4
Particulate matter	1.0; 0.6-1.5 P=0.9	1.1; 0.8-1.7 P=0.3	0.8; 0.5-1.3 P=0.4
VOCs	0.7; 0.3-1.5 P=0.4	0.4; 0.6-2.6 P=0.5	0.6; 0.2-1.6 P=0.3
Formaldehyde	0.5; 0.2-1.1 P=0.1	0.5; 0.2-1.1 P=0.1	1.3; 0.6-2.7 P=0.3
Carbon monoxide	0.9; 0.5-1.4 P=0.6	1.3; 0.7-2.5 P=0.3	1.4;0.7-2.5 P=0.2
Dampness	0.9; 0.8-1.1 P=0.8	1.0; 0.9-1.2 P=0.4	1.1; 0.9-1.3 P=0.1
Cotinine	0.6; 0.3-1.2 P=0.2	1.1; 0.6-2.1 P=0.5	1.1; 0.6-1.9 P=0.6

Table 5.2: The association between the frequency of URT, LRT, PEF episodes and *indoor air pollutants: multivariate analysis*

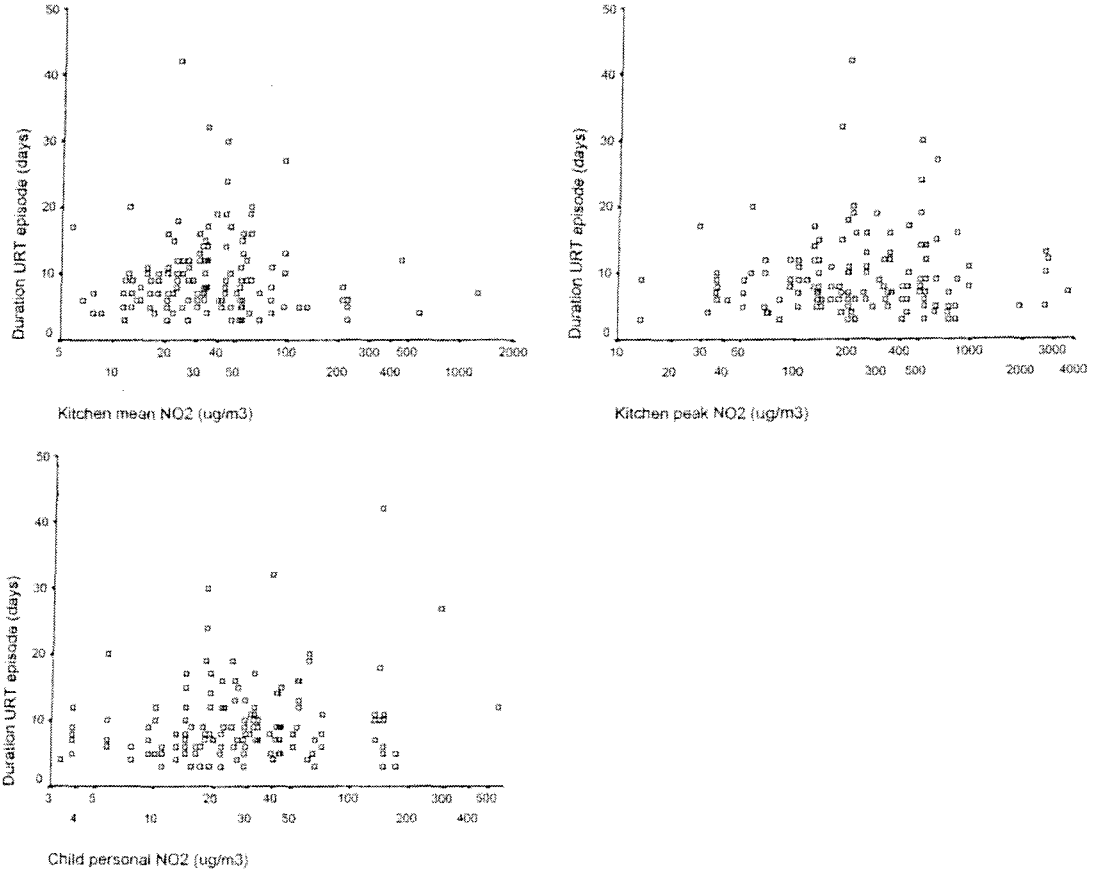
Indoor pollutant	URT (IRR;95%CI) P	LRT (IRR; 95%CI P	PEF (IRR; 95%CI) P
Kitchen mean NO2	1.1; 0.8-1.6 P=0.4	1.4; 1.0-2.1 P=0.04	1.2; 0.7-1.9 P=0.3
Kitchen peak NO2	1.1; 0.8- 1.4 P=0.4	1.4; 0.9-2.2 P=0.06	1.0; 0.7- 1.5 P=0.7
Personal NO2	1.1; 0.7-1.6 P=0.5	1.4;1.0-2.0 P=0.01	1.3; 0.9- 1.3 P=0.1
VOCs	0.6; 0.3- 1.4 P=0.2	1.3; 0.5- 3.1 P=0.4	0.5; 0.2- 1.3 P=0.1
Formaldehyde	0.5; 0.2- 1.3 P=0.1	0.4; 0.2- 1.0 P=0.07	1.8; 1.0- 3.4 P=0.03
Dampness	1.0; 0.8- 1.1 P=0.6	1.0; 0.8-1.2 P=0.7	1.1; 0.9- 1.3 P=0.1
Cotinine	0.7; 0.3- 1.2 P=0.2	1.2; 0.6- 2.3 P=0.4	1.2; 0.9- 2.5 P=0.1

5.1.2 Duration of URT, LRT and PEF episodes and the indoor environment

5.1.2.1 Duration of the URT, LRT and PEF episodes and NO_2 exposure

No significant relationship was found between kitchen mean, kitchen peak and personal nitrogen dioxide and the duration of upper respiratory tract epiosdes (Beta= - 0.09, 95%CI: -0.3-0.8; Beta= -0.04,95%CI:-0.2-0.1;Beta=0.1,95%CI: -0.2-0.4, respectively) (table 5.3, fig 5.12). This association remained statistically insignificant in the multivariate analysis (Beta= - 0.1, 95%CI: -0.5-0.1; Beta= -0.07,95%CI: -0.3 - 0.01; Beta=0.1, 95%CI: -0.2-0.4, respectively)(table 5.4).

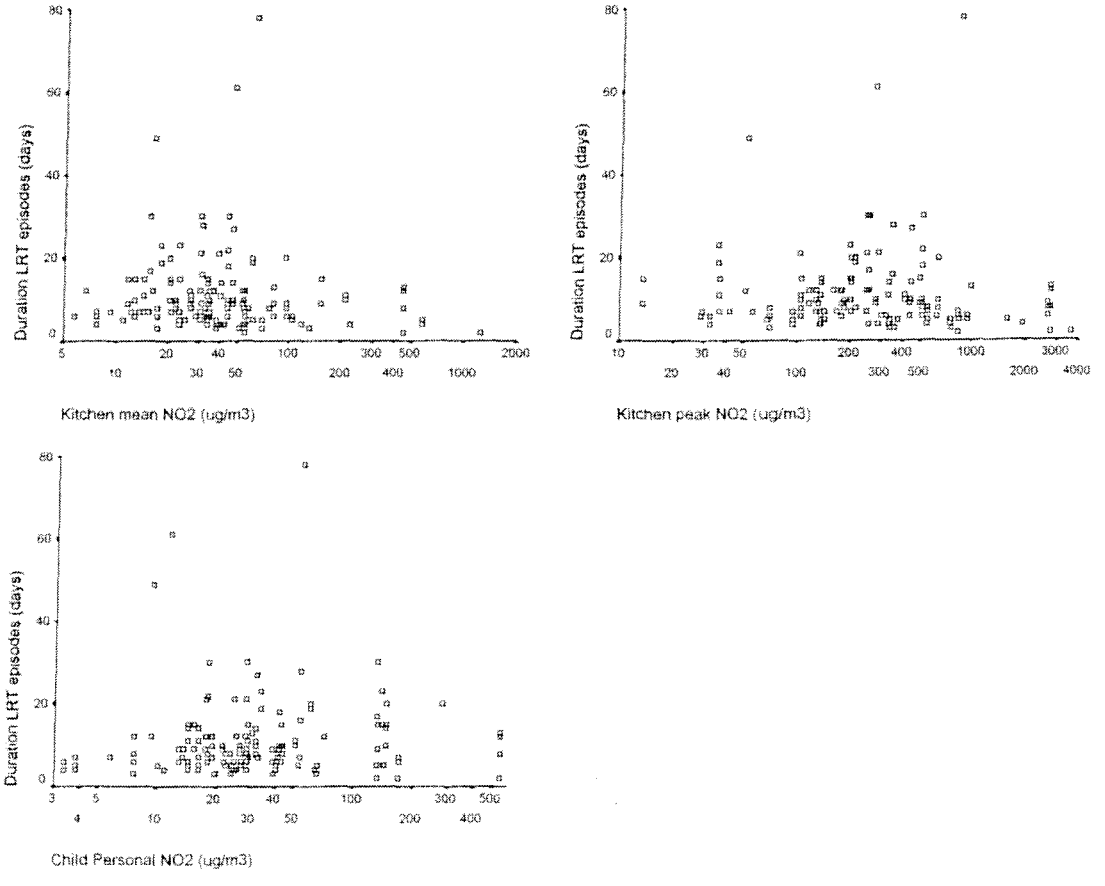
Fig 5.12: The Association between nitrogen dioxide and the duration of URT episodes



It seems that children with high kitchen nitrogen dioxide had suffered shorter lower respiratory tract episodes (Beta= -0.3, 95%CI: -0.7 - -0.01; Beta= -0.2, 95%CI:- 0.5 - -0.01, respectively)(table 5.4). It is possible that this finding was a chance finding as our study was underpowered, alternatively the medication used during the respiratory episodes could have contributed to this observation (for example children who had suffered frequent respiratory episodes, had used higher inhaled corticosteroid and frequent bronchodilator).

Personal nitrogen dioxide did not have any influence on the duration of lower respiratory tract episodes before and after adjustment (Beta=0.2,95%CI:-0.1- 0.5; Beta=0.1, 95%CI: –0.2-0.5; Beta).

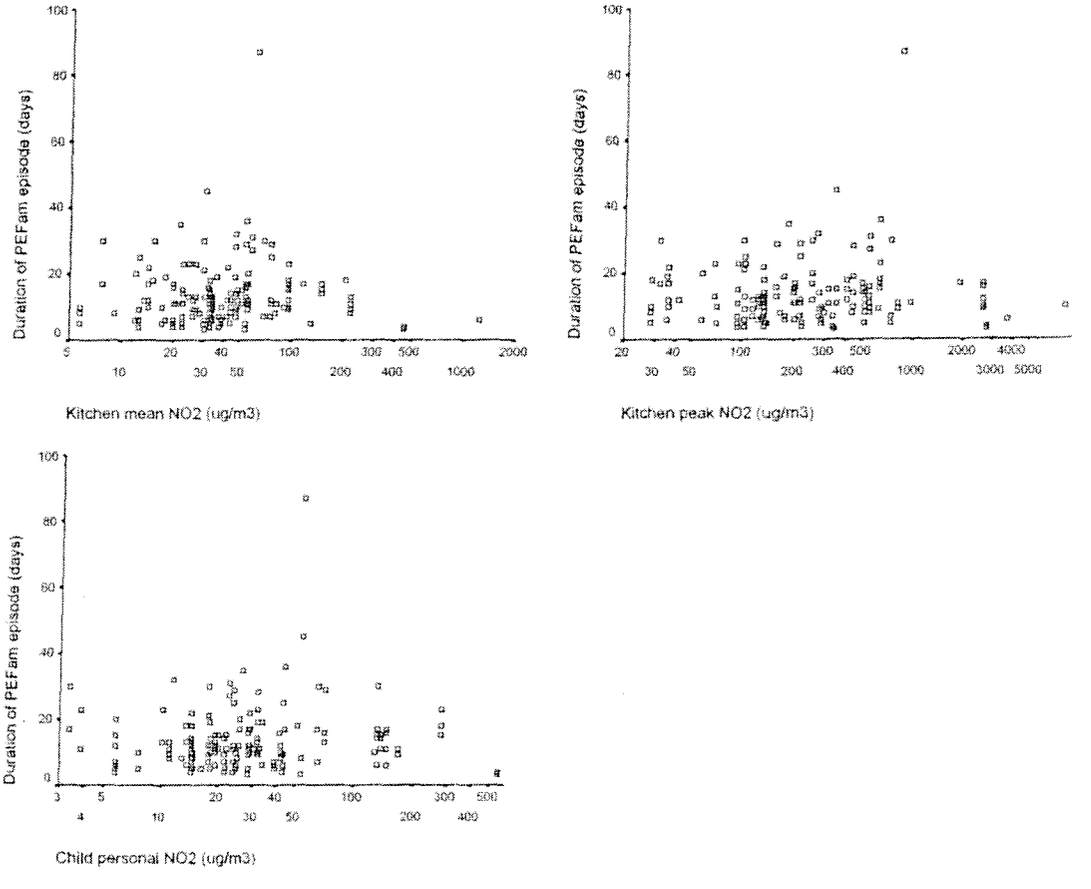
Fig 5.13: The association between nitrogen dioxide and the duration of LRT episodes



Exposure to nitrogen dioxide in the kitchen (mean & peak) has not influenced the duration of the PEF episodes among asthmatic children (univariate analysis: Beta=0.07, 95%CI: -0.1 – 0.3; Beta=0.06,95%CI: -0.1-0.2, respectively) (table 5.3, fig 5.14). This relationship remained insignificant after adjustment for the other variables (Beta= 0.1, 95%CI: -0.1-0.4; Beta= 0.05,95%CI:-0.1-0.2, respectively).

Similarly, no significant association was found between personal nitrogen dioxide and the duration of the PEF episodes (Beta=0.1, 95%CI –0.1-0.3; Beta=0.1, 95%CI:-0.2-0.4, respectively) (tables 5.3 & 5.4).

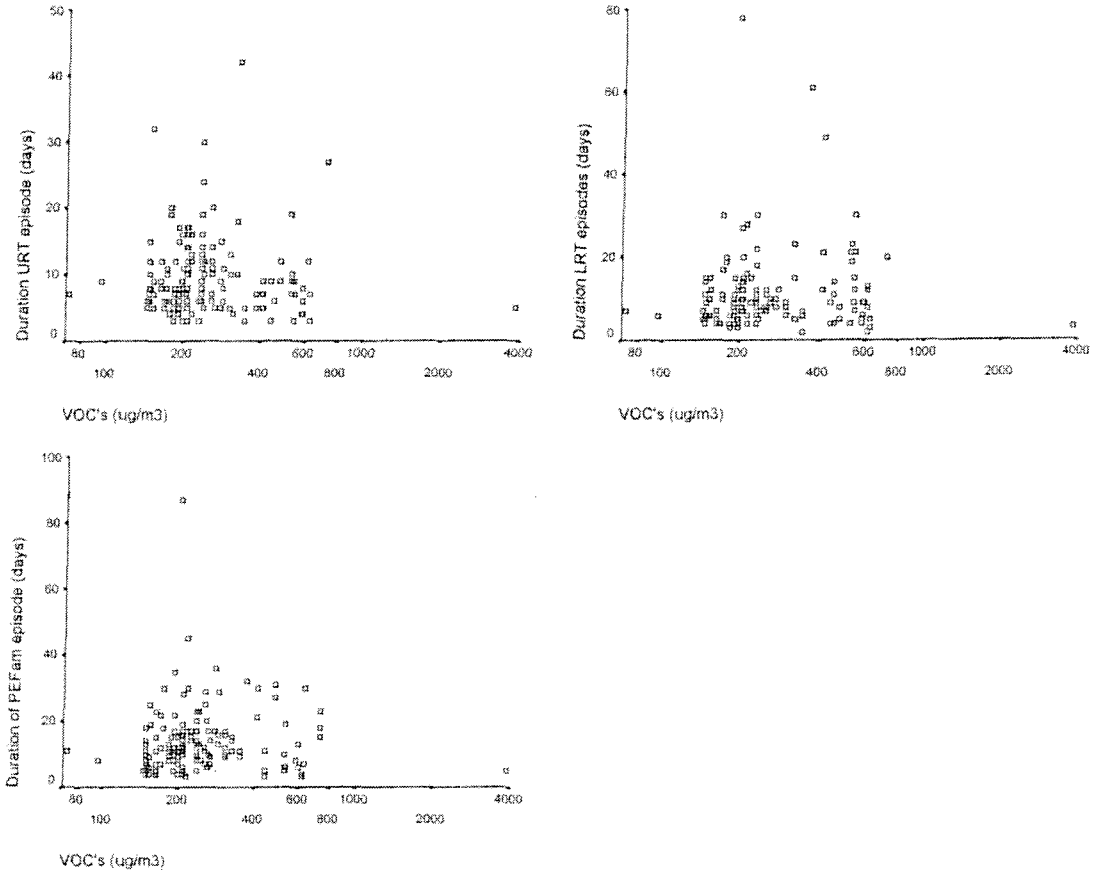
Fig 5.14: The association between nitrogen dioxide and the duration of PEF episodes



5.1.2.2 Volatile organic compounds, formaldehyde and the duration of URT, LRT and PEF episodes

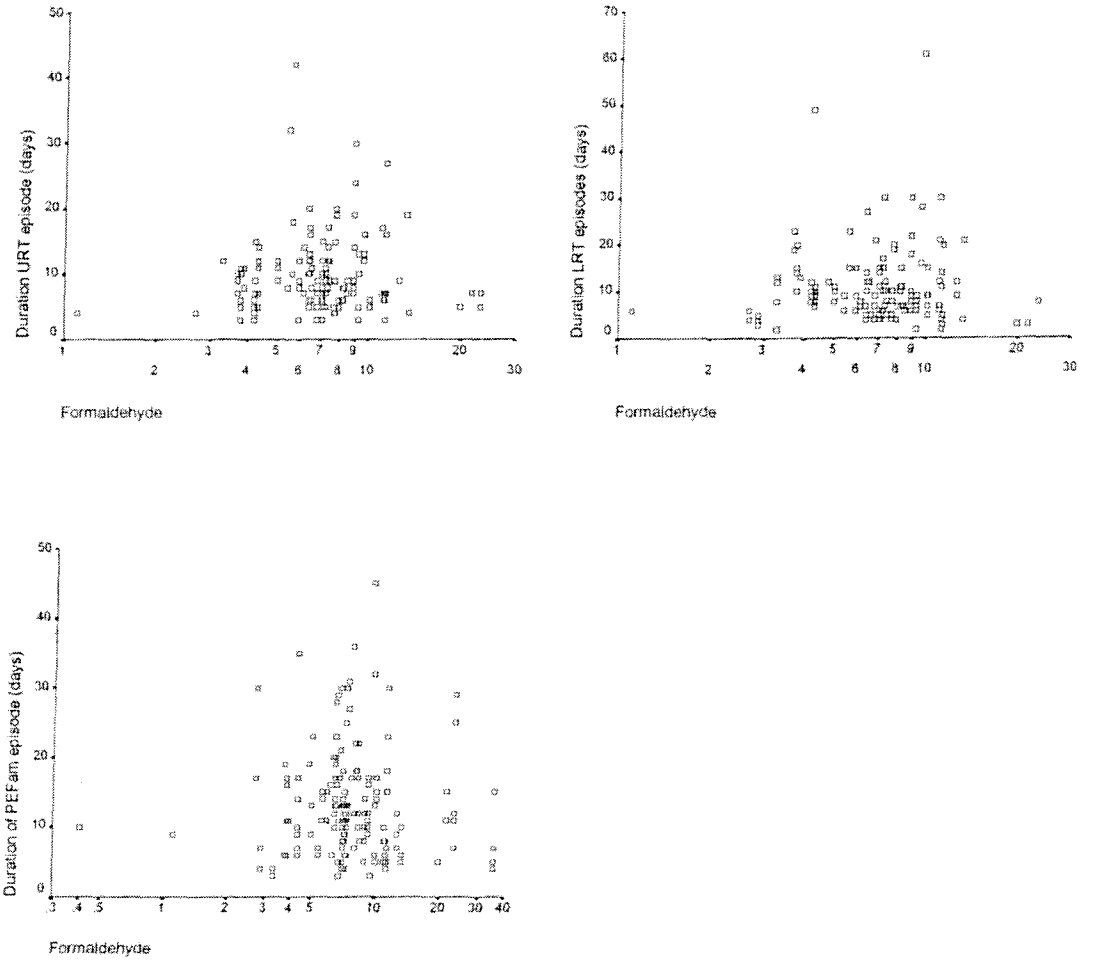
Indoor volatile organic compounds did not have a significant impact on the duration of URT, LRT and PEF episodes (Beta= 0.02, 95%CI: -0.5-0.5; Beta= -0.01,95%CI:-0.7-0.7;Beta=-0.03,95%CI: -0.1-0.3, respectively) (table 5.3 , fig 5.15). In the multivariate analysis, the association between VOCs the duration of URT, LRT and PEF episodes has remained statistically insignificant (Beta= 0.2, 95%CI: -0.5-0.1; Beta= 0.2, 95%CI:-0.4-1.0;Beta=0.05,95%CI: -0.5-0.6, respectively) (table 5.4).

Fig 5.15: The association between VOCs and the duration of URT, LRT and PEF episodes



There was no significant association between formaldehyde and the duration of URT, LRT and PEF episodes (Beta= 0.05, 95%CI: -0.5-0.6; Beta= -0.5,95%CI:-1.3-0.2;Beta=-0.2,95%CI: -0.6-0.1, respectively)(table 5.3, fig 5.16). Adjusting for the other environmental factors had not demonstrated a significant association between formaldehyde and the duration of URT, LRT and PEF episodes (Beta=-0.01,95%CI:-0.7-0.6; Beta=-0.2, 95%CI:-1.1-0.6; Beta=-0.2,95%CI:-0.7-0.1, respectively).

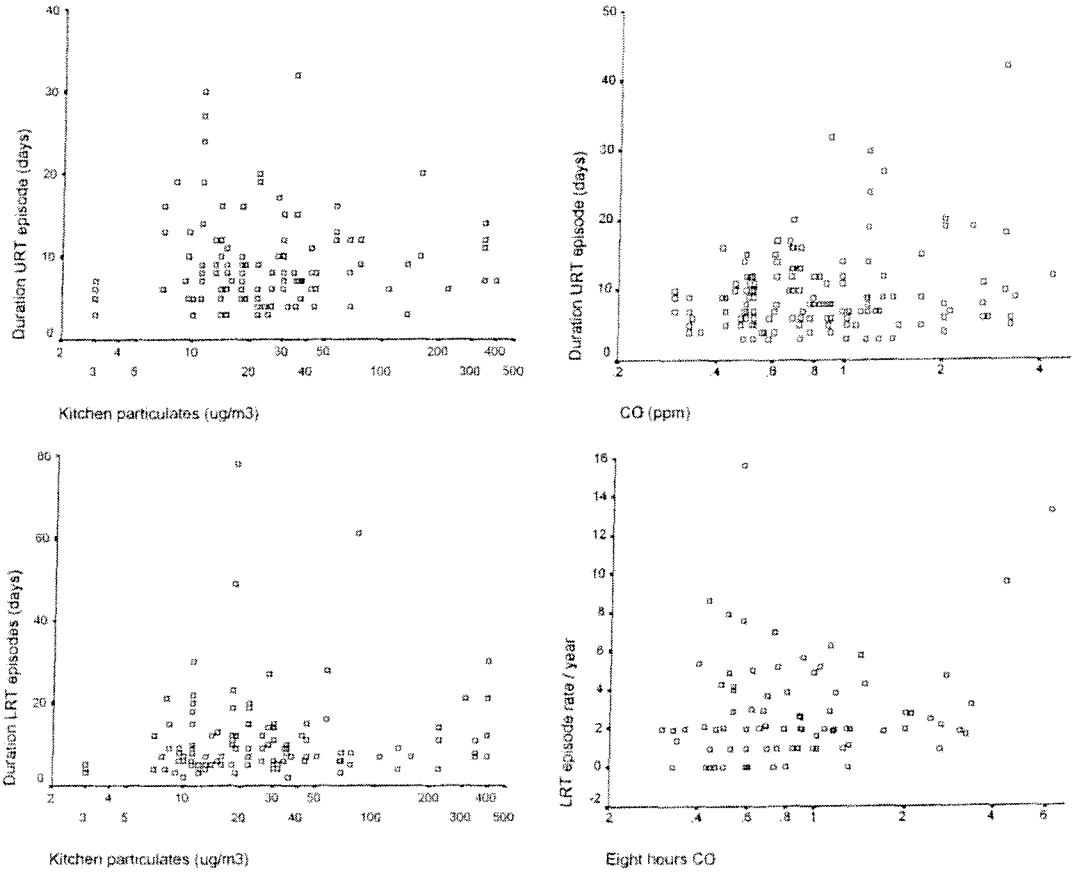
Fig 5.16: The association between formaldehyde and the duration URT, LRT and PEF episodes

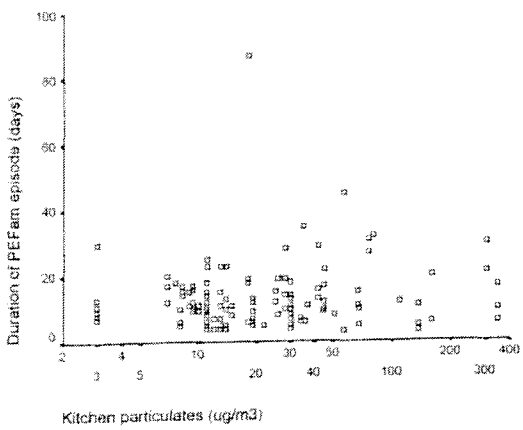


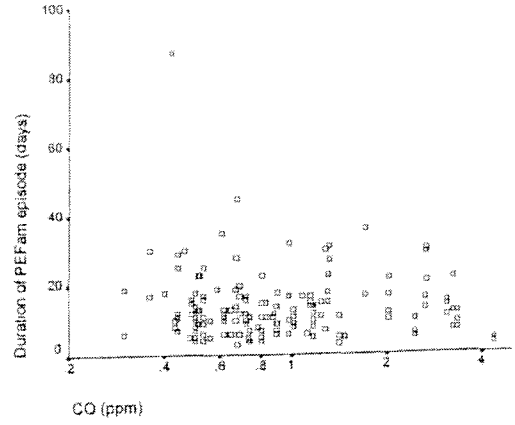
5.1.2.3 Particulate matter, carbon monoxide and the duration of URT, LRT and PEF episodes

Exposure to indoor particulate matter and carbon monoxide did not show a significant increase in the duration of URT episodes (Beta=0.2, 95%CI: -0.01-0.4; Beta=0.3,95%CI: -0.08-0.7, respectively), LRT episodes (Beta=0.3, 95%CI: -0.05-0.6; Beta=0.02,95%CI: -0.5-0.5, respectively) and PEF episodes (Beta=0.1, 95%CI: -0.1-0.3; Beta=-0.2,95%CI: -0.6-0.1, respectively) (table 5.3, fig 5.17).

Fig 5.17: The association between carbon monoxide, particulate matter and the duration of URT, LRT and PEF episodes




Duration of PEFam episode (days)
100
80
60
40
20
0
2
3
4
5
10
20
30
40
50
100
200
300
400
Kitchen particulates (ug/m3)

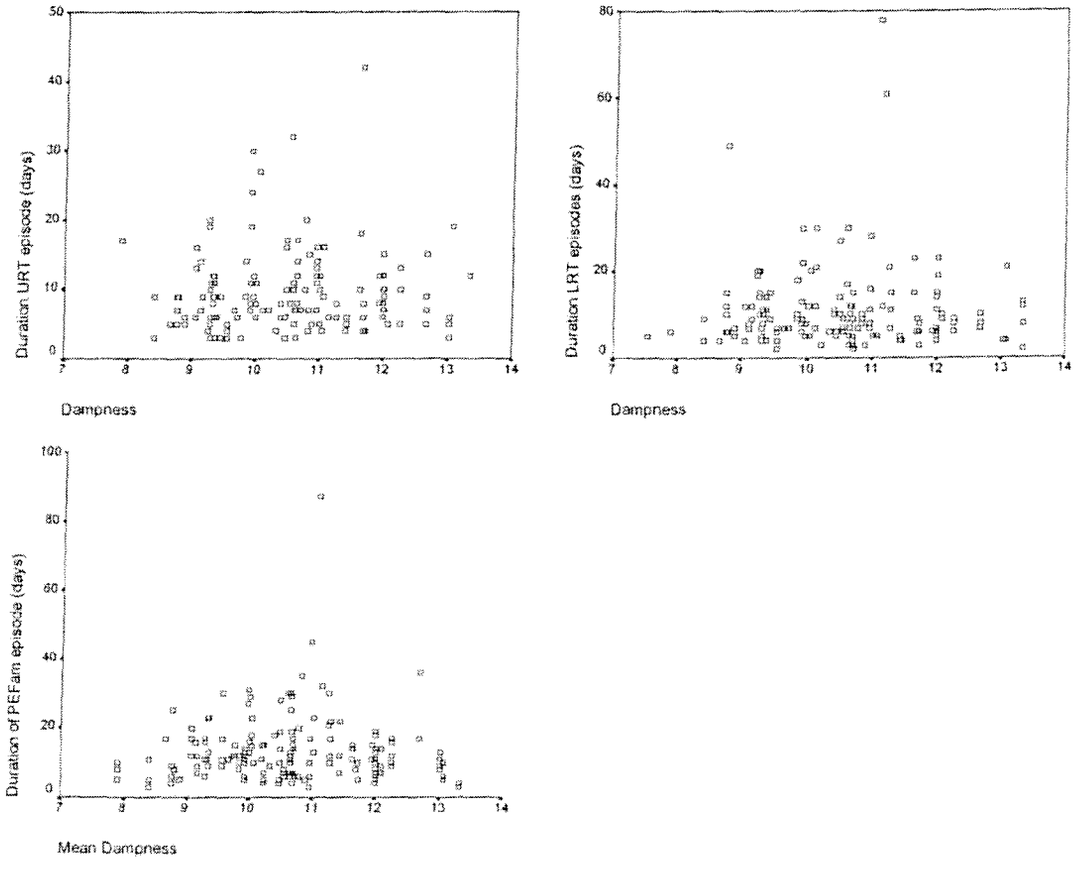

Duration of PEFam episode (days)
100
80
60
40
20
0
2
.4
.6
.8
1
2
4
CO (ppm)

5.1.2.4 Dampness and the duration of the episodes

There was a trend towards a positive association between the duration of upper respiratory tract, lower respiratory tract and peak expiratory flow episodes and dampness, but this did not reach statistical significance (Beta=0.5, 95%CI: –0.06-0.1; Beta=0.02, 95%CI: -0.07-0.1; Beta=0.02, 95%CI: -0.04-0.09, respectively)(table 5.3, fig 5.18).

In the multivariate analysis, adjusting for gender, atopy, der pI and other indoor environmental factors, no significant association was found between dampness and the duration of URT, LRT and PEF episodes among asthmatic children (Beta=0.05, 95%CI: –0.04-0.5; Beta=0.04, 95%CI: -0.06-0.1; Beta=-0.006, 95%CI: -0.08-0.06, respectively) (table 5.4).

Fig 5.18: The association between dampness and URT, LRT and PEF episodes



5.1.2.5 Environmental tobacco smoke and the duration of the episodes

Exposure to environmental tobacco smoke as measured by urine cotinine did not lead to any increase in the duration of the URT, LRT and PEF episodes (Beta= -0.1, 95%CI: –0.6-0.2; Beta=0.4, 95%CI: -0.08-0.9; Beta= -0.08, 95%CI: -0.6-0.4, respectively) (table 5.3, fig 5.19). This association remained statistically insignificant in the multivariate analysis (table 5.4).

Fig 5.19: The association between Environmental tobacco smoke and URT, LRT and PEF episodes

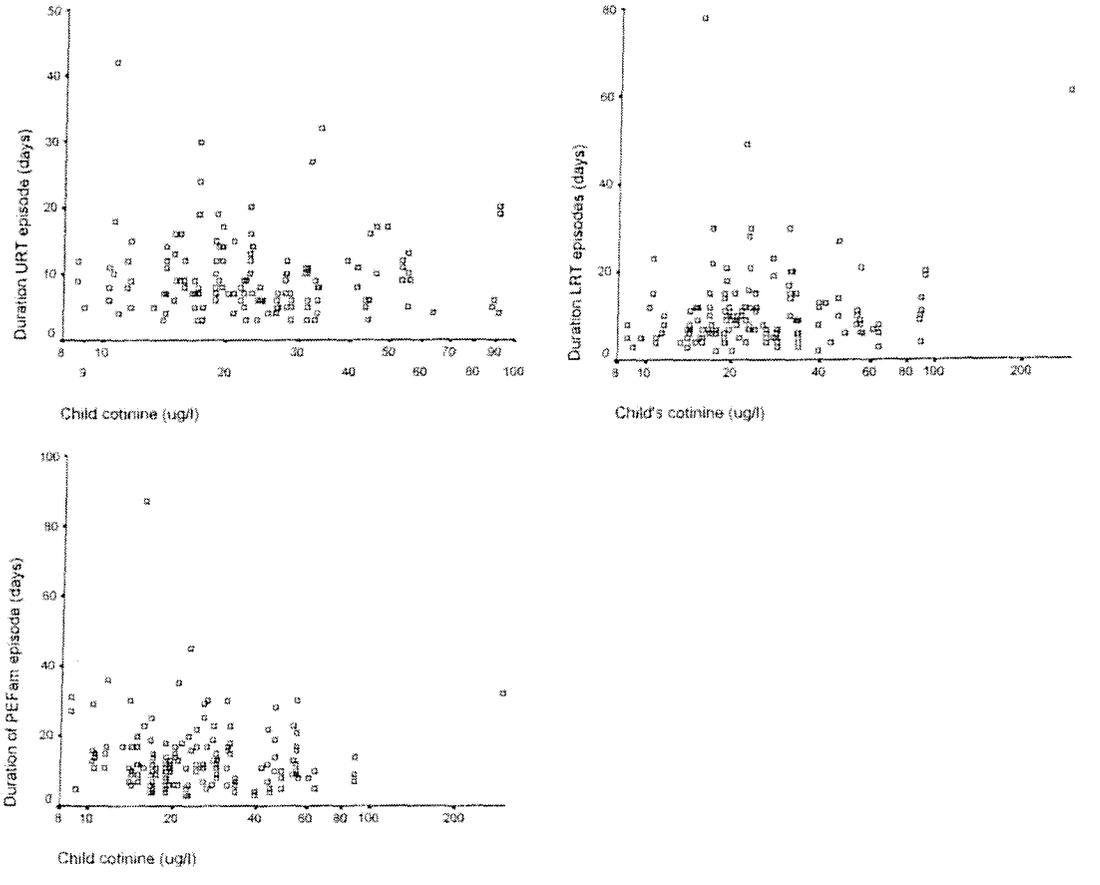


Table 5.3:The association between the duration of URT, LRT, PEF episodes and indoor air pollutants : univariate analysis

Indoor pollutant	URT(Beta; 95%CI) P	LRT(Beta; 95%CI) P	PEF(Beta; 95%CI) P
Kitchen mean NO2	-0.09; -0.3- 0.8 P=0.5	-0.3; -0.6- 0.04 P=0.08	0.07; -0.1- 0.3 P=0.5
Kitchen peak NO2	-0.04; -0.2- 0.1 P=0.6	-0.2; -0.5- 0.08 P=0.1	0.06; -0.1-0.2 P=0.5
Kitchen personal NO2	0.1; -0.2- 0.4 P=0.4	0.2; -0.1-0.5 P=0.1	0.1; -0.1- 0.3 P=0.3
Particulate matter	0.2; -0.01- 0.4 P=0.06	0.3; P=-0.05- 0.6 P=0.09	0.1; -0.1- 0.3 P=0.4
VOCs	0.02; -0.5- 0.5 P=0.9	-0.01; -0.7- 0.7 P=0.9	-0.03; -0.1- 0.3 P=0.4
Formaldehyde	0.05; -0.5- 0.6 P=0.8	-0.5; -1.3- 0.2 P=0.2	-0.2; -0.6- 0.1 P=0.2
Carbon monoxide	0.3; -0.08- 0.7 P=0.1	0.02; -0.5- 0.5 P=0.9	-0.2; -0.6- 0.1 P=0.2
Dampness	0.5;-0.06- 0.1 P=0.5	0.02; -0.07- 0.1 P=0.6	0.02; -0.04- 0.09 P=0.4
Cotinine	-0.1; -0.6- 0.2 P=0.4	0.4; -0.08- 0.9 P=0.09	-0.08; -0.6- 0.4 P=0.7

Table 5.4:The association between the duration of URT, LRT, PEF episodes and indoor air pollutants: multivariate analysis

Indoor air pollutant	URT(Beta;95%CI) P	LRT(Beta,95%CI) P	PEF(Beta,95%CI) P
Kitchen peak NO2	-0.07; -0.3- 0.01 P=0.5	-0.2; -0.5- -0.01 P=0.04	0.05;-0.1- 0.2 P=0.5
Kitchen mean NO2	-0.1; -0.5 - 0.1 P=0.3	-0.3; -0.7 - -0.01 P=0.04	0.1; -0.1 - 0.4 P=0.2
Personal NO2	0.1; -0.2 – 0.4 P=0.4	0.1;-0.2 – 0.5 P=0.3	0.1; - 0.2 – 0.4 P=0.4
VOCs	0.2; -0.5- 0.1 P=0.3	0.2 ; -0.4-1.0 P=0.4	0.05; -0.5- 0.6 P=0.8
Formaldehyde	-0.01; -0.7 -0.6 P=0.9	-0.2; -1.1- 0.6 P=0.5	-0.2; -0.7- 0.1 P=0.2
Dampness	0.05;-0.04-0.50 P=0.2	0.04; -0.06- 0.1 P=0.4	-0.006;-0.08- 0.06 P=0.8
Cotinine	-0.005; -0.4-0.4 P=0.9	0.5; -0.05-1.0 P=0.07	-0.06;-0.6-0.4 P=0.8

5.1.3 The association between indoor air pollution and the severity of URT, LRT and PEF episodes

The severity of the upper and lower respiratory tract episodes were defined as the area under the curve for the episodes, median of the respiratory symptoms over the study period was used as a base line. Area above the curve was used to define the severity of the peak flow episodes.

Our study demonstrated that carbon monoxide has detrimental effect on the severity of lower respiratory symptoms.

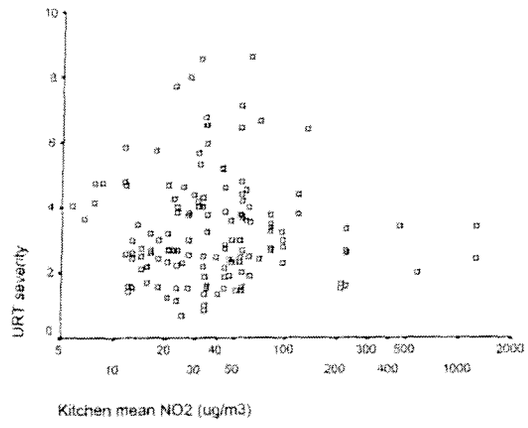
Our data also suggests that kitchen peak nitrogen dioxide increases the severity of upper respiratory tract episodes, and particulate matter has impact on the severity of asthma attacks (PEF episodes).

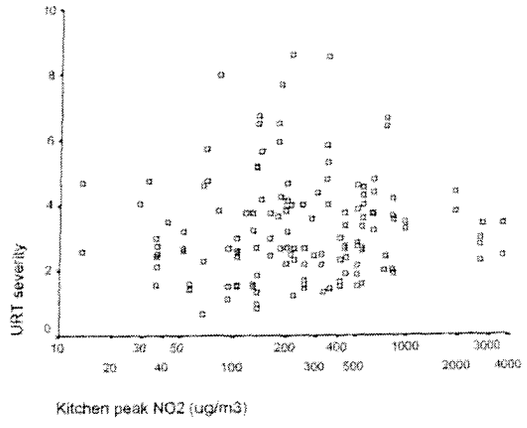
5.1.3.1 Nitrogen dioxide and the severity of URT, LRT and PEF episodes

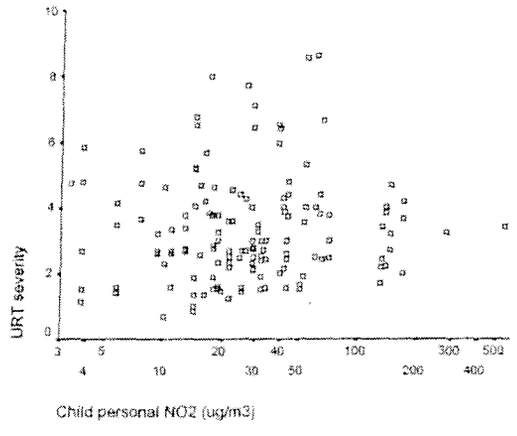
Our study demonstrated a trend towards a positive association between the severity of the URT episodes and the levels of kitchen mean, kitchen peak and personal nitrogen dioxide (Beta=0.01, 95%CI:-0.2-0.2; Beta=0.1, 95%CI:-0.02-0.3; Beta=0.1,95%CI:-0.08-0.3, respectively)(table 5.5, Fig 5.20).

Similarly, in the multivariate analysis, there was a tendency towards an increase in the severity of URT episodes in relation to kitchen peak nitrogen dioxide and personal nitrogen dioxide (Beta=0.2, 95%CI: -0.005-0.4; Beta=0.04, 95% CI: -0.2-0.2, respectively), but not with kitchen mean (Beta= -0.04, 95%CI:-0.3-0.2) (table 5.6)

Fig 5.20: The association between nitrogen dioxide and the severity of URT episodes

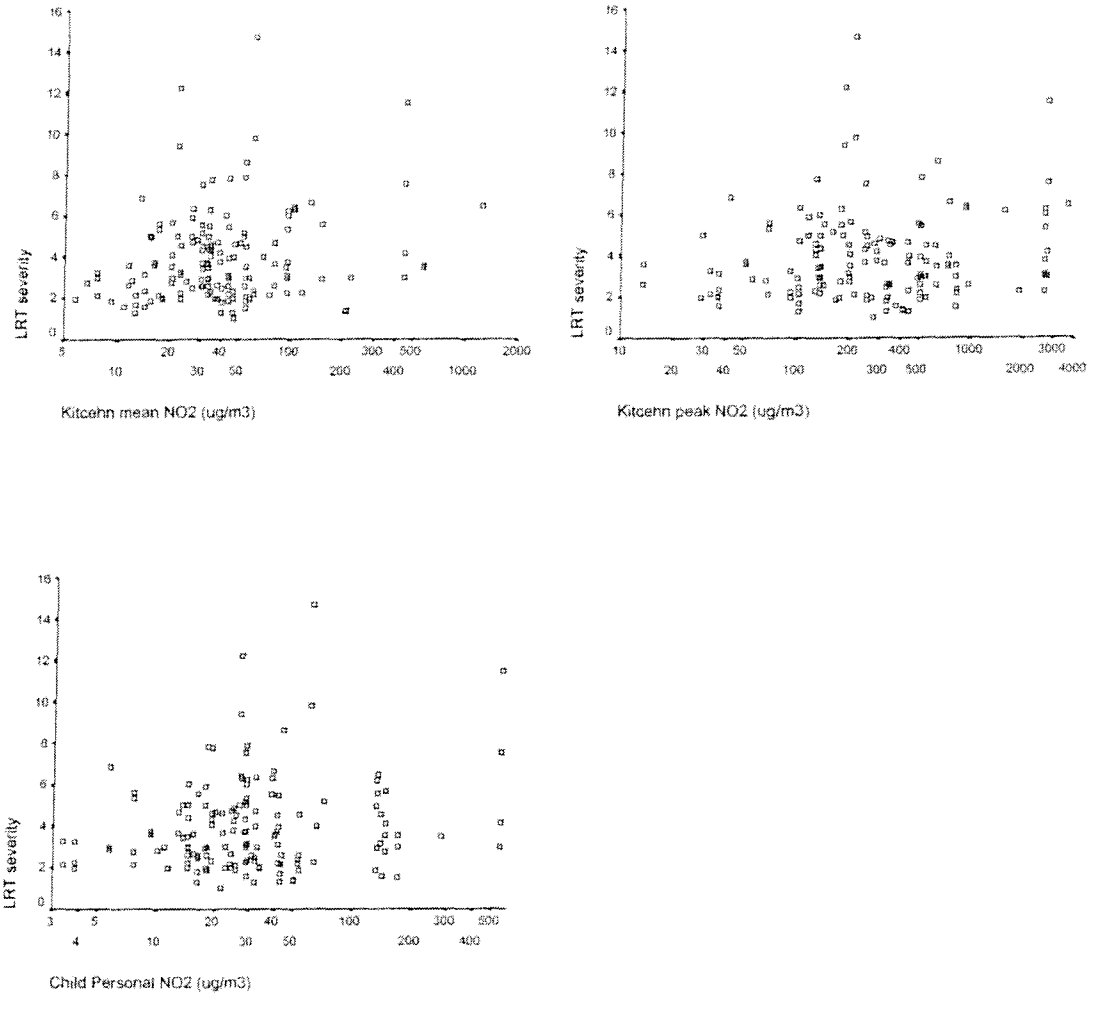






In the analysis of the LRT episodes and indoor nitrogen dioxide, no significant relationship was found with kitchen peak nitrogen dioxide (Beta=0.1, 95%CI:-0.08-0.2), kitchen mean nitrogen dioxide (Beta=0.1,95%CI;-0.1-0.4) and personal nitrogen dioxide(Beta=0.1, 95%CI:-0.05-0.4)(table 5.5, Fig 5.21). After adjusting for other indoor air pollutants, atopy, der pI and gender, the relationship has not changed.

Fig 5.21: The association between nitrogen dioxide and the severity of LRT episodes

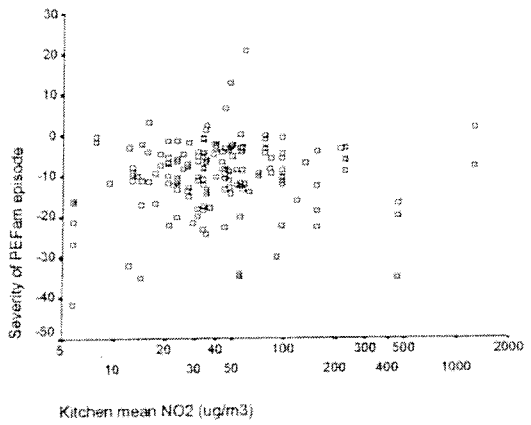


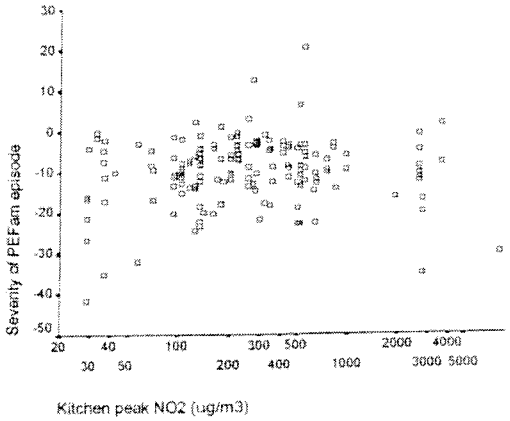
The severity of the PEF episodes was not influenced by the level of kitchen mean nitrogen dioxide (Beta=-2.2; 95%CI:-8.7-4.2), kitchen peak nitrogen dioxide (Beta=-1.0, 95%CI:-6.0-3.9). There was a tendency towards an increase in the severity of PEF episodes in relation to personal nitrogen dioxide, but this did not reach statistical significance (Beta=2.0; 95%CI:-2.0-7.0)(table 5.5, Fig 5.22). The association between the severity of PEF episodes and exposure to kitchen mean, peak and personal nitrogen dioxide did not reach statistical significance in the multivariate analysis Beta=-0.9;

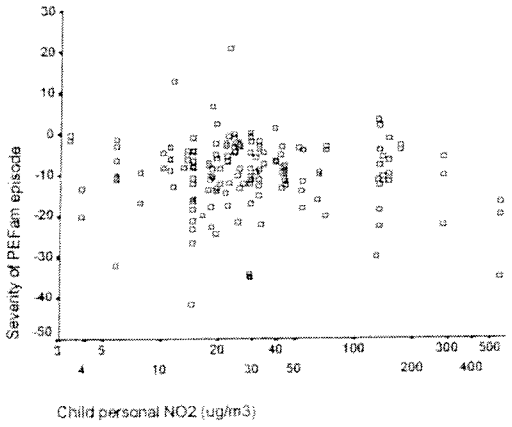
95%CI:-7.9-6.0;Beta=-1.0;95%CI:-5.4-3.3;Beta=0.04;95%CI:-0.2-0.2,respectively)

(table 5.6).

Fig 5.22: The association between nitrogen dioxide and the severity of PEF episodes



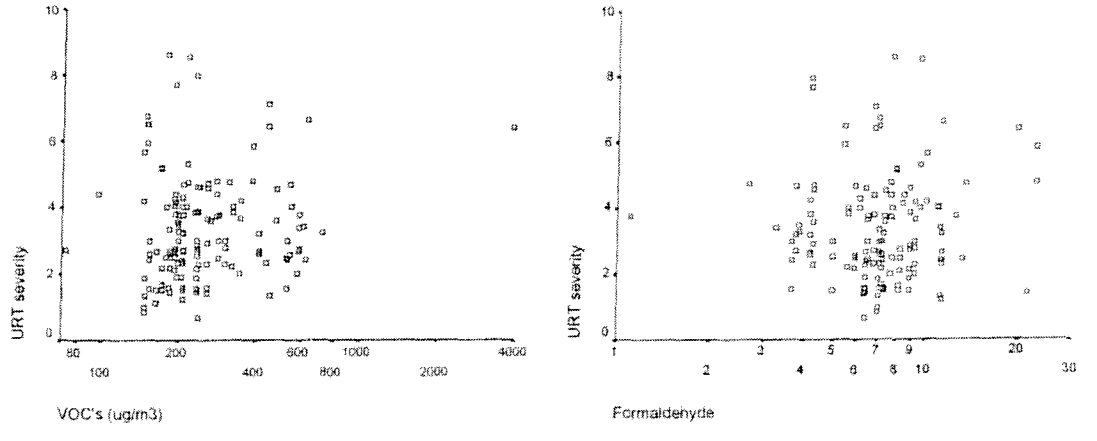




5.1.3.2 Volatile organic compounds, formaldehyde and the severity of URT, LRT and PEF episodes

Among asthmatic children, neither VOCs nor formaldehyde had any influence on the severity of upper respiratory tract symptoms (Beta=0.4, 95%CI: –0.05- 0.9; Beta=-0.03, 95%CI:-0.6-0.5, respectively) (table 5.5, Fig 5.23). This association has not changed in the multivariate analysis (Beta=0.2, 95%CI: –0.3- 0.8; Beta=-0.07, 95%CI:-0.8-0.6, respectively).

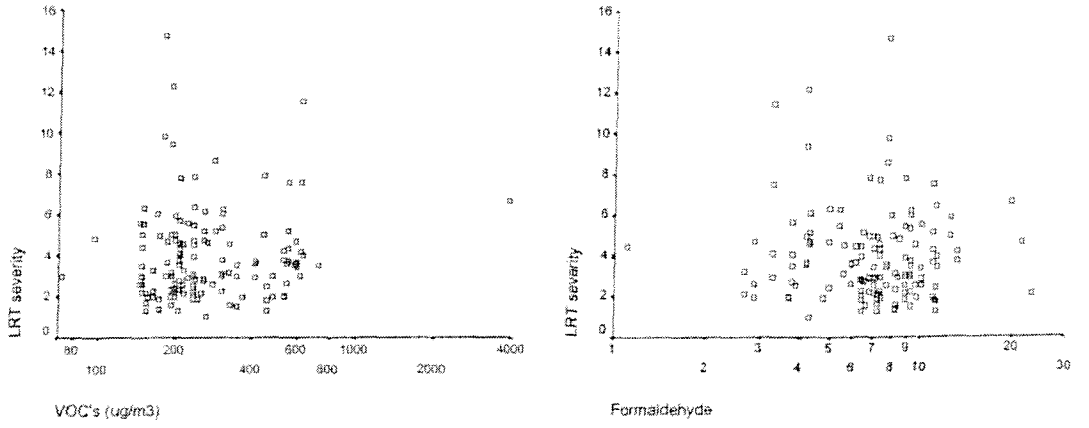
Fig 5.23: The association between formaldehyde, VOCs and the severity of URT episodes



Similarly, neither VOCs nor formaldehyde had any impact on the severity score of LRT symptoms among asthmatic children (Beta=0.2, 95%CI: –0.2- 0.7; Beta=-0.4, 95%CI:-1.0-0.1, respectively)(table 5.5, fig 5.24).

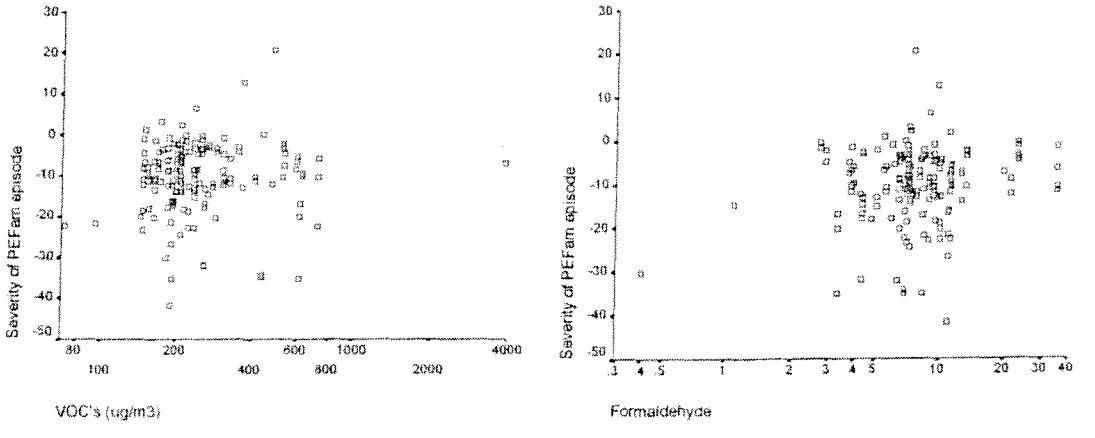
After adjusting for other indoor air pollutants, dampness, atopy, gender, and der pl, no significant association was found between the severity of LRT episodes and indoor levels of VOCs and formaldehyde (Beta=0.08, 95%CI: –0.5- 0.7; Beta=-0.3, 95%CI:-0.9-0.2, respectively)(table 5.6).

Fig 5.24: The association between formaldehyde, VOCs and the severity of LRT episodes



Our study did not demonstrate a significant relationship between the severity of asthma attacks and indoor VOCs and formaldehyde (Beta=-3.0, 95%CI: –13.3- 7.2; Beta=-7.0, 95%CI:-14.8-0.8, respectively)(table 5.5, fig 5.25). Similarly, no association was found in the multivariate analysis (IRR=-2.1, 95%CI: –10.4- 6.2; IRR=-1.8, 95%CI:-11.0-7.3, respectively)(table 5.6).

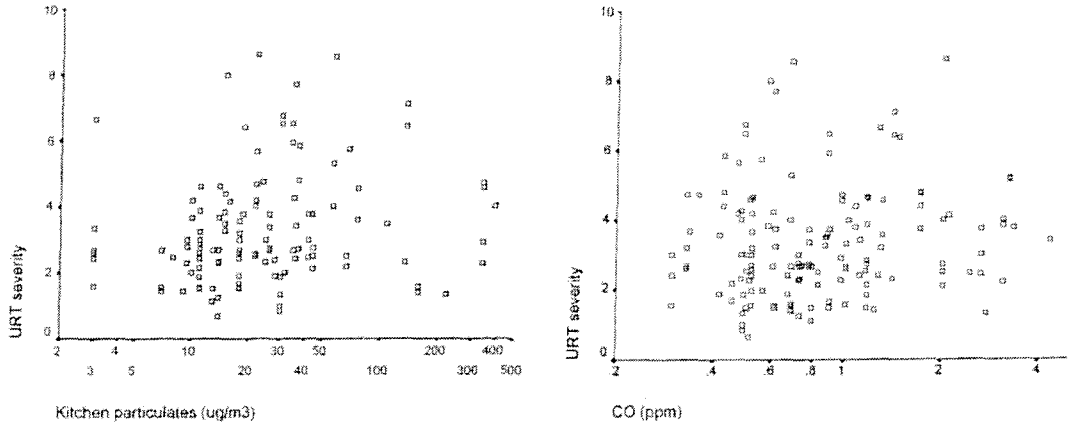
Fig 5.25: The association between formaldehyde, VOCs and the severity of PEF episodes



5.1.3.3 Carbon monoxide, particulate matter and the severity of URT, LRT and PEF episodes

The severity score of URT symptoms among asthmatic children did not seem to have been influenced by the levels of indoor carbon monoxide and particulate matter (Beta=0.2, 95%CI: –0.06- 0.63; Beta=0.2, 95%CI:-0.06-0.4, respectively)(table5.5,fig 5.26).

Fig 5.26:The association between carbon monoxide, particulate matter and the severity of URT episodes

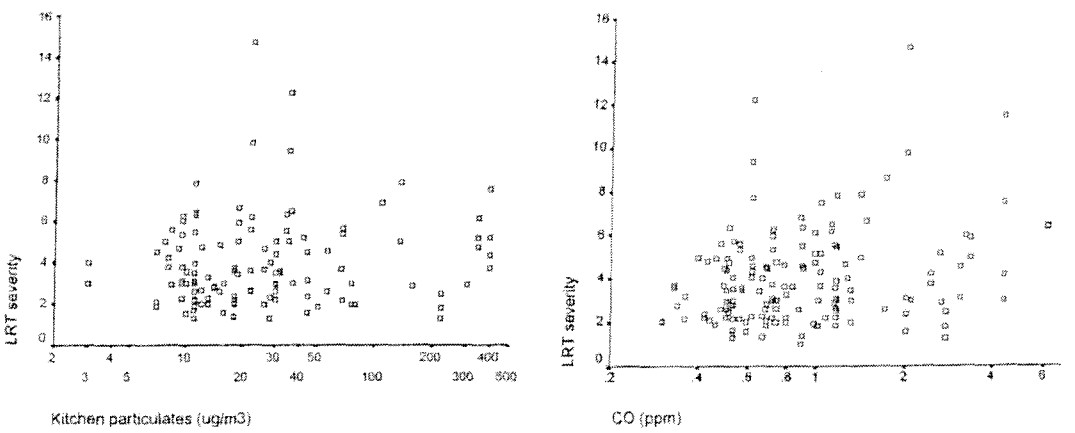


A significant association was found between the severity of LRT episodes and indoor exposure to carbon monoxide (Beta=0.4, 95%CI: 0.05- 0.8) (table 5.5,fig 5.27), no such association was found with particulate matter Beta=0.2, 95%CI:-0.03-0.4) (table 5.5,fig 5.27).

It is not possible to draw a definite conclusion on the finding we demonstrated between carbon monoxide and the severity of the LRT episodes, as carbon monoxide was excluded from the multivariate analysis (because of considerable missing data), the question which arises here is that whether this observation was solely due exposure to indoor carbon monoxide or was it confounded by the other air pollutants (mixed effect). Previous studies has demonstrated a link between cardiovascular morbidity and

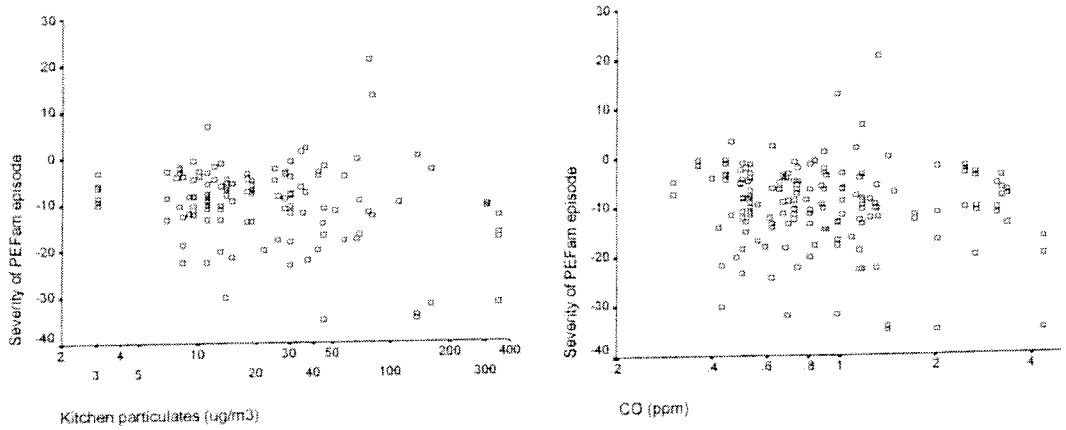
mortality and the ambient level of carbon monoxide, to-date we are not aware of any epidemiological, human/animal studies which had looked at the association between carbon monoxide and the respiratory illnesses. Therefore, future focus on the link between carbon monoxide and the respiratory illnesses is required.

Fig 5.27: The association between carbon monoxide, particulate matter and the severity of LRT episodes



There was a significant correlation between the severity of PEF episodes and the indoor exposure to particulate matter Beta=5.6, 95%CI: 1.5- 9.7), and only a trend towards an increase in the severity of PEF episodes in relation to indoor carbon monoxide but this did not reach statistical significance Beta=3.7, 95% CI: –3.8- 11.2) (table 5.5,fig 5.28).

Fig 5.28: The association between carbon monoxide, particulate matter and the severity of PEF episodes

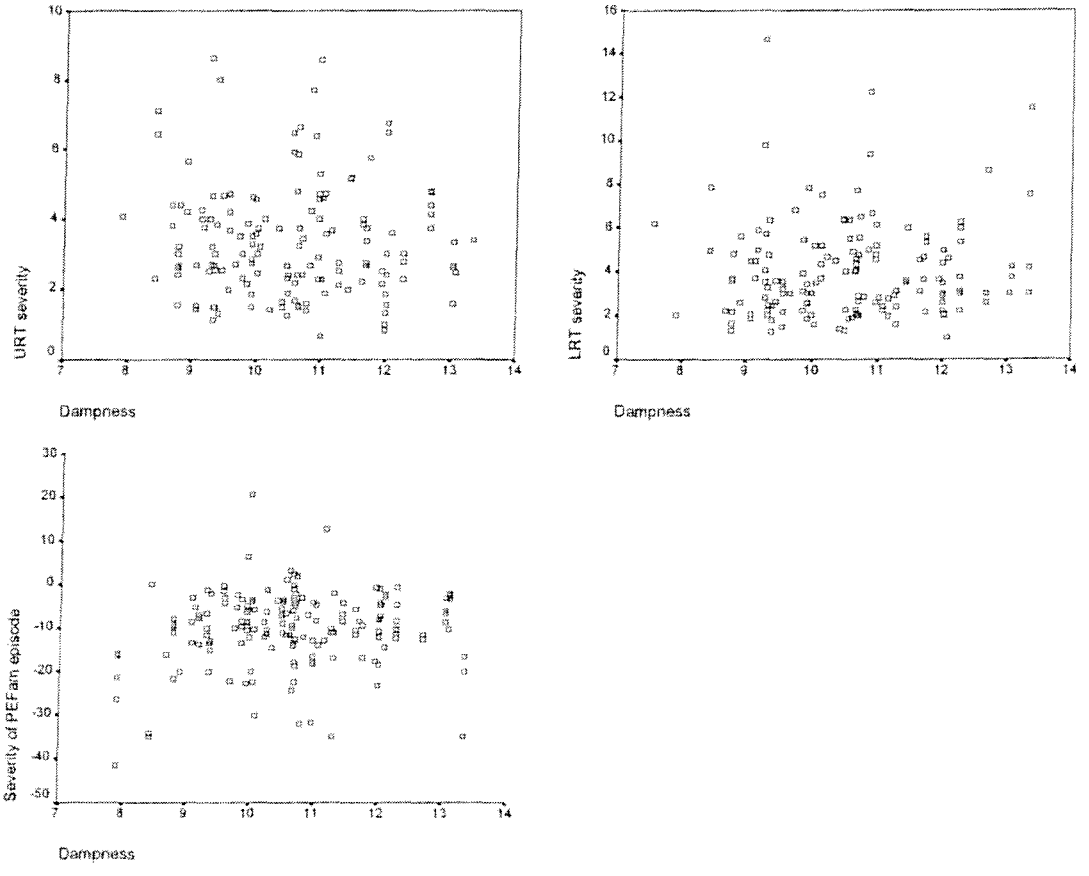


5.1.3.4 Dampness and severity of URT, LRT and PEF episodes

No association was found between the severity of URT, LRT and PEF episodes and dampness (Beta=-0.02,95%CI:-0.11-0.06; Beta =0.07,95%CI: -0.01-0.1; Beta=-1.1, 95%CI:-3.0-0.7, respectively)(table 5.5, Fig 5.29).

This association has remained statistically insignificant in the multivariate analysis (Beta=-0.02,95%CI:-0.1-0.06; Beta=0.07,95%CI:-0.01-0.1; Beta=-0.4,95%CI:-1.8-0.9, respectively) (table 5.6)

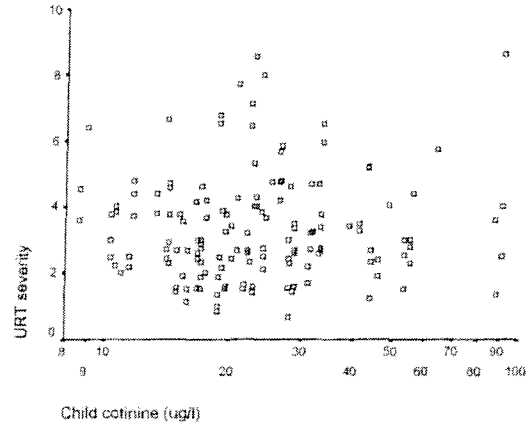
Fig 5.29: The association between the severity of URT, LRT, PEF episodes and dampness

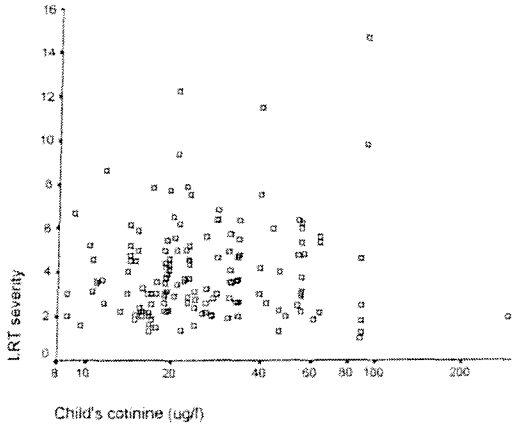


5.1.3.5 Environmental tobacco smoke and the severity of the episodes

Exposure to environmental tobacco smoke as measured by urine cotinine did not have an impact on the severity of URT, LRT and PEF episodes (Beta=-0.01,95%CI:-0.4-0.4; Beta=0.03,95%CI: -0.4-0.5; Beta=-0.5,95%CI:-6.3-5.1, respectively) (table 5.5, Fig 5.30). This association remained statistically insignificant in the multivariate analysis (table 5.6).

Fig 5.30: The association between the severity of URT, LRT, PEF episodes and environmental tobacco smoke





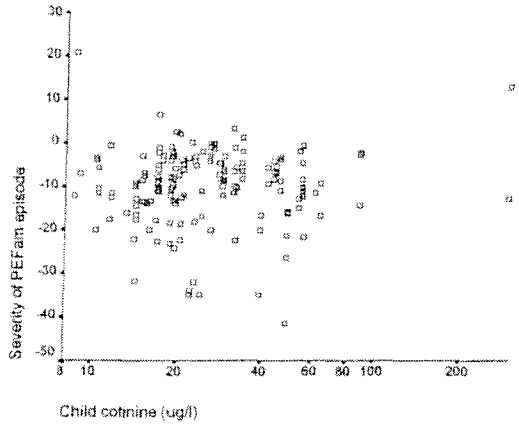


Table 5.5: The association between the severity of the episodes and indoor air pollutants: univariate analysis

Indoor pollutant	URT Beta(95%CI) P	LRT Beta(95%CI) P	PEF Beta (95% CI) P
KITCHEN MEAN NO2	0.01 (-0.2- 0.2) P=0.9	0.1 (-0.1 - 0.4) P=0.2	-2.2 (-8.7-4.2) P=0.4
KICHEN PEAK NO2	0.1 (-0.02- 0.3) P=0.08	0.10 (-0.08 - 0.2) P=0.2	-1.0 (-6.0- 3.9) P=0.6
PERSONAL NO2	0.1 (-0.08- 0.3) P=0.2	0.1 (-0.05- 0.4) P=0.1	2.0 (-2.0-7.0) P=0.4
PARTICULATE MATTER	0.2(-0.06-0.4) P=0.1	0.2(-0.03- 0.4) P=0.08	5.6(1.5-9.7) P=0.007
VOCs	0.4 (-0.05-0.9) P=0.08	0.2 (-0.2- 0.7) P=0.27	-3.0 (-13.3-7.2) P=0.5
FORMALDEHYDE	-0.03 (-0.6-0.5) P=0.8	-0.4(-1.0- 0.1) P=0.1	-7.0 (-14.8- 0.8) P=0.07
CO	0.2 (-0.06- 0.6) P=0.1	0.4(0.05- 0.8) P=0.02	3.7 (-3.8-11.2) P=0.3
DAMPNESS	-0.02(-0.11- 0.06) P=0.5	0.07(-0.01- 0.1) P=0.09	-1.1 (-3.0- 0.7) P=0.2
COTININE	-0.01(-0.4- 0.4) P=0.9	0.03(-0.4-0.5) P=0.8	-0.5 (-6.3- 5.1) P=0.8

Table 5.6: The association between the severity of the episodes and indoor air pollution: multivariate analysis

Indoor pollutant	URT;Beta (95%CI) P value	LRT;Beta (95%CI) P value	PEF;Beta (95%CI) P value
Kitchen mean NO2	-0.04;(-0.3-0.2) P=0.7	0.06; (-0.3- 0.4) P=0.7	-0.9;(-7.9- 6.0) P=0.7
Kitchen peak NO2	0.2; (-0.005- 0.4) P=0.05	0.02;(-0.1- 0.2) P=0.8	-1.0;(-5.4 – 3.3) P=0.6
Personal NO2	0.04; -0.2- 0.2 P=0.7	0.1; -0.1- 0.3 P=0.2	0.04; -0.2- 0.2 P=0.7
VOCs	0.2; (-0.3- 0.8) P=0.3	0.08;(-0.5-0.7) P=0.8	-2.1;(-10.4, 6.2) P=0.6
Formaldehyde	-0.07;(-0.8-0.6) P=0.8	-0.3;(-0.9- 0.2) P=0.2	-1.8;(-11.0- 7.3) P=0.6
Dampness	-0.02;(-0.1-0.06) P=0.5	0.07;(-0.01-0.1) P=0.1	-0.4; (-1.8- 0.9) P=0.5
Cotinine	-0.06;(-0.5-0.3) P=0.7	0.01;(-0.4-0.5) P=0.9	1.3;(-3.4- 6.2) P=0.5

5.2 Respiratory episodes and indoor air pollution (mothers)

All diary cards were inspected visually by an experienced physician and all the respiratory episodes were identified.

Univariate and multivariate linear regression analysis were carried out to study the relationship between the respiratory episodes and the indoor environment.

5.2.1 Frequency of the URT, LRT and PEF episodes and the indoor environment

5.2.1.1 Frequency of the URT, LRT and PEF episodes and indoor exposure to nitrogen dioxide

There was no significant association between kitchen mean & personal nitrogen dioxide and the frequency of URT episodes (IRR=0.5, 95%CI: 0.3-1.0; IRR=0.8, 95%CI: 0.6-1.1, respectively) (table 5.7). This association has not changed in the multivariate analysis (IRR=0.6, 95%CI: 0.3-1.0; IRR=0.9, 95%CI: 0.7-1.1, respectively)(table 5.8).

Mothers with high exposure to kitchen peak nitrogen dioxide seem to have less upper respiratory tract symptoms, before and after adjustment for other indoor environmental factors (IRR=0.8, 95%CI: 0.6-0.9; IRR=0.8, 95%CI: 0.7-0.9, respectively)(table 5.7&5.8). Clinically, it is difficult to explain our finding on the association between nitrogen dioxide and the incidence of the URT episodes. It is possible that low nitrogen dioxide levels may cause more pulmonary toxicity, however this is only speculative. Indeed, Harrington et al had reviewed the studies on the relationship between the ambient nitrogen dioxide and the respiratory illnesses (Chattanooga, Tennessee Cities) and found that there was a significant relationship between nitrogen dioxide and the respiratory illnesses in children, respiratory illnesses was more associated with low nitrogen dioxide (Harrington & Krupnick 1985). It was concluded

from this study that there is a U-shaped relationship between nitrogen dioxide and the respiratory illnesses.

No association was found between kitchen (mean & peak) and personal nitrogen dioxide and the frequency of LRT episodes (IRR=0.6, 95%CI: 0.3-1.1; IRR=0.9, 95%CI: 0.7-1.1; IRR=0.8, 95%CI: 0.5-1.1, respectively) (table 5.7). This association has remained statistically insignificant in the multivariate analysis (IRR=0.5, 95%CI: 0.2-1.1; IRR=0.9, 95%CI: 0.7-1.1; IRR=0.8, 95%CI: 0.5-1.1, respectively)(table 5.8).

Neither kitchen (mean & peak nitrogen) nor personal nitrogen dioxide was associated with any increase in the rate of PEF episodes (IRR=0.7, 95%CI: 0.4-1.1; IRR=0.8, 95%CI: 0.6-1.0; IRR=0.8, 95%CI: 0.6-1.0, respectively) (table 5.7). The multivariate analysis did not show a significant relationship between the PEF episodes and kitchen (mean & peak) and personal nitrogen dioxide (IRR=0.8, 95%CI: 0.4-1.4; IRR=0.9, 95%CI: 0.7-1.1; IRR=0.8, 95%CI: 0.6-1.1, respectively)(table 5.8).

5.2.1.2 Frequency of URT, LRT and PEF episodes and exposure to VOCs and formaldehyde

Exposure to indoor volatile organic compounds and formaldehyde was not associated with any increase in the frequency of URT episodes (IRR=1.3, 95%CI: 0.5-3.2; IRR=0.6, 95%CI: 0.2-1.7, respectively) (table 5.7). After adjusting for gender, atopy, der pI and other indoor air pollutants, this association has remained insignificant (IRR=1.4, 95%CI: 0.6-3.2; IRR=1.0, 95%CI: 0.9-1.0, respectively)(table5.8).

There was a trend towards a positive association between the frequency of lower respiratory tract episodes and exposure to indoor formaldehyde and VOCs (IRR=1.4, 95%CI: 0.4-4.4; IRR=2.3, 95%CI: 0.8-5.9, respectively) (table 5.7).

In the multivariate analysis this relationship has remained insignificant (VOCs: IRR = 2.4; 95%CI: 0.8-6.8; formaldehyde: IRR=1.0; 95% 0.9-1.0).

In the analysis of the frequency of PEF episodes in relation to indoor exposure to formaldehyde, there was no association before and after adjusting for other indoor air pollutants (IRR=0.6;95%CI 0.5-1.3, IRR=1.0;95% CI:0.9-1.0, respectively)(table 5.7&5.8). Similarly, no association was found between VOCs and the frequency of PEF episodes in both the univariate and multivariate analysis (IRR=1.3, 95%CI: 0.5-3.7; IRR=1.3, 95%CI: 0.5-3.5, respectively) (table 5.7&5.8).

5.2.1.3 Frequency of URT, LRT and PEF episodes and indoor exposure to particulate matter and carbon monoxide

No significant relationship was found between particulate matter, carbon monoxide and the frequency of URT episodes (IRR=1.1, 95%CI: 0.6-1.7; IRR=0.7, 95%CI: 0.2-1.7, respectively)(table 5.7).

Similarly, the frequency of the LRT episodes did not seem to have been influenced by the exposure to indoor particulate matter (IRR=1.5;95%CI: 0.8-2.7) and carbon monoxide(IRR=1.7;95%CI: 0.7-4.2).

Neither carbon monoxide nor particulate matter has a significant influence on the rate of PEF episodes (IRR=0.9, 95%CI: 0.3-2.3; IRR=1.1, 95%CI: 0.7-1.8, respectively) (table 5.7).

5.2.1.4 Dampness and the frequency of the episodes

Dampness did not increase the incidence of URT episodes among mothers (IRR=1.0; 95% CI: 0.8-1.1), LRT episodes (IRR=1.1;95%CI: 0.9-1.4) and PEF episodes

(IRR=1.0; 95% CI: 0.8-1.1). This association has remained statistically insignificant after adjusting for atopy, gender, der pI and other indoor air pollutants (IRR=1.0, 95%CI: 0.9-1.1; IRR=1.1, 95%CI: 0.9-1.4; IRR=1.0, 95%CI: 0.8-1.2, respectively)(table 5.7).

5.2.1.5 Environmental tobacco smoke and the frequency of URT, LRT and PEF episodes

Exposure to environmental tobacco smoke as measured by urine cotinine was not associated with any increase in the frequency of URT, LRT and PEF episodes (IRR=0.8, 95%CI: 0.7-1.0; IRR=1.0, 95%CI: 0.8-1.2; IRR=1.0, 95%CI: 0.9-1.1, respectively) (table 5.7). This association has remained statistically insignificant in multivariate analysis model (table 5.8).

Table 5.7: The association between indoor air pollutants and the frequency of LRT, URT and PEF episodes (univariate analysis)

Indoor air Pollutant	URT,IRR (95% CI) p	LRT, IRR (95% CI) p	PEF, IRR (95% CI) p
Kitchen mean NO2	0.5 (0.3- 1.0) p=0.09	0.6 (0.3- 1.1) p=0.1	0.7 (0.4- 1.1) p=0.2
Kitchen peak NO2	0.8, (0.6-0.9) p=0.04	0.9(0.7-1.1) P=0.08	0.8 (0.6-1.0) p=0.2
Personal NO2	0.8 (0.6- 1.1) p=0.3	0.8 (0.5- 1.1) p=0.2	0.8 (0.6- 1.0) p=0.1
Particulate matter	1.1 (0.6- 1.7) p=0.6	1.5 (0.8- 2.7) p=0.1	1.1 (0.7- 1.8) p=0.5
VOCs	1.3 (0.5- 3.2) p=0.4	2.3 (0.8- 5.9) p=0.08	1.3 (0.5- 3.7) p=0.5
Formaldehyde	0.6 (0.2- 1.7) p=0.4	1.4 (0.4- 4.4) p=0.5	0.6 (0.5- 1.3) p=0.2
Carbon monoxide	0.7 (0.2- 1.7) p=0.4	1.7 (0.7- 4.2) p=0.1	0.9 (0.3- 2.3) p=0.9
dampness	1.0 (0.8- 1.1) p=0.7	1.1 (0.9- 1.4) p=0.2	1.0 (0.8- 1.1) p=0.7
Cotinine	0.8 (0.7- 1.0) p=0.1	1.0 (0.8- 1.2) p=0.5	1.0 (0.9- 1.1) p=0.3

Table 5.8: The association between indoor air pollutants and the frequency of LRT, URT and PEF episodes (multivariate analysis)

Indoor air pollution	URT,IRR (95% CI) p	LRT,IRR (95% CI) p	PEF,IRR (95% CI) p
Kitchen mean NO2	0.6 (0.3 - 1.0) P=0.06	0.5 (0.2 - 1.1) P=0.10	0.8 (0.4 - 1.4) P=0.4
Kitchen peak NO2	0.8 (0.7 - 0.9) P=0.03	0.9 (0.7 - 1.1) P=0.51	0.9 (0.7 - 1.1) P=0.5
Personal NO2	0.9 (0.7 - 1.1) P=0.4	0.8 (0.5 - 1.1) P=0.19	0.8 (0.6 - 1.1) P=0.3
VOCs	1.4 (0.6 - 3.2) p=0.3	2.4 (0.8 - 6.8) p=0.08	1.3 (0.5 - 3.5) p=0.5
formaldehyde	1.0 (0.9 - 1.0) P=0.6	1.0 (0.9 - 1.0) P=0.1	1.0 (0.9 - 1.0) P=0.9
dampness	1.0 (0.9 - 1.2) P=0.3	1.1 (0.9 - 1.4) P=0.1	1.0 (0.8 - 1.2) P=0.8
Cotinine	0.8 (0.7 - 0.9) P=0.02	0.9 (0.8 -1.1) P=0.6	1.0 (0.8-1.2) P=0.8

5.2.2 Duration of URT, LRT and PEF episodes and the indoor environment

5.2.2.1 Duration of the URT, LRT and PEF episodes and exposure to nitrogen dioxide

The duration of URT episodes was not affected by exposure to indoor nitrogen dioxide (kitchen mean, peak and personal) (Beta= 0.1, 95%CI: -0.1-0.3 ; Beta= 0.04,95%CI:-0.03-0.1;Beta=-0.02,95%CI: -0.1-0.06, respectively) (table 5.9). This association remained insignificant in the multivariate analysis (Beta= 0.1, 95%CI: -0.1-0.3; Beta= 0.05,95%CI:-0.03-0.1;Beta=-0.004, 95%CI: -0.1-0.1, respectively)(table 5.10)

No significant association was found between kitchen (mean & peak), personal nitrogen dioxide and the duration of the LRT episodes, in the univariate analysis (Beta= - 0.04, 95%CI: -0.5-0.4; Beta= 0.005,95%CI:-0.1-0.1;Beta=-0.09,95%CI: -0.2-0.08, respectively) (table 5.9). The association between nitrogen dioxide and the duration of LRT episodes had not changed after adjusting for other indoor air pollutants and co-factors (table 5.10).

Exposure to nitrogen dioxide in the kitchen (mean & peak) did not influence the duration of the PEF episodes (Beta=0.09, 95%CI: -0.2 – 0.4; Beta=0.04,95%CI: -0.05-0.1, respectively) (table 5.9). After adjusting for indoor environmental factors, this relationship has remained insignificant (Beta= -0.06, 95%CI: -0.3-0.2; Beta= 0.005,95%CI:-0.08-0.09, respectively) (table 5.10).

Similarly, no significant association was found between personal nitrogen dioxide and the duration of the PEF episodes, in both univariate and multivariate analysis (Beta = -0.03, 95%CI –0.1-0.07; Beta=-0.04, 95%CI:-0.1- 0.06, respectively) (table 5.9&5.10).

5.2.2.2 Volatile organic compounds, formaldehyde and the duration of URT, LRT and PEF episodes

Indoor exposure to volatile organic compounds did not have a significant impact on the duration of URT, LRT and PEF episodes (Beta=0.1, 95%CI: -0.2-0.5; Beta= 0.2,95%CI:-0.4-0.9;Beta=0.02,95%CI: -0.5-0.5, respectively) (table 5.9). In the multivariate analysis, the association between the duration of URT, LRT and PEF episodes and VOCs has remained statistically insignificant (Beta= 0.1, 95%CI: -0.2-0.5; Beta= 0.2, 95%CI:-0.3-0.7;Beta=-0.06,95%CI: -0.6-0.4, respectively) (table 5.10). There was no significant association between formaldehyde and the duration of URT, LRT and PEF episodes (Beta= -0.1, 95%CI: -0.5-0.2; Beta= -0.3,95%CI:-1.2-0.6; Beta=0.2,95%CI: -0.05-0.4, respectively)(table 5.9). In multivariate analysis, the association between the formaldehyde and the duration of the episodes has remained statistically insignificant (Beta= -0.1, 95%CI: -0.5-0.2; Beta= -0.9,95%CI:-1.7-0.1; Beta=0.2,95%CI: -0.1-0.5, respectively)(table 5.10)

5.2.2.3 Particulate matter, carbon monoxide and the duration of URT, LRT and PEF episodes

Neither indoor particulate matter nor carbon monoxide posed a risk on the duration of URT episodes (Beta=-0.1,95%CI: -0.4-0.2 ; Beta=-0.05, 95%CI: -0.3-0.1, respectively) , LRT episodes (Beta=0.02, 95%CI: -0.2-0.2; Beta=0.09,95%CI: -0.4-0.6, respectively) and PEF episodes (Beta= -0.04, 95%CI: -0.3-0.2; Beta =0.02,95%CI: -0.4 - 0.5, respectively) (table 5.9).

5.2.2.4 Dampness and the duration of the episodes

There was a positive relationship between dampness and the duration of PEF episodes in both the univariate and multivariate analyses (Beta=0.1, 95%CI: 0.04-0.2; Beta=0.1, 95%CI: 0.07-0.2, respectively).

The duration of the URT, LRT episodes were not influenced by the degree of dampness in the house (Beta=0.009, 95%CI: –0.06-0.08; Beta=0.05, 95%CI: -0.1-0.2, respectively). In the multivariate analysis, adjusting for gender, atopy, der pI and other indoor environmental factors, no significant association was found between dampness and the duration of URT, LRT (Beta=0.01, 95%CI: –0.06-0.08; Beta=0.01, 95%CI: -0.1-0.1, respectively) (table 5.10).

5.2.2.5 Environmental tobacco smoke and the duration of the episodes

Exposure to environmental tobacco smoke as measured by urine cotinine did not lead to an increase in the duration of the URT, LRT and PEF episodes (Beta= -0.005, 95%CI: –0.07-0.08; Beta=0.02, 95%CI: -0.1-0.1; Beta= 0.02, 95%CI: -0.05-0.1, respectively)(table 5.9). This association remained statistically insignificant in the multivariate analysis (table 5.10).

Table 5.9:The relationship between indoor air pollution and the duration of LRT, URT and PEF episodes (Univariate analysis)

Indoor air pollutant	URT,Beta (95% CI) P	LRT,Beta (95% CI) P	PEF,Beta (95% CI) P
Kitchen mean NO2	0.1 (-0.1- 0.3) P=0.4	-0.04 (-0.5- 0.4) P=0.8	0.09 (-0.2-0.4) P=0.5
Kitchen peak NO2	0.04 (-0.03-0.1) P=0.2	0.005 (-0.1- 0.1) P=0.9	0.04 (-0.05-0.1) P=0.2
Personal NO2	-0.02 (-0.1- 0.06) P=0.5	-0.09 (-0.2 -0.08) P=0.3	-0.03 (-0.1-0.07) P=0.5
Particulate matter	-0.10 (-0.4 - 0.2) P=0.5	0.02 (-0.2- 0.2) P=0.8	-0.04 (-0.3- 0.2) P=0.7
VOCs	0.1 (-0.2 - 0.5) P=0.4	0.2 (-0.4-0.9) P=0.527	0.02 (-0.5- 0.5) P=0.9
Formaldehyde	-0.1 (-0.5 - 0.2) P=0.3	-0.3 (-1.2-0.6) P=0.5	0.2 (-0.05- 0.4) P=0.1
Carbon monoxide	-0.05 (-0.3 -0.1) P=0.6	0.09 (-0.4- 0.6) P=0.7	0.02 (-0.4- 0.5) P=0.9
dampness	0.009 (-0.06-0.08) P=0.8	0.05 (-0.1- 0.2) P=0.4	0.1 (0.04- 0.2) P=0.002
Cotinine	-0.005 (-0.07- 0.08) P=0.8	0.02 (-0.1-0.1) P=0.7	0.02 (-0.05- 0.1) P=0.5

Table 5.10:The relationship between indoor air pollution and the duration of LRT, URT and PEF episodes (Multivariate analysis)

Indoor air pollutant	URT Beta (95% CI) P	LRT Beta (95% CI) P	PEF Beta (95% CI) P
Kitchen mean NO2	0.1 (-0.1 - 0.3) P=0.4	0.1 (-0.3 - 0.5) P=0.5	-0.06 (-0.3 - 0.2) P=0.7
Kitchen peak NO2	0.05 (-0.03 - 0.1) P=0.2	0.05 (-0.04 - 0.16) P=0.2	0.005 (-0.08,0.09) P=0.9
Personal NO2	-0.004 (-0.1 - 0.1) P=0.9	0.06 (-0.1 - 0.2) P=0.5	-0.04 (-0.1 - 0.06) p=0.4
VOCs	0.1 (-0.2 - 0.5) P=0.4	0.2 (-0.3 - 0.7) P=0.4	-0.06 (-0.6 - 0.4) P=0.8
Formaldehyde	-0.1 (-0.5 - 0.2) P=0.4	-0.9 (-1.7 - 0.1) P=0.01	0.2 (-0.1 - 0.5) P=0.2
Dampness	0.01 (-0.06 - 0.08) P=0.8	0.01 (-0.1 - 0.1) P=0.9	0.1 (0.07 - 0.2) P=0.000
Cotinine	-0.04 (-0.1 - 0.05) P=0.3	0.09 (-0.06 - 0.2) P=0.2	-0.002 (-.09 - 0.08) P=0.9

5.2.3 Severity of the episodes

5.2.3.1 Nitrogen dioxide and severity of URT, LRT and PEF episodes

In the univariate analysis, no significant association was found between the severity of the URT episodes and the levels of kitchen mean, kitchen peak and personal nitrogen dioxide (Beta=-0.08, 95%CI:-0.3-0.1; Beta=-0.03, 95%CI:-0.1-0.03; Beta=0.01, 95%CI:-0.07-0.1, respectively)(table 5.11).

Similarly, the multivariate analysis has not demonstrated any significant association between the severity of URT episodes and the kitchen mean nitrogen dioxide (Beta=-0.1, 95%CI:-0.3-0.08), kitchen peak nitrogen dioxide (Beta=-0.02, 95%CI:-0.08-0.03), personal nitrogen dioxide (Beta= 0.03, 95%CI:-0.08-0.1) (table 5.12)

There was a tendency towards less severe LRT episodes among mothers with higher kitchen peak nitrogen dioxide (Beta=-0.1, 95%CI:-0.2- -0.04), kitchen mean nitrogen dioxide (IRR=-0.4,95%CI;-0.8- -0.05) and personal nitrogen dioxide (Beta=-0.1, 95%CI:-0.2- -0.008)(table). After adjusting for other indoor air pollutants, atopy, der pI and gender, The relationship has remained significant between the severity of the episodes and kitchen mean and peak nitrogen dioxide (Beta=-0.4, 95%CI:-0.8- -0.01; Beta=-0.1, 95%CI:-0.2- -0.05, respectively) (table 5.11), but not with personal nitrogen dioxide (Beta=-0.1, 95%CI:-0.3-0.04)(table 5.12).

Similarly, mothers with high exposure to kitchen mean nitrogen dioxide appears to have reported less decline in the peak expiratory flow measurements, this finding was demonstrated in the univariate as well as the multivariate analysis (Beta=- 4.1, 95%CI:- 8.3- -0.09; Beta=- 4.7, 95%CI:- 8.7- -0.7, respectively) .

Only in the multivariate analysis, there was a significant reduction in the severity of the PEF episodes in relation to kitchen peak nitrogen dioxide (Beta=-1.3, 95%CI:-2.5- -0.2) (table 5.12)

The association between the severity of PEF episodes and personal nitrogen dioxide did not reach statistical significance before and after adjustment for other variables Beta=-0.9;95%CI:-2.5- 0.6; Beta=- 0.6;95%CI:- 2.4- 1.0,respectively)(tables 5.11 &5.12).

5.2.3.2 Volatile organic compounds, formaldehyde and severity of URT, LRT and PEF episodes

The severity of URT episodes has not been influenced by the indoor level of formaldehyde, before and after adjustment for other variables (Beta=0.03, 95%CI: –0.2 - 0.3; Beta=0.005, 95%CI:-0.2-0.2, respectively) (table 5.11). Whereas exposure to indoor volatile organic compounds increases the severity of the URT episodes (Beta=0.4, 95%CI: 0.05- 0.8; Beta=0.4, 95%CI:0.03-0.8) (table 5.11 &5.12).

Neither VOCs nor formaldehyde had influenced the severity of LRT episodes (Beta=0.1, 95%CI: –0.3- 0.5; Beta=-0.3, 95%CI:-0.7-0.09, respectively).

After adjusting for other indoor air pollutants, dampness, atopy, gender, and der pI, no significant association was found between the severity of LRT episodes and indoor levels of VOCs and formaldehyde (Beta=0.1, 95%CI: –0.3- 0.5; Beta=-0.09, 95%CI:-0.5-0.4, respectively)(table 5.12).

Mothers who have high formaldehyde exposure during the study period seem to have fewer declines in peak expiratory flow measurements as opposed to those with low indoor formaldehyde exposure (Beta=-5.1, 95%CI: –8.9- -1.3; Beta=-6.4, 95%CI:-10.0- -2.9, respectively)(table 5.11&5.12). No association was found between the

severity of PEF episodes and indoor exposure to VOCs, before and after adjustment for other variables (Beta=-0.8, 95%CI: –11.9- 10.1; Beta=-1.1, 95%CI:-1.1- 8.8)(table 5.11&5.12).

5.2.3.3 Carbon monoxide, particulate matter and the severity of URT, LRT and PEF episodes

Exposure to indoor carbon monoxide did not influence the severity of URT & LRT episodes (Beta= -0.2, 95%CI: -0.5 - 0.04; Beta=-0.4, 95%CI:-1.0-0.01). It appears that subjects with high indoor exposure to particulate matter, have reported more severe upper and lower respiratory tract symptoms as compared to those who lived in homes with low particulate matter level (Beta=0.4, 95%CI: 0.1- 0.6; Beta=0.4, 95%CI: 0.2-0.5, respectively) (table 5.11).

There was no significant association between the severity of PEF episodes and the indoor exposure to particulate matter and carbon monoxide (Beta=4.2, 95%CI: -1.6-10.1; Beta=-2.3, 95% CI: –7.6- 2.9, respectively).

5.2.3.4 Dampness and severity of URT, LRT and PEF episodes

No association was found between the severity of URT, LRT and PEF episodes and dampness (Beta=0.01,95%CI:-0.07-0.1;Beta=-0.001,95%CI:-0.1-0.1;Beta=0.6,95% CI: -0.9-2.1, respectively).

This association remained statistically insignificant in the multivariate analysis (Beta=0.01,95%CI:-0.06-0.01; Beta=0.002,95%CI: -0.1-0.1;Beta=1.1,95%CI:-0.2- 2.5, respectively) (table 5.12).

5.2.3.5 Environmental tobacco smoke and the severity of the episodes

Our study demonstrated that subjects with high urine cotinine levels, have reported more severe lower respiratory tract symptom. This association was demonstrated in the univariate as well as the multivariate analyses (Beta=0.1,95%CI:0.01-0.2;Beta=0.1,95%CI: 0.05-0.2, respectively). However, There was a reduction in the severity of the URT episodes, demonstrated in the multivariate analysis (Beta=-0.07,95%CI:-0.1- -0.02) (table 5.12).

Neither univariate nor multivariate analysis showed any significant association between the severity of PEF episodes and cotinine (Beta=0.2,95%CI:-0.8-1.3; Beta=0.2,95%CI:-0.9-1.3, respectively).

Table 11:The relationship between the severity of LRT, URT, PEF episodes and indoor air pollution (univariate analysis)

Indoor air Pollutant	URT episodes Beta (95%CI) P	LRT episodes Beta (95%CI) P	PEF episodes Beta(95%CI) P
Kitchen mean NO2	-0.08 (-0.3 -0.1) P=0.4	-0.45 (-0.8 - -0.05) P=0.02	-4.1 (-8.3 --0.09) P=0.05
Kitchen peak NO2	-0.03 (-0.10 - 0.03) P=0.3	-0.12 (-0.2- -0.04) P=0.002	-0.95 (-2.3 - 0.4) P=0.1
Personal NO2	0.01 (-0.07 - 0.10) P=0.7	-0.1 (-0.2 - -0.008) P=0.03	-0.9 (-2.5 --0.6) P=0.2
Particulate matter	0.4 (0.1 - 0.6) P=0.002	0.4 (0.2 - 0.5) P=0.000	4.2 (-1.6 -10.1) P=0.1
VOCs	0.4 (0.05 - 0.8) P=0.02	0.10 (-0.3 - 0.5) P=0.67	-0.8 (-11.9 - 10.1) P=0.8
Formaldehyde	0.03 (-0.2 - 0.3) P=0.8	-0.3 (-0.7 -0.09) P=0.1	-5.1 (-8.9 - -1.3) P=0.008
Carbon monoxide	-0.2 (-0.5 - 0.04) P=0.09	-0.4 (-1.01 - 0.01) P=0.06	-2.3 (-7.6 -2.9) P=0.3
Dampness	0.01 (-0.07 - 0.10) P=0.7	-0.001 (-0.1 - 0.1) P=0.9	0.6 (-0.9 - 2.1) P=0.4
Cotinine	-0.04 (-0.10 - 0.01) P=0.1	0.11 (0.01 - 0.2) P=0.03	0.2 (-0.8 - 1.3) P=0.6

Table 5.12:The relationship between the severity of LRT, URT, PEF episodes and indoor air pollution (multivariate analysis)

Indoor air pollutant	URT episodes Beta (95%CI) P	LRT episodes Beta (95%CI) P	PEF episodes Beta (95%CI) P
Kitchen mean NO2	-0.1 (-0.3 - 0.08) P=0.2	-0.4 (-0.8 - -0.01) P=0.04	-4.7 (-8.7 - -0.7) P=0.02
Kitchen peak NO2	-0.02 (-0.08 - 0.03) P=0.3	-0.1 (-0.2 - -0.05) P=0.003	-1.3 (-2.5 - -0.2) P=0.01
Personal NO2	0.03 (-0.08 - 0.1) P=0.5	-0.1 (-0.3 - 0.04) P=0.1	-0.67 (-2.40- 1.0) P=0.4
VOCs	0.4 (0.03 - 0.8) P=0.03	0.1 (-0.3 - 0.5) P=0.6	-1.1 (-1.1 - 8.8) P=0.8
Formaldehyde	0.005 (-0.2 - 0.2) P=0.9	-0.09 (-0.5 - 0.4) P=0.7	-6.4 (-10.0 - -2.9) P=0.000
Dampness	0.01 (-0.06 - 0.01) P=0.6	0.002 (-0.1 - 0.1) P=0.9	1.13 (-0.2 - 2.5) P=0.1
Cotinine	-0.07(-0.1 - -0.02) P=0.005	0.1 (0.05 - 0.2) P=0.05	0.2 (-0.9 - 1.3) P=0.6

5.3 The incidence of LRT and PEF episodes following the occurrence of URT episodes, in relation to indoor air pollutants (Asthmatic children)

The second objective of the study was to determine whether, among these individuals at times of upper respiratory tract symptoms exposure to these indoor environmental factors increases the risk of

a. Lower respiratory tract symptoms
b. Episodes of reduced peak expiratory flow

Logestic regression analysis (univariate analysis) was used to study the incidence of lower respiratory tract and peak expiratory flow episodes within five days from the onset of upper respiratory tract episodes (table 5.14). Odd ratio (OR) is significant when 1 does not fall in the range of the 95%CI and OR is ≥1. The study was underpowered, therefore some of the positive association we found in this study would been stronger and the 95%CI would been less wider had we have a larger sample size.

5.3.1 The incidence of LRT episodes following the occurrence of URT episodes, in relation to indoor air pollutants

A total number of 52 LRT episodes occurred within the first five days from the onset of URT episodes. The majority of these episodes (31 episodes) started at the same day of URT episodes. There was an interval of 2-4 days between the development of LRT episodes and the onset of URT episodes in fourteen episodes.

Only two LRT episodes occurred at the fifth day following the incidence of URT episode, and 5 episodes happened one day after the onset of URT episode (table 5.13). Exposure to nitrogen dioxide (kitchen mean and personal), did not show a significant increase in the rate of the LRT episodes following URT episodes (OR=0.8, 95%CI 0.3-2.2; OR=0.8, 95%CI 0.3-1.7, respectively). There was a tendency towards an increase

in the risk of developing LRT episodes following URT episodes, with indoor exposure to kitchen peak nitrogen dioxide, but this association did not reach statistical significance (OR=1.5, 95%CI 0.7-3.4) (table 5.14).

Our study has demonstrated that particulate increases the frequency of LRT episodes, within five days from the onset of URT episodes (OR=2.0, 95%CI 1.1-4.1). There was a trend only towards an increase in the incidence of LRT episodes in relation to carbon monoxide exposure (OR=2.4, 95%CI 0.6-9.3).

No influence was demonstrated by exposure to formaldehyde and VOCs on the rate of LRT episodes following URT episodes (OR=0.6, 95%CI 0.07-5.7; OR=0.4, 95%CI 0.09-2.4, respectively).

Environmental tobacco smoke as measured by urine cotinine did not increase the incidence of LRT episodes following the occurrence of URT episodes (OR=0.5, 95%CI 0.1-2.1). Similarly, dampness did not increase the risk of developing LRT episodes (OR=1.0, 95%CI 0.7-1.3).

5.3.2 The incidence of PEF episodes following the occurrence of URT episodes, in *relation to indoor air pollutants*

Thirty PEF episodes occurred within five days from the onset of URT episodes. Fifteen episodes occurred on the same day of URT episodes. There was an interval of 1-5 days between the development of fifteen PEF episodes and the occurrence of the URT episodes (table 5.13).

Our study demonstrated that exposure to indoor particulate matter has increased the risk of developing PEF episodes following URT episodes (OR=3.3, 95%CI 1.1-8.1).

Exposure to nitrogen dioxide (kitchen mean, peak and personal) showed no significant effect on the incidence of PEF episodes following URT episodes (OR=1.4, 95%CI 0.5-3.9; OR=1.2, 95%CI 0.4-2.9; OR=1.5, 95%CI 0.5-4.4, respectively).

Neither formaldehyde nor VOCs had any significant effect on the incidence of PEF episodes following URT episodes (OR=0.1, 95%CI 0.01-1.8 ;OR=0.4, 95%CI 0.03-6.4, respectively).

There was a trend only towards an increase in the incidence of PEF episodes in relation to carbon monoxide exposure, but this did not reach statistical significance (OR=1.7, 95%CI 0.3-8.2)

No significant relationship was found between the incidence of PEF episodes following the occurrence of URT episodes and indoor exposure to environmental tobacco smoke OR=1.0, 95%CI 0.2-5.3). Similarly, no association was found between dampness and the incidence of PEF (OR=0.7, 95%CI 0.4 -1.0).

Table 5.13:The number of LRT and PEF episodes within five days of the occurrence of URT episodes (asthmatic children)

Interval between URT & the start of PEF and LRT episodes	Number of PEF episodes	Number of LRT episodes
0	15	31
1	7	5
2	3	6
3	4	5
4	1	3
5	0	2

Table 5.14: Odd ratio and confidence interval of LRT, PEF episodes following URT episodes (asthmatic children)

Indoor pollutants And co-factors	OR (95%CI); P value PEF	OR (95%CI); P value LRT
Kitchen mean NO2	1.4 (0.5-3.9); 0.4	0.8(0.3-2.2); 0.7
Kitchen peak NO2	1.2 (0.4-2.9); 0.4	1.5(0.7-3.4); 0.2
Personal NO2	1.5 (0.5-4.4); 0.4	0.8(0.3-1.7); 0.5
Particulate Matter	3.3 (1.1-8.1); 0.02	2.0(1.1-4.1); 0.04
Carbon monoxide	1.7 (0.3-8.2); 0.4	2.4(0.6-9.3); 0.2
Formaldehyde	0.1 (0.01-1.8); 0.1	0.6(0.07-5.7); 0.7
VOCs	0.4 (0.03-6.4); 0.5	0.4(0.09-2.4); 0.3
ETS (Urine cotinine)	1.0 (0.2-5.3); 0.9	0.5(0.1-2.1); 0.3
Dampness	0.7 (0.4-1.0); 0.1	1.0(0.7-1.3); 0.9

5.4 The incidence of LRT and PEF episodes following the occurrence of URT episodes, in relation to indoor air pollutants (mothers data)

Logestic regression analysis was carried out to test the relationship between exposure to indoor air pollutants and the risk of developing lower respiratory tract and peak expiratory flow episodes following upper respiratory tract episodes (table 5.16).

5.4.1 The incidence of LRT episodes following the occurrence of URT episodes, in relation to indoor air pollutants

A total number of 44 LRT episodes occurred within the first five days of the identified URT episodes. The majority of the LRT episodes (34 episodes) have started within two days from the onset of URT episodes.

In our study, formaldehyde seems to have increased the risk of developing lower respiratory tract episodes following URT episodes (OR=6.4, 95%CI 1.5-29.8), no such association was found with volatile organic compounds (OR=1.9, 95%CI 0.3-11.6).

Exposure to nitrogen dioxide (kitchen mean, kitchen peak and personal), did not show a significant increase in the rate of the LRT episodes following URT episodes (OR=1.2, 95%CI 0.4-3.4; OR=1.1, 95%CI 0.7-1.7; OR=1.2, 95%CI 0.8-1.7, respectively).

No association was found between exposure to particulate matter and the risk of developing LRT episodes, within five days from the onset of URT episodes (OR=0.4, 95%CI 0.1-1.4). There was a trend only towards an increase in the incidence of LRT episodes following the URT episodes, in relation to carbon monoxide exposure (OR=2.5, 95%CI 0.7-8.9).

Neither Environmental tobacco smoke as measured by urine cotinine nor dampness has shown any significant increase in the incidence of LRT episodes following the occurrence of URT episodes (OR=0.9, 95%CI 0.6-1.4; OR=1.0, 95%CI 0.7-1.5).

5.4.2 The incidence of PEF episodes following the occurrence of URT episodes, in relation to indoor air pollutants

In this study 31 PEF episodes occurred within five days of the onset of the URT episodes. Eleven episodes occurred on the same day of URT episodes. Twenty PEF episodes developed 1-5 days following the occurrence of URT episodes (table 5.15).

Exposure to nitrogen dioxide (kitchen mean, peak and personal) did not affect on the incidence of PEF episodes following URT episodes (OR=0.9, 95%CI 0.3-3.1; OR=0.9, 95%CI 0.6- 1.6; OR=0.8, 95%CI 0.5-1.2, respectively).

Exposure to particulate matter showed no increase in the incidence of PEF episodes following URT episodes (OR=0.1, 95%CI 0.03-1.0).

Neither formaldehyde nor VOCs had a significant effect on the incidence of PEF episodes following URT episodes (OR=0.5, 95%CI 0.1-2.6 ;OR=1.3, 95%CI 0.1-9.6, respectively). Similarly no effect was found on the rate of PEF episodes in relation to indoor carbon monoxide exposure, cotinine and dampness (OR=0.7, 95% CI 0.2-2.6; OR=1.0, 95%CI 0.7-1.3; OR=0.8, 95%CI 0.5 -1.2).

Table 5.15: The number of LRT and PEF episodes within five days of the occurrence of URT episodes (mothers data)

Interval between URT & the start of PEF and LRT episodes	Number of PEF episodes	Number of LRT episodes
0	11	15
1	7	9
2	5	10
3	3	4
4	4	4
5	1	2

Table 5.16: Odd ratio and confidence interval of LRT, PEF episodes following URT episodes (Mothers data)

Indoor pollutants And co-factors	Odd ratio (95% CI);P value (PEF)	Odd ratio (95% CI);P value (LRT)
Kitchen mean NO2	0.9 (0.3-3.1); 0.9	1.2(0.4-3.4); 0.7
Kitchen peak NO2	0.9(0.6-1.6) ; 0.9	1.1(0.7-1.7); 0.4
Personal NO2	0.8(0.5-1.2) ; 0.3	1.2(0.8-1.7); 0.3
Particulate matter	0.1(0.03-1.0); 0.06	0.4(0.1-1.4); 0.1
Carbon monoxide	0.7(0.2-2.6); 0.6	2.5(0.7-8.9); 0.1
Formaldehyde	0.5(0.1-2.6); 0.4	6.4(1.5-29.8); 0.01
VOCs	1.3(0.1-9.6); 0.7	1.9(0.3-11.6); 0.4
ETS (urine cotinine)	1.0(0.7-1.3); 0.8	0.9(0.6-1.4); 0.9
Dampness	0.8(0.5-1.2); 0.6	1.0(0.7-1.5); 0.6

CHAPTER 6

Discussion, conclusion and implications for future studies

6.1 Over all discussion (our study versus previous studies)

- **Nitrogen dioxide**

Nitrogen dioxide is an oxidant that not only causes direct lung injury, but may increase susceptibility to respiratory infections through its effect on ciliary clearance and macrophage function. At high concentrations, nitrogen dioxide is known to cause diffuse pulmonary damage, not only in the animel model but in humans (Gold, 1992). The main mechanisms of pulmonary toxicity of nitrogen dioxide have, however, been suggested to be due to its oxidant capacity and involve lipid peroxidation in cell membranes (Mustafa and Tierney, 1978) (Patel and Block, 1986), as well as various actions of free radicals on structural and functional molecules (Proctor and Reynolds, 1984) (Pryor and Lightsey, 1981;Thomas and Rhoades, 1970). Particularly strong free radicals are formed when nitrogen dioxide oxidizes lecithin in cell membranes or surfactant, and interaction with haeme (Rowlands and Gause, 1971) (Maples *et al*, 1991).

Mixed results have occurred in the few studies that measured indoor nitrogen dioxide levels and attempted to estimate personal levels of exposure. Florey et al found a positive association of respiratory illness prevalence with nitrogen dioxide exposure (Florey *et al*, 1979).

Houthuijs and co-workers also found a positive relationship of the prevalence of respiratory symptoms with the estimated personal exposure levels of nitrogen dioxide (Houthuijs *et al*, 1987).

Berwick and colleagues, using a prospective design study found an increase in lower respiratory tract symptoms in children aged under seven years exposed to more than 0.015ppm of nitrogen dioxide (Berwick *et al*, 1987). However this study included only 121 children. Neas et al using Palmes diffusion tubes to estimate the mean annual house hold nitrogen dioxide exposure, found that a 15 ppb increase in the mean exposure level was associated with an increased cumulative incidence of lower respiratory tract symptoms (Neas *et al*, 1991).

Four other studies, however, have found no such positive relationship. Melia and co-workers detected no significant relationship between average measured nitrogen dioxide levels in bedrooms and living rooms and respiratory illness (Melia *et al*, 1982). Hoek and co-workers, using Palmes tubes and activity data to determine personal exposure in a case –control study, found no difference in exposure between cases reported to suffer from bronchitis, asthma, frequent coughs or colds, and allergy, and controls (Hoek *et al*, 1984).

Koo and colleagues used passive diffusion badge-style monitors, worn for 24 hours to measure personal nitrogen dioxide exposure (Koo *et al*, 1990). Monitoring was conducted during one week only for each subjects and no association was found between the children's nitrogen dioxide exposure levels and respiratory symptoms. Dijkstra and colleagues estimated weekly average nitrogen dioxide concentrations at home using Palmes diffusion tubes and found no association between nitrogen dioxide home exposure and respiratory symptoms (Dijkstra *et al*, 1990).

In our study, we found a positive association between the frequency of the lower respiratory tract episodes and kitchen mean and personal nitrogen dioxide levels among asthmatic children. There was only a trend towards an increase in the frequency of

lower respiratory episodes and indoor exposure to kitchen peak nitrogen dioxide, but this did not reach statistical significance.

Children with high kitchen nitrogen dioxide seems to have had shorter lower respiratory tract episodes. This observation may be due to the fact that children with frequent lower respiratory tract symptoms have used more bronchodilator medications as well as they might have had increased their daily inhaled corticosteroid.

Our study also demonstrated a significant association between the severity of upper respiratory tract episodes and indoor peak kitchen nitrogen dioxide.

Among mothers, It appears that exposure to nitrogen dioxide reduces the frequency of the upper respiratory episodes among mothers. Our study also demonstrated a negative association between exposure to nitrogen dioxide and the severity of lower respiratory tract and peak expiratory flow episodes.

The different findings on the relationship between nitrogen dioxide and the respiratory episodes among adults and asthmatic children, would suggest that the physiological and pathological impacts of nitrogen dioxide are different among different age groups. It would also suggest that asthmatics would probably respond differently to nitrogen dioxide as compared to healthy subjects.

The prospective design of this study, the personal indoor nitrogen dioxide measurement, and the adjustment for the confounding factors are the strengths of this study. Personal measurement of nitrogen dioxide is probably the most accurate estimate of what level of nitrogen dioxide, the subjects are exposed to in the home.

The daily recording of the symptoms had probably given the most accurate measure of the health outcomes, as compared to a retropective cross-sectional study which has the potential recall bias of the respiratory symptoms.

Examing the relationship between kitchen nitrogen dioxide (peak & mean) and the respiratory episodes is a potential weakness in this study, as the measured nitrogen dioxide might have not been what the subject is exposed to. Personal exposure to nitrogen dioxide depends on the amount of time spent in different locations and the estimated nitrogen dioxide concentrations in these locations.

Our findings suggest that nitrogen dioxide concentrations in the home are associated with an increased risk in the developing of lower respiratory tract infections among children. This is consistent with previous reports from previous studies that have used direct measurements of indoor nitrogen dioxide.

- **Volatile organic compounds & Formaldehyde**

Animal experiments demonstrated that formaldehyde and VOCs are largely absorbed on the upper respiratory tract and very little reaches the lower respiratory tract (Chang *et al*, 1983;Egle, 1972). Therefore, the state of transient bronchial hyperreactivity demonstrated from exposure nitrogen dioxide in normal and asthmatic subjects appears less likely to occur with formaldehyde (Imbus, 1985).

Several studies have looked at the effect of formaldehyde and volatile organic compounds on the upper airways and shown significant inflammatory response. Two previous studies looked at the effect of VOCs on the nose (nasal lavage) and demonstrated an inflammatory response (elevated neutrophil counts) (Koren *et al*, 1990;Koren *et al*, 1992). To-date, we are not aware of any studies which have looked at the effect of volatile organic compounds and formaldehyde on the lower respiratory tract.

Several epidemiological studies have reported a positive association between indoor concentrations of formaldehyde and volatile organic compounds and the respiratory

illnesses. In Horvath's' study, it was demonstrated that formaldehyde can contribute to short term decline in lung function, but dose response-response relationships were often quick (Horvath *et al*, 1988). Similar observation was reported by Kilburn et al (Kilburn *et al*, 1983).

Krzyzanowski et al (Krzyzanowski *et al*, 1990) demonstrated a significant increase in the incidence of bronchitis in children from houses with formaldehyde levels ranged 60 –120 ppb than those less exposed. Peak expiratory flow rate was also decreased linearly with formaldehyde exposure. It was demonstrated that the effects on asthmatic children exposed to formaldehyde below 50 ppb were greater than in healthy ones, but there was less evidence of any effect on adults. Similarly, Garrett et al (Garrett *et al*, 1999) reported significantly higher respiratory symptom scores in children with high formaldehyde exposure.

Norback et al reported that there is a relationship between indoor concentrations of formaldehyde, volatile organic compounds and the frequency of lower respiratory tract symptoms (Norback *et al*, 1995).

Similarly, in an American study on the relation between volatile organic compounds and respiratory symptoms, it was demonstrated that the incidence and the severity of lower respiratory symptoms were positively associated with the indoor concentration of volatile organic compounds (Ware *et al*, 1993).

We demonstrated that formaldehyde was associated with an increased in the frequency of peak expiratory flow episodes among the asthmatic children.

Our study suggests that subjects (mothers) with high indoor formaldehyde level had developed more lower respiratory tract episodes following the incidence of upper respiratory tract infections. It also suggests that mothers, who had exposed to high

volatile organic compounds, appeared to have suffered more severe upper respiratory tract symptoms as opposed to those with low indoor levels.

This study has demonstrated that the impact of formaldehyde and volatile organic compounds is different among asthmatic children and their mothers.

Adjustment for the confounding factors (atopy, der p1), and daily reporting of the respiratory symptoms are the strengths of this study. One of the weaknesses of this study is the fact that we have not taken into account the subjects' daily activities as well as the seasonal variability of indoor formaldehyde measurement. It has been shown that diurnal formaldehyde fluctuation can occur, which is related to temperature changes (Spengler, 1991). It was also reported that formaldehyde concentrations are higher in the summer season (Spengler, 1991).

Our findings are consistent with the results of the previous epidemiological studies which have demonstrated that volatile organic compounds and formaldehyde increase the risk of developing respiratory symptoms among asthmatic and non-asthmatic subjects.

- **Particulate Matter (PM_{10})**

One of the major factors which determines the toxicity of inhaled particles is their dosimetry characteristics, which includes particle deposition, clearance, retention, translocation and dissolution within different regions of the lung, factors which are important for their persistence within the lung (Heyder *et al*, 1986). Generally, as the particle size and breathing rates increase, particles deposit more in the proximal areas, whereas enhanced distal deposition takes place with small sized particles and slow breathing rates (Heyder *et al*, 1986). Alveolar macrophages rapidly phagocyte particles which deposit in the alveoli, however their phagocytic activity decreases when the

particle load is high, this results in their prolonged retention in the lung and increased interaction with epithelial and other cells (MacNee *et al*, 1997).

Damage and activation of the macrophages leads to the release of several pro-inflammatory mediators, which initiate an acute cellular and mediator inflammatory response in the airways. Particles which penetrate into the interstitium make contact with interstitial macrophages and subsequently leads to the release of the inflammatory mediators which can enter the blood stream to produce a low grade systemic response, which can lead to cardiovascular compromise, particularly among patients with pre-existing cardiac disease (Peters *et al*, 1997).

Honicky and co-workers (Honicky *et al*, 1985), conducted a survey on 62 children aged 1-7 years, half of the children lived in homes using wood stoves and the rest lived in homes with no wood stoves. A significant increase in the severity of respiratory symptoms was seen in children who were exposed to the wood stoves. Similar finding was reported in the study carried out by Morris and co-workers (Morris *et al*, 1990), on children aged 24 months or younger.

In the six cities studies (Watertown, Kingston, St Louis, Steubenville, Portage, and Topeka), Neas et al showed no direct association between indoor particulate matter and children's pulmonary function measurements, but found an increase in the cumulative incidence of lower respiratory symptoms (Neas *et al*, 1994).

Ostro et al (Ostro *et al*, 1994) carried out a study on the effect of gas stove versus wood stove, on a panel of 164 asthmatic children. Children were asked to report daily occurrence of respiratory symptoms, using diary cards. The use of wood stove was associated with shortness of breath, cough and nocturnal asthma. In contrast, Tuthill

and co-workers (Tuthill, 1984) found no association between the usage of wood stove and respiratory diseases among children.

Our study demonstrated that exposure to particulate matter increases the severity of peak expiratory flow episodes among asthmatic children. Among mothers, there was a positive association between indoor particulate matter and the severity of upper and lower respiratory tract episodes.

Our data also suggests that exposure to high indoor particulate matter increases the risk of developing lower respiratory tract episodes and asthma attacks following upper respiratory tract infections among asthmatic children.

Measuring particulate matter once over the study period is a potential weakness in our study, as the level of the particulate matter could be different from one day to another, depending upon the extent of cooking and smoking. Furthermore, measuring particulate matter in the kitchen did not necessarily reflected what the subject had exposed to, as the amount of the exposure depends upon the pollutant's concentration and the time spent by the subject in any particular place.

- **Environmental Tobacco Smoke (Cotinine)**

Inhaled cigarette smoke exposes the surface of the respiratory tract to a high oxidant burden which might play an important role in the pathogenesis of lung function impairment. Glutathione, a sulfhydryl-containing tripeptide, plays an important role in the protection of the cellular constituents against oxidative damage and in the detoxification of many electrophilic compounds. It is present in high concentrations in normal epithelial lining fluid. Exposure to oxidizing agents (environmental tobacco smoke) can lead to a decrease in pulmonary glutathione level (Cantin *et al*, 1987).

It has been shown that cigarette smoke can affect mucociliary function on animal studies, it inhibits the activity of adenylate kinase in the ciliated tracheal cells. Inhibition of this enzyme results in a decrease of intracellular adenosine triphosphate, which is required for ciliary movement (Mattenheimer and Mohr, 1975). Cigarette smoke also has detrimental effect on the capacity of the lung to generate a cellular immune response, it impairs the capacity of the macrophage to phagocyte and kill bacteria (Holt, 1987).

Previous studies have demonstrated that exposure to environmental tobacco smoke adversely affects the health of children with asthma (Evans *et al*, 1987;Murray and Morrison, 1986;Walshaw and Evans, 1987). A study conducted by Chilmonczyk et al (Chilmonczyk *et al*, 1993) measured urine cotinine in 199 asthmatic children accompanied with a questionnaire about child's exposure to environmental tobacco smoke, and demonstrated a positive association between exposure to environmental tobacco smoke and asthma exacerbations.

In a large Swiss study (Schwartz *et al*, 1994) on air pollution and lung diseases in adults (n= 4197 never smokers), environmental tobacco smoke was significantly associated with wheezing, shortness of breath, bronchitis and asthma.

In the prospective study (4800 children aged 5-11 years) conducted by Somerville and co-workers(Somerville *et al*, 1988), there was a significant association between the number of cigarettes smoked by parents and the frequency of wheeze, cough and the episodes of bronchitis in their children. The relative risk of having frequent wheeze rose from 1.0 if neither parent smoked to 1.3 if they smoked 10 cigarettes per day, and to 1.6 if they smoked 20/day.

Two previous studies showed no relationship between respiratory symptoms and passive smoking. Ehrlich et al (Ehrlich *et al*, 1992) found no association between passive smoking as measured by urine cotinine and asthma exacerbation.

On a cross sectional study conducted by Strachan, the effect of passive smoking on upper respiratory tract symptoms was assessed on 770 children (7 yrs of age) (Strachan *et al*, 1990). Urine cotinine was used as a quantative biochemical marker of exposure, after adjusting for housing tenure, most respiratory symptoms were unrelated to cotinine level.

In our study we found a positive association between the severity of lower respiratory tract episodes and environmental tobacco smoke (mothers).

There was a reduction in the severity and frequency of upper respiratory tract episodes, in relation to environmental tobacco smoke among mothers. Since regular exposure to environmental tobacco smoke is associated with throat, nose and eye symptoms (Bascom, 1991) (Bascom *et al*, 1996), it is possible that subjects had underestimated/under-reported the frequency and severity of these symptoms.

In children, we found no significant association between environmental tobacco smoke and the frequency, duration and severity of upper, lower respiratory tract and peak expiratory flow episodes. One possible explanation of these negative results is that parents with asthmatic children are fully aware of the implications of smoking on asthma symptoms. Therefore, it is possible that parents with asthmatic children are less likely to smoke indoors.

Previous studies on the relationship between environmental tobacco smoke and the respiratory symptoms have not addressed the issue of the potential effects of other indoor air pollution and cofactors (like dampness and der p1). Therefore, it is difficult

to conclude from those studies with a positive relationship between passive smoking and the respiratory episodes,whether these findings were solely reflect the effect of indoor exposure to environmental tobacco smoke.

Measuring cotinine twice only over the study period is a potential weakness in this study, particularly given the fact that cotinine level could vary considerably from to time over a given period, it depends upon the number of smokers.

Because of interindividual differences in metabolism, however, the variation in cotinine among subjects for a given exposure may be considerable. Therefore, the use of cotinine level as a measure of exposure to environmental tobacco smoke has raised methodological questions that need to be resolved. Coultas and co-workers reported wide variation in urinary cotinine:creatine ratios over a period of 11 weeks (correlation coefficient between cotinine:creatine ratio and ambient nicotine was 0.15) (Coultas *et al*, 1990).

It also remains to be confirmed whether urinary cotinine levels in an individual subject are stable over time, so that a single measure reflects " average " exposure, or whether they are sufficiently sensitive to changes over and above this back ground exposure level to detect short term "peak" increases.

Given these conflicting data, assessing the influence of environmental tobacco smoke on the frequency, duration and the severity of upper, lower respiratory tract episodes and asthma exacerbations as measured by peak expiratory flow episodes, would require a prospective study, with frequent measurements of urine cotinine.

- **Carbon Monoxide**

Carbon monoxide is an odorless, colourless gas with well characterized effects on oxygen transport. Carbon monoxide interferes with oxygen transport by avidly binding to haemoglobin to form carboxyhaemoglobin and by shifting the oxyhaemoglobin dissociation curve to the left (National Research Council, 1977). It also binds to myoglobulin, but the physiologic significance of the formation of carboxymyoglobin has not been established (Coburn, 1979). Tissues with highest oxygen needs, myocardium, brain, and exercising muscle, are most affected by the formation of carboxyhemoglobin.

Most of the epidemiological studies on the link between carbon monoxide and the health have focused on the cardiovascular system. These studies looked at the association between ambient carbon monoxide and mortality and morbidity in the population. A study in Athens found an association between day-to-day fluctuations in carbon monoxide concentrations and mortality (Touloumi *et al*, 1996). The effect was greatest when same day data were used in the comparison and was independent of variables such as temperature, humidity, season, and day of the week. Similarly, studies in Los Angeles have shown that carbon monoxide concentrations are related to deaths from all causes (Shumway *et al*, 1988) and to deaths from cardiovascular diseases (Hexter and Goldsmith, 1971) (Shumway *et al*, 1988), allowing for all other pollutants and air temperature.

In studies of hospital admissions and carbon monoxide, an American study showed that ambient carbon monoxide levels were positively correlated with hospital admissions for congestive heart failure, adjusting for other pollutants and temperature (Morris *et al*, 1995).

Another American study showed an association between ambient carbon monoxide concentrations and hospital admissions for cardiovascular disease(Schwartz, 1997). In this study an increase of 10ppm would correspond to a rise of 16.8% in admissions.

A study in London found significant relationships between average daily carbon monoxide concentrations and hospital admissions from 1987-1994 (Poloniecki *et al*, 1997). A rise of 10ppm in mean daily carbon monoxide corresponded to 23% more admissions of acute myocardial infarction, 6.9% more heart failure admissions and 23% more admissions for all circulatory diseases.

The above studies suggest that fluctuations in carbon monoxide levels increase the risk of hospital admissions or death due to cardiovascular disease. So far, no studies have looked at the association between indoor carbon monoxide and cardiovascular and respiratory diseases.

Our study suggests that indoor carbon monoxide has an influence on the severity of lower respiratory tract episodes, in asthmatic children. This relationship was only demonstrated in the univariate analysis, therefore it is difficult to conclude whether this finding was predominantly due to the exposure to carbon monoxide.

Measuring carbon monoxide once over the study period and also the lack of the adjustment for other air pollutants are potential weaknesses in our study. Future studies are required to address the issues of frequent indoor carbon monoxide measurements, reporting daily subjects activities to reflect an accurate estimate of exposure, as well as taking into account the level of ambient carbon monoxide.

- **Dampness**

Several previous studies have reported associations between damp housing and asthma. However, 'dampness' is a rather vague concept, with variable definitions, and specific chemical or biological factor that can explain association needs to be identified.

Some authors attributed the association between dampness and health to allergy to mites. However, there is evidence that this association remain positive even after adjusting for the levels of mite in the homes (Nafstad *et al*, 1998). It is not clear which agents in indoor air due to dampness that cause the health effects.

Most of the previous studies have relied on questionnaire to elicit information on both the subjects health and indicators of dampness in the dwelling, raising the possibility of respondent bias (Strachan, 1988) (Brunekreef, 1992).

The study of Spengler et al (Spengler *et al*, 1994) on 9-11 yr old children in 24 North American communities, demonstrated a significant association between respiratory symptoms and dampness.

In a cross sectional study of pre-school children in Finland, Jaakkola et al (Jaakkola *et al*, 1993) found that persistent cough, wheezing, phlegm and nasal symptoms were positively associated with the presence of moisture and visible moulds.

The study conducted by Andriessen et al (Adriessen *et al*, 1998), peak expiratory flow variability and respiratory symptoms in atopic children were found to be associated with the reported presence of moulds and dampness in the home. In non-atopic children, there was no relationship between home dampness and peak expiratory flow variability.

Our study has demonstrated no relationship between dampness and the frequency, duration and severity of the episodes.

The reported association between dampness and health may be due to casual links or as a result of characterization and information bias and/or as a result of confounding. Information bias occurs when the individual measurements or classifications of the symptoms or exposure to dampness are incorrect. The study group may be aware that there is a concern that dampness may cause health problems, therefore respondents with respiratory diseases may be more prone to observe and report dampness. Likewise, if dampness is present in the home, then the subject might be more incline to remember and report respiratory symptoms. The lack of the previous studies to adjust for other indoor air pollution and cofactors (like der pI), is another contributory factor to the inconsistency in the results of the studies on dampness and the respiratory illnesses.

Despite the fact that we have not demonstrated a positive relationship between dampness and the respiratory illnesses, there is a considerable evidence in the literature to suggest that there is a link between dampness and the respiratory illnesses.

6.2 Misclassification of health outcomes

There is a potential bias of reporting respiratory symptoms, particularly among mothers since they were required to answer daily to diary question of measuring peak nitrogen dioxide in the kitchen. This may suggest to some mothers that their symptoms must be linked to this exposure, and therefore affect their daily reported respiratory symptoms.

It is also difficult to establish whether the cough reported in diary cards is due to poor asthma control (compliance or under treated asthma), as opposed to being one of the features of the lower respiratory tract episode. The same would apply to the nasal symptoms, whether the reported symptoms were representing rhinitis symptoms as opposed to upper respiratory tract episode.

Bias due to misclassification of health outcomes has been highlighted as a major limitation of epidemiological studies investigating the health effects of air pollutants (Committee of the Environment and Occupational Health Assembly of the American Thoracic Society, 1996b). Retrospective questionnaires have been used to assess respiratory illness in several studies, and are believed to be particularly prone to misclassification, which may explain in part the inconsistencies in the findings of epidemiological studies

In an attempt to overcome this problem, an increasing number of investigators have used daily diary cards to assess prospectively the frequency and severity of respiratory illness (Mukala *et al*, 1996;Samet *et al*, 1993). By recording the respiratory health of each subject on a daily basis over time, diaries provide a sensitive means of detecting short term changes in an individual's health. These can then be related to fluctuations in concentrations of pollutants to which the individual has been exposed.

Diary symptom-recording has also proved to be a more sensitive means of monitoring asthma than the more commonly used objective measurement of peak expiratory flow (Clough and Sly, 1995).

One complication arising from the use of diary studies is the variability (heterogeneity) among individuals in their rating of symptoms. An individual's threshold for recording symptoms may be influenced by factors such as illness history, for example subjects with chronic symptoms may underestimate and consequently underreport episodes of illness (Clough and Sly, 1995). It may also depend upon who fills out the diary cards on a particular day (i.e parent or child). Researchers have observed a tendency for individuals to record more symptoms in the early weeks of diary keeping, whereas towards the end of the study, participants may tire of the procedure, and be inclined to maintain less accurate records of their health status (Hammer *et al*, 1974).

In our study, we looked at the association between the respiratory episodes and the indoor environment, using a physician defined episodes in the analysis. This method is probably, gives more accurate estimate of the relationship between the health and the indoor environment as opposed to looking at the prevalence of respiratory symptoms .

Previous studies reported a positive association between the prevalence of respiratory symptoms and indoor pollution. It is not possible to establish whether these symptoms due to the effect of indoor pollutants, or due to undertreatment or poor compliance with therapy.

6.3 Indoor air pollutants measurement: sampling issues

The concentration of indoor air pollutants is usually influenced by the outdoor concentration of the pollutants, the number and location of indoor sources, the size and the structure of the building, the ventilation and the rate of removal of the pollutants. In our project, the personal measurements are probably the most accurate estimate of what the subject encountered over the measured period. However, individual commitment to wear the tubes indoors, was probably different from one subject to another. This would also apply to the measurements of peak nitrogen dioxide in the kitchen, as this was largely dependent on the mothers to carry out the sampling during cooking.

Samplers used in the kitchen as well as in the living room are representing the indoor levels of the measured air pollutants, and not necessarily reflecting personal exposure. For example, measuring the peak level of kitchen nitrogen dioxide does not necessarily mean that subjects had exposed to those peaks as they may not be in the kitchen during this period.

Particulate matter and carbon monoxide were measured in the kitchen only. One of the limitations in the analysis of these pollutants and respiratory episodes, was the fact that we had significant missing data (due to noise intolerance), this led to excluding them from multivariate analysis (to retain the sample's power).

A previous study showed that both personal and indoor microenvironmental concentrations are strongly influenced by the outdoor particulate matter concentration (Sexton, 1984). It was also demonstrated that personal exposure levels were higher than indoor air levels. Taking in consideration these two outcomes, measuring

particulate matter in the kitchen will probably not have given an accurate assessment personal exposure.

Formaldehyde and volatile organic compounds were both measured over a period of 1-4 weeks, which probably represents a reasonable estimate of the indoor concentrations, that subjects were exposed to.

As regards formaldehyde, it has been shown that diurnal fluctuation can occur related to temperature changes, (Spengler, 1991). It was also reported that formaldehyde concentrations are higher in the summer season (Spengler, 1991).

The sampling duration of formaldehyde is important because of the documented temporal variation in concentration, and the possibility that certain activities, such as the use of a product, could cause significant exposure, in addition to the more stable exposure related to emission of formaldehyde from building materials and furnishings.

The use of longterm diffusive samplers does not provide data about peak concentrations. By contrast, the use of occasional short term measurements may not provide a representative measure of an occupant's exposure, and this may be of special interest in the study of chronic health effects.

Measuring peak & mean nitrogen dioxide in the kitchen and relating this to the health outcomes, has some limitations as subjects were unlikely to have spent most of their time in the kitchen. Ideally correction was needed to take subject's movement into account. However, This would have meant that subjects needed to record their indoor activities on daily basis, which would have added another task for the subjects to take on. This is less of an issue in the measurement of formaldehyde and volatile organic compounds, as one would expect that subjects are likely to spend most of their time in the living rooms.

6.4 Conclusion and implications for future studies

This study demonstrated a positive association between certain indoor air pollutants and respiratory illnesses among asthmatic children and their mothers. Our findings suggest that nitrogen dioxide, formaldehyde, carbon monoxide, particulate matter, volatile organic compounds and dampness have an adverse effects on health.

These results suggest improvement in health may be achieved by taking measures to minimize the exposure to the above indoor pollutants. These measures include alteration in the methods of cooking and heating as well as providing better ventilation systems.

Improvements in ambient air quality over the past 40 years do not necessarily mean that human exposures to harmful pollutants have also declined. Indoor air quality is not directly regulated, and use of some sources of indoor air pollution, such as wood stoves and kerosene space heaters, is increasingly widespread. Low air exchange rates in newer homes and office buildings may also increase personal exposures. Thus if air quality policy is to be designed to fully protect public health must address exposures to pollutants indoors as well as outdoors.

Since most individuals spend the majority of their time indoors. Therefore, knowledge of exposure to air pollution indoors is critical in assessing potential health effects. This study has raised many questions that need to be addressed in the future:

- The concentration of indoor air pollutants is usually influenced by the outdoor concentration of the pollutants. Therefore, it is possible that some of the positive findings between the health and indoor air pollutants, were confounded by the outdoor levels of air pollution.

- In this study a positive association was observed between personal and kitchen mean nitrogen dioxide and the frequency of lower respiratory episodes (asthmatic children), in the multivariate analysis only. No association was found between peak nitrogen dioxide in the kitchen and the respiratory episodes. It is possible that measured concentration of the peak nitrogen dioxide in a fixed place was not what the subject was exposed to, due to a variable daily activity of the subject. Therefore measuring personal peak nitrogen dioxide, would probably give an accurate estimate of the exposed concentration.
- Our study focused on a specific group of asthmatic children (asthmatic children who were on mild to moderate dose of inhaled corticosteroid). Further studies are required to look at the effect of air pollution on the other groups of subjects, for example patients who are steroid naïve and those who suffers with severe disease.
- This study was not a case-controlled study, which is one of the weaknesses of this study. Controlled study is required to elicit whether children with respiratory diseases are more susceptible to contract respiratory infections, in relation to the indoor environment.
- Pollutant monitors were placed at specific fixed locations. While this approach to monitoring has considerable value, it gives a very poor indication of the actual pollution exposure experienced by individuals because of their mobility. Since it is the actual exposure of an individual which will determine the likelihood of any adverse effect on the health of that individual, the ability to determine personal exposure is of crucial importance in assessing the health effects of air pollution (Samet *et al*, 1987). Therefore, further studies are

needed to look at the association between personal indoor exposure and the health, using personal monitors.

- This study suggests that carbon monoxide and particulate matter increases the severity of lower respiratory tract and peak expiratory flow episodes. This observation was shown in the univariate analysis. It is difficult to establish whether this effect was largely due to these pollutants as opposed to a mixture effect with other air pollutants. Further studies are required to elicit this relationship.

APPENDICIES

1. Letter to the Health center
2. Letter to the family (inviting the family to take part in the study)
3. Information sheet about the study
4. Consent form
5. Letter to the family doctor (about the family involvement in the study)
6. Diary cards
7. Information about filling in the diary cards
8. Samplers
9. Graphs of URT, LRT and PEF episodes

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Dear Dr

Re: Exposure to indoor air pollution and the risk of upper and lower respiratory diseases in asthmatic children and their mothers (046/98)

We wrote to you some time ago for a list of your asthmatic children (aged 5-21) for our genetic study, which you very kindly sent to us. We are now about to start a new study commissioned by the Department of Health on the role of indoor air pollution in respiratory symptoms in children with asthma and adult women exposed to gas stoves. We intend to recruit 120 children and their mothers into the study. We would like to use the lists you sent to us before, but approaching different children from those selected for the previous study.

This time we wish to enrol asthmatic children aged 8-14 years inclusive, with current symptoms (wheeze in the last 12 months) who have taken corticosteroids within the last three months.

At our first meeting, the families of these children would be invited to complete a questionnaire about potential sources of indoor air pollutant exposure and to join the 12-month longitudinal study. Those who agree will be given diary cards to practice recording and to provide baseline peak flow measurements. An appointment will then be made for the entry visit 1-2 weeks later.

Once consent had be given by both the child and the parent/guardian, the method of air pollution monitoring would be discussed and demonstrated. Each family will be supplied with diffusion tubes to measure indoor pollutants. Individual appointments will be made with each family for our staff to measure other pollutants within the home.

Measurements of height, weight, pulmonary function tests and a skin prick test will be performed. We will schedule visits every three months for each family to exchange diary cards and distribute more diffusion tubes.

If you wish to help us, this study would involve no extra workload for you. I enclose a copy of the letter we would send to the asthmatic children we identify from your existing list . We would prefer to send this letter out on your own letterhead in your name as patients seem happier with this method. We will administrate this from here and "pp" the signature. If you are able to help us please could you sign the attached slip and post it in the pre-paid envelope enclosed with a sheet of your letter head paper.

Yours sincerely,

Dr S Matti MB.ch. B MRCP

Clinical Research Fellow

Please tick as appropriate:

I would be willing for you to identify children to participate in the Department of Health air pollution study from my patient list

I would not like my previous list to be used for this study

Signed_____ Date_____

Address of surgery:_____

Phone number:_____

Appendix 1

Dear Mr and Mrs

Would your family like to join a study (046/98)

In December, the University of Southampton were awarded a major grant by the Department of Health to investigate the effect of the indoor air pollutants on our lungs. There has been a lot of work done on the effects of air pollution outside but, to-date, we know very little about air pollution inside the home, which is where we spend most of our time.

We are therefore looking for families **who have an asthmatic child between the age of 8 and 14** years who would be willing to join a year-long study. We would not only be wanting to study the asthmatic child, but also the child's mother.

The study will last for one year. If you agree to take part, we will arrange to meet with you to explain in detail what the study involves and to show you the small tubes with which we will measure the level of indoor pollutants. We will also visit each family individually at home approximately four times over the period of the year, to set up small devices which will be used to measure the level of addtional air pollutants.

I enclose an information sheet which explains which substances the University will be measuring and what tubes and devices we will be using. However, if you feel that you would like further information or if you have any queries, please contact our research doctor (Dr S Matti)/ Nurse (Ali Bolt) on 01703 794476.

If you then decide you would like to take part in our study **please sign the slip below and post it back in the prepaid envelope to the University**

Yours sincerely

Dr

.....

I would/would not like to participate in this study (please delete as appropriate)

Signed..... Print name.....

Address.....

.....

Telephone number.....

Appendix 2

University
of Southampton

University Medicine
Level D (810), Centre Block
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Tel 01703 796867

INFORMATION SHEET ABOUT INDOOR POLLUTANT STUDY (046/98)

Certain forms of air pollutants are found indoors at work, at school and in our homes. These pollutants have been found to have effects on our lungs. Thus, we are interested in measuring the levels of these **pollutants in the indoor environment.**

What you need to know

If you would like to enter this study, we will invite you to your local Health Centre to meet up with you to discuss the aim of this study, describe what it would involve and give you the opportunity to ask any questions. Then we will make an appointment to see you at home, at your convenience, to install our measuring equipment.

At the first visit:

1. We would show you small tubes and devices, we will be using to measure the levels of the pollutants. None of these are harmful in any way.

2. We would test your son or daughter for allergy to a number of allergens. This is done by skin pricking test, which is a painless test in which drops of substances which may cause allergy are placed on the forearm, and the skin lightly scratched so the allergen gets below the surface. The resulting redness is then measured after ten minutes to estimate the extent of the allergy.

3. We would measure your child's height and weight, and will ask your child to perform simple breathing tests.

During the study:

1. Both the mother and the child would be asked to fill in a diary card each morning and evening. This would involve:
a) giving a yes/no answer to a question about any chest symptoms experienced that day.
b) recording a measurement of their breathing using a peak flow meter. This is a small, simple device used by people with asthma to monitor their breathing.

2. We would need weekly gas and electricity meter readings to be recorded.

Which particular pollutants are we measuring and how?

We are planning to measure the following pollutants.

1. Nitrogen dioxide
2. Formaldehyde
3. Particulates
4. Carbon monoxide
5. Total volatile compounds.
6. House dust mite, dampness , environmental tobacco smoke

Measurement procedures:-

1. **Nitrogen dioxide:-**This is measured using small tubes, some of them you need to wear and the others are placed in the kitchen. The period of measurement is seven days. This measurement is repeated twice over a period of one year.

2. **Formaldehyde:-** This is measured by small tubes which are placed in the kitchen. The period of measurement is 24h. The measurement is repeated twice over a period of one year.

3. **Carbon monoxide and Particulates:-** These are measured using small devices which are placed in the kitchen for a period of 24h. The device measures approximately 50x30 cm.

4. **House dust mite:-** This is measured in a sample collected by hoovering the carpet.

5. **Total volatile compounds:-** These are measured using a small tube, which is placed in the lounge for a period of twenty eight days.

6. **Environmental tobacco smoke, Dampness & Humidity:-** Environmental tobacco smoke is measured in the urine, therefore you will be asked to provide a urine sample at some stage during the study. Dampness and humidity are both measured by using small devices which give instant readings.

Is our participation voluntary?

Your participation in this research study is voluntary and you may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which you are entitled to.

Who should we contact if we have any questions about this study?

The study doctor or nurse will be happy to answer all of your questions. If you would like to more information on this study, please contact Dr Matti on (01703) 796736 or our Research Nurse Ali Bolt on (01703) 794476. Alternatively, you can write to them at:

University Medicine, Level D, Centre Block,
Southampton General Hospital,
Tremona Road, Southampton, SO16 6YD.

Appendix 3

University of Southampton

University Medicine
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Tremona Road
Southampton SO16 6YD

Tel 01703 796867

Consent Form

INDOOR POLLUTION STUDY (LONGITUDINAL)

Please ask the mother and child to complete the following:

	Please tick Yes	No
Have you read the Information Sheet?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Have you received satisfactory answers to all your questions?	☐	☐
Have you received enough information about the study?	☐	☐
Have you had enough time to decide about taking part?	☐	☐

Who have you spoken to?

_____

Do you understand that you and your child are free to withdraw from the study: *Please tick*

	Yes	No
• At any time	☐	☐
• Without having to give a reason for withdrawing	☐	☐
• And without affecting your future medical care	☐	☐
Do you agree to take part in this study?	☐	☐

Signed (mother): _____ Date: _____

(Name in block letters)

_____

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of Southampton

University Medicine
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Tel 01703 796867

Signed (child): _____ Date: _____

Signed (Investigator): _____ Date: _____

Appendix 4

University
of Southampton

University Medicine
Level D (810), Centre Block
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Tel 01703 796867

Date:

Dear Dr

Re: Your patient: _____ and their mother/guardian

_____

Date of Birth: Child _____mother/guardian _____

Address:

_____

I am writing to inform you that your patients have consented to take part in a year-long study investigating exposure to indoor air pollution and the risk of upper and lower respiratory disease in asthmatic children and their mothers (LREC ref: 046/98)

The child and mothers height and weight will be measured; pulmonary function tests and skin prick testing will also be performed. Each family will be supplied with diffusion tubes for monitoring purposes. Individual appointments will be made with each family for our staff to measure other pollutants at their home. During the study, the asthmatic children will document peak flow measurements, symptoms, medication use and any life events such as absence from school. We will schedule visits at the Health Centre every 3 months for each family. The visits to distribute the pollutant monitoring tubes will be used to maintain subjects interest, check their records, and to emphasise the need for continued commitment. Social events will be organised during the year to maintain compliance.

I hope that you will not object to your patients' participation in this study, but please do not hesitate to contact me on (01703) 796867 if you require any further information.

Yours sincerely,

Dr S. Matti
Clinical Research Fellow (Honorary SPR)
University Medicine

Appendix 5

Appendix 6

NAME_____ DATE CARD STARTED_____ FINISHED_____

Please score symptoms in the boxes as shown.

1 = MILD	2 = MODERATE	3 = SEVERE	LEAVE BLANK IF NO SYMPTOMS

DAY	Box	MON	TUE	WED	THUR	FRI	SAT	SUN	MON	TUE	WED	THUR	FRI	SAT	SUN	
Cough on waking	A															A
Wheeze on waking	B															B
Cough during the day	C															C
Wheeze during the day	D															D
Shortness of breath during the day	E															E
Cough, wheeze or shortness of breath during the night	F															F
TOTAL CHEST SCORE Add up boxes A to F																
Runny nose or sneezing	G															G
Blocked or stuffy nose	H															H
Sore throat or hoarse voice	I															I
Headaches or faceaches	J															J
Aches or pains elsewhere	K															K
Chill, fever or shivery	L															L
TOTAL COLD SCORE Add up boxes G to L																
PEAK FLOW [Best of 3 blows]	AM															AM
	PM															PM

HOW TO USE THE DIARY RECORD CARDS

Thank you for agreeing to help us with this study. Here is a brief explanation of how to use the diary card. Each record lasts only two weeks, we ask you to fill in the card each evening starting on the day you entered the study.

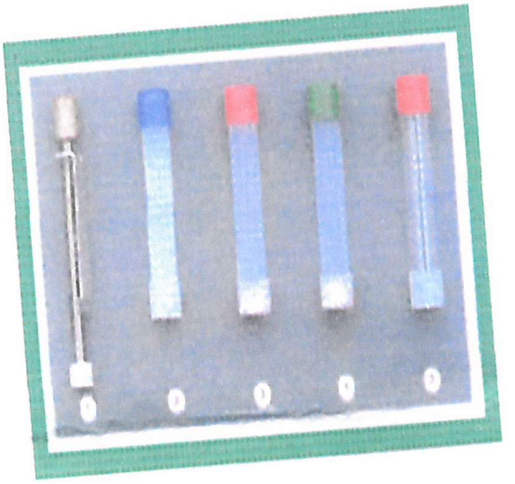
At the top we have left spaces for you to enter your initials, the subject number, and the date of both when you started and finished filling in the diary card.

We would like you to score your symptoms at the end of each evening, recording the symptoms you had for the last twenty-four hours.

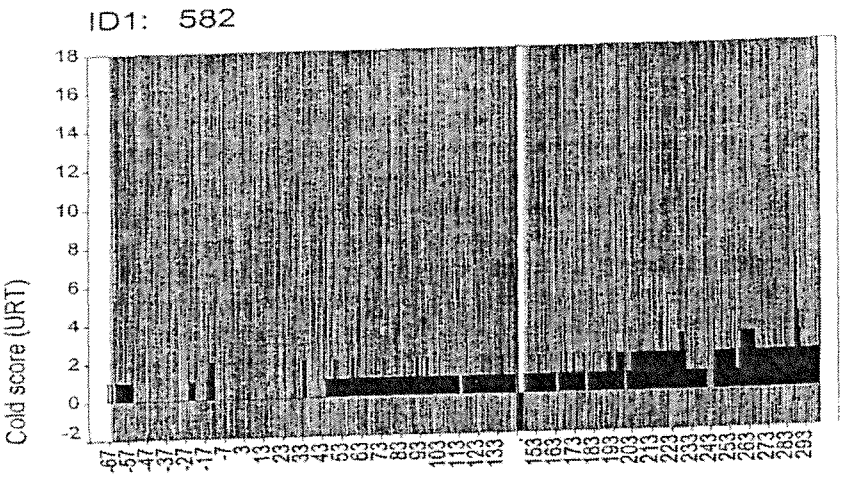
You have to score daily each symptom according to how bad it is. A score of **1** means mild symptom, a score of **2** is a moderate symptom, and a score of **3** means that you have severe symptom. Add up boxes **A-F** for the chest scores, and boxes **G-L** for the cold scores. If you have no chest or cold symptoms at all, then leave the spaces **A-F and G-L** blank, and write **'0'** in the space of the total score.

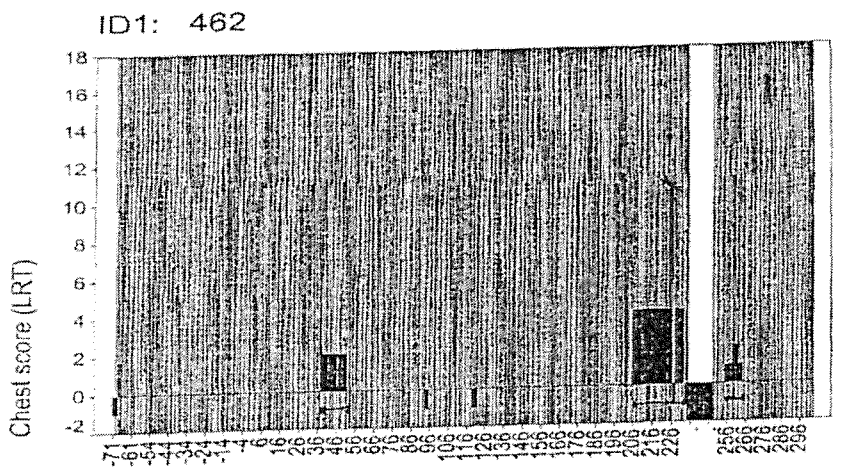
You also need to record your peak flow measurement twice daily. Only record the best of 3 blows. If you take ventoline or any other asthma medications, then record the peak flow measurement before you take them.

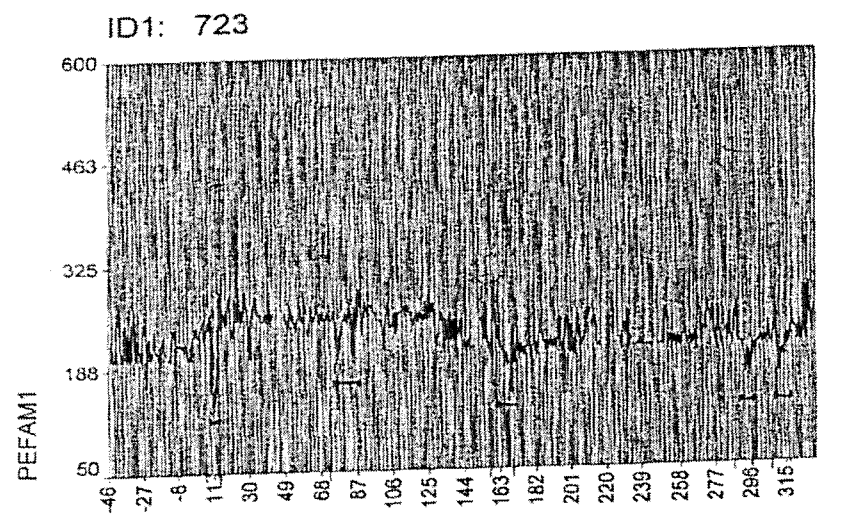
a . VOCs and NO_2 Diffusion Samplers



b. Formaldehyde sampler







Appendix 9

Abramson, M., and T. Voigt. 1991. Ambient air pollution and respiratory disease. *Med. J. Aust* 154(8):543-53.

Adriessen, J. W., B. Brunekreef, and W. Roemer. 1998. Home dampness and respiratory health status in european children. *Clin.Exp.Allergy* 28:1191-1200.

Akbar-Khanzadeh, F., and J. S. Mlynek. 1997. Changes in respiratory function after one and three hours of exposure to formaldehyde in non-smoking subjects. *Occup Environ Med* 54(5):296-300.

Allred, E. N., E. R. Bleecher, B. R. Chaitman, and e. al. 1989. Short term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N. Engl. J. Med.* 321:406-412.

Anderson, H. R. 1978. Respiratory abnormalities, in Papua New Guinea children: the effects of locality and domestic woodsmoke popullation. *Int.J.Epidemiol.* 7:63-72.

Anderson, I., and L. Molhave. 1983. Controlled studies with formaldehyde. In: Gibson JE ed. Formaldehyde toxicity. *Washington,Dc. Hemisphere publishing Corporation.*:154-165.

Andrae, S., O. Axelson, I. Bjorksten, M. Fredriksson, and N. Kjellman. 1988. Symptoms of hyperreactivity and asthma in relation to environmental factors. *Arch. Dis. Child* 63:473-478.

Andriessen, J. W., B. Brunekreef, and W. Roemer. 1998. Home dampness and respiratory health status in european children [see comments]. *Clin. Exp. Allergy* 28(10):1191-200.

Aronow, W. S. 1983. Carbon monoxide and cardiovasculaar disease. *Compr. Ther.* 9:21-6.

Ashley, D. L., M. A. Bonin, F. L. Cardinali, J. M. McCraw, and J. V. Wooten. 1996. Measurement of volatile organic compounds in human blood. *Environ. Health. Perspect.* 104 Suppl 5:871-7.

Bascom, R. 1991. The upper respiratory tract: mucous membrane irritation. *Environ Health Perspect* 95:39-44.

Bascom, R., J. Kesavanathan, T. Permutt, and T. K. Fitzgerald. 1996. Tobacco smoke and upperrespiratory response relationships in healthy nonsmokers. *Fund. Appl. Toxicol* 29:86-93.

Bauer, M. A., M. J. Utell, P. E. Morrow, D. M. Speers, and F. R. Gibb. 1986. Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. *Am. Rev. Respir. Dis.* 134(6):1203-8.

Beard, R. R. 1982. Patty's Industrial Hygiene and toxicology. John Wiley & Sons, New York.

Beil, M., and W. T. Ulmer. 1976. [Effect of NO2 in workroom concentrations on respiratory mechanics and bronchial susceptibility to acetylcholine in normal persons (author's transl)]. *Int. Arch. Occup. Environ. Health* 38(1):31-44.

Bellomo, R., Gigliotti, A. Treloar, P. Holmes, C. Suphioglu, M. B. Singh, and B. Knox. 1992. Two consective thunderstorm associated epidemics of asthma in the city of Melbourne. The possible role of rye grass pollen. *Med. J. Australia* 156:834-837.

Berwick, M., B. p. Lederer, J. A. Stolwijk, and R. Zagraniski. 1987. Association between nitrogen dioxide levels and lower respiratory symptoms in children exposed to unvented combustion sources. *Indoor Air* 1:298-303.

Boezen, M., J. Schouten, B. Rijcken, and e. al. 1998. Peak expiratory flow variability, bronchial responsiveness and susciptibilty to ambient air pollution in adults. *Am.J.Respir.Crit.Care.Med* 158:1848-1854.

Bornehag, C. G., G. Blomquist, F. Gyntelberg, and e. al. 2001. Dampness in buildings and health. Nordic interdisciplinary review on associations between exposure to dampness in buildings and health effects. *Indoor Air* 11(2):72-86.

Braback, L., A. Breborowicz, S. Dreborg, A. Knutsson, H. Pieklik, and B. Bjorksten. 1994. Atopic sensitization and respiratory symptoms among Polish and Swedish school children. *Clin. Exp. Allergy* 24(9):826-35.

Brown, S. 1994. Concentrations of VOCs in indoor air. *Indoor air* 4:123-134.

Brunekreef, B. 1992. Associations between questionnaire reports of home dampness and childhood respiratory symptoms. *Sci Total Environ* 127(1-2):79-89.

Brunekreef, B., D. W. Dockery, and M. Krzyzanowski. 1995. Epidemiologic studies on short-term effects of low levels of major ambient air pollution components. *Environ. Health. Perspect.* 103 Suppl 2:3-13.

Burchfiel, C. M., M. W. Higgins, J. B. Keller, W. F. Howatt, W. J. Butler, and I. T. Higgins. 1986. Passive smoking in childhood. Respiratory conditions and pulmonary function in Tecumseh, Michigan. *Am.Rev.Respir. Dis.* 133:966-973.

Bylin, G., T. Lindvall, T. Rehn, and B. Sundin. 1985. Effects of short-term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function. *Eur J Respir Dis* 66(3):205-17.

Bylin, G., T. Lindvall, T. Rehn, and B. Sundin. 1985. Effects of short term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function. *Eur. J. Respir. Dis.* 66:205-217.

Bylin, G., G. Hedenstierna, T. Lindvall, and B. Sundin. 1988. Ambient nitrogen dioxide concentrations increase bronchial responsiveness in subjects with mild asthma. *Eur Respir J* 1(7):606-12.

Campbell-Hewson, G., A. Cope, C. V. Egleston, H. M. Sherriff, S. M. Robinson, and U. Allitt. 1994. Epidemic of asthma possibly associated with electrical storms. *BMJ* 309:1086-1087.

Cantin, A. M., S. L. North, R. C. Hubbard, and e. al. 1987. Normal alveolar epithelial lining fluid contains high levels of glutathione. *J A ppl Physiol* 63:152-157.

Casale, R., G. Natali, D. Colantonio, and e. al. 1992. Rythem of peak expiratory flow in children passively exposed and not exposed to cigarette smoke. *Thorax* 47:801-3.

Chang, J. C. F., E. A. Gross, J. A. Swenberg, and C. S. Barrow. 1983. Proliferation after single exposure or repeated formaldehyde exposures in B6C3F1 mice and F-344 rats. *Toxicol.Appl. Pharmacol.* 68:161.

Chauhan, A. J., M. T. Krishna, A. J. Frew, and S. T. Holgate. 1998. Exposure to nitrogen dioxide (NO2) and respiratory disease risk. *Rev. Environ. Health* 13(1-2):73-90.

Chilmonczyk, B. A., L. M. Salmun, K. N. Megathlin, L. M. Neveux, G. E. Palomaki, G. J. Knight, A. J. Pulkkinen, and J. E. Haddow. 1993. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children [see comments]. *N Engl J Med* 328(23):1665-9.

Clough, J. B., and P. D. Sly. 1995. Association between lower respiratory tract symptoms and falls in peak expiratory flow in children. *Eur.Res.J.* 8(5):718-722.

Coburn, R. F. 1979. Mechanismsof carbon monoxide toxicity. *Prev. Med.* 8:310-22.

Cogswell, J. J., E. B. Mitchell, and J. Alexander. 1993. Parental smoking, breast feeding, and respiratory infection in developement of allergic diseases. *Arch.Dis.Child.* 68:724-728.

Coultas, D. B., J. M. Samet, J. F. McCarthy, and J. D. Spengler. 1990. Variability of measures of exposure to environmental tobacco smoke in the home. *Am. Rev.Respir.Dis* 142:602-6.

Cullinan, P., D. Lowson, M. J. Nieuwenhuijsen, and e. al. 1994. Work related symptoms, sensitization, and estimated exposure in workers not previously exposed to laboratory rats. *Occup.Environ. Med.* 51:589-592.

D'Amato, G., G. Liccardi, and M. D'Amato. 1994. Environment and development of respiratory allergy. II. Indoors. *Monaldi. Arch. Chest. Dis.* 49(5):412-20.

Devalia, J. L., C. Rusznak, M. J. Herdman, C. J. Trigg, H. Tarraf, and R. J. Davies. 1994. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet* 344(8938):1668-71.

Dijkstra, L., D. Houthuijs, B. Brunekreef, I. Akkerman, and J. S. Boleij. 1990. Respiratory health effects of the indoor environment in a population of Dutch children. *Am. Rev. Respir. Dis.* 142(5):1172-8.

Dodge, R. 1982. The effects of indoor pollution on Arizona children. *Arch Environ Health* 37(3):151-5.
Edfors-Lubs, M.-L. 1971. Allergy in 7000 twin pairs. *Acta. Allergol.* 26:249-285.

Egle, J. L. 1972. Retention of inhaled formaldehyde, propionaldehyde, and acrolein in the dog. *Arch.Environ.Health.* 25:119.

Ehrlich, R., M. Kattan, J. Gogbold, and e. al. 1992. Childhood asthma and passive smoking. *Am.Rev.Respir. Dis.* 145:594-599.

Ekwo, E. E., M. M. Weinberger, P. A. Lachenbruch, and W. H. Huntley. 1983. Relationship of parental smoking and gas cooking to respiratory disease in children. *Chest* 84:662-8.

Evans, D., M. J. Levison, C. H. Feldman, and e. al. 1987. The impact of passive smoking on emergency room visits of urban children with asthma. *Am. Rev. Respir. Dis.* 135:567-572.

Fielder, M. P., R. A. Lyons, M. Heaven, M. Huw, P. Govier, and M. Hooper. 1999. Effect of environmental tobacco smoke on peak flow variability. *Arch. Dis. Child* 80:253-256.

Florey, C. V., R. J. Melia, S. Chinn, B. D. Goldstein, A. G. Brooks, H. H. John, I. B. Craighead, and X. Webster. 1979. The relation between respiratory illness in primary schoolchildren and the use of gas for cooking--III. Nitrogen dioxide, respiratory illness and lung infection. *Int J Epidemiol* 8(4):347-53.

Frampton, M. W., P. E. Morrow, C. Cox, F. R. Gibb, D. M. Speers, and M. J. Utell. 1991. Effects of nitrogen dioxide exposure on pulmonary function and airway reactivity in normal humans. *Am. Rev. Respir. Dis.* 143(3):522-7.

Frigas, E., W. V. Filley, and C. E. Reed. 1984. Bronchial challenge with formaldehyde gas: lack of bronchoconstriction in 13 patients suspected of having formaldehyde-induced asthma. *Mayo Clin Proc* 59(5):295-9.

Garrett, M. H., M. A. Hooper, B. M. Hooper, and M. J. Abramson. 1998. Respiratory symptoms in children and indoor exposure to nitrogen dioxide and gas stoves. *Am J Respir Crit Care Med* 158(3):891-5.

Garrett, M. H., M. A. Hooper, B. M. Hooper, P. R. Rayment, and M. J. Abramson. 1999. Increased risk of allergy in children due to formaldehyde exposure in homes [published erratum appears in Allergy 1999 Dec;54(12):1327]. *Allergy* 54(4):330-7.

Glasgow, J. E., G. G. Pietra, W. R. Abrams, J. Blank, D. M. Oppenheim, and G. Weinbaum. 1987. Neutrophil recruitment and degranulation during induction of emphysema in the rat by nitrogen dioxide. *Am Rev Respir Dis* 135(5):1129-36.

Gold, D. 1992. Indoor Air Pollution. *occupational Lung Diseases* 13(2):215-227.

Gordon, R. E., A. A. Shaked, and D. F. Solano. 1986. Taurine protects hamster bronchioles from acute NO2-induced alterations. A histologic, ultrastructural, and freeze-fracture study. *Am J Pathol* 125(3):585-600.

Goren, A. L., and S. Hellman. 1995. Respratory conditions among school children and their relationship to environmental tobacco smoke and other combusion products. *Arch.Environ.Health* 50:112-118.

Greenberg SD, G. F., Jenkins D, Gyorkey P. 1971. Alveolar epithelial cells following exposure to nitric acids. *Arch Environ Health* 22:655-662.

Haahtela, P. 1990. Prevalence of asthma in Finnish young men. *British Medical Journal* 301:266-268.

Hackney, J. D., F. C. Thiede, W. S. Linn, E. E. Pedersen, C. E. Spier, D. C. Law, and D. A. Fischer. 1978. Experimental studies on human health effects of air pollutants. IV. Short-term physiological and clinical effects of nitrogen dioxide exposure. *Arch Environ Health* 33(4):176-80.

Hammer, D. I., V. Hasselblad, B. Portnoy, and P. F. Wehrle. 1974. Los Angeles student nurse study. Daily symptom reporting and photochemical oxidants. *Arch Environ Health* 28(5):255-60.

Harrington, W., and A. J. Krupnick. 1985. Short-term nitrogen dioxide exposure and acute respiratory disease in children. *J. Air. Pollut. Control. Assoc.* 35(10):1061-7.

Harving, H., R. Dahl, and L. M-ed-Ihave. 1991. Lung function and bronchial reactivity in asthmatics during exposure to VOCs. *Am.Rev.Respir.Dis.* 143:751-754.

Hasselblad, V., D. M. Eddy, and D. J. Kotchmar. 1992. Synthesis of environmental evidence: nitrogen dioxide epidemiology studies. *J Air Waste Manage Assoc* 42(5):662-71.

Hazucha, M. J., J. F. Ginsberg, W. F. McDonnell, E. D. Haak, Jr., R. L. Pimmel, S. A. Salaam, D. E. House, and P. A. Bromberg. 1983. Effects of 0.1 ppm nitrogen dioxide on airways of normal and asthmatic subjects. *J. Appl. Physiol.* 54(3):730-9.

Helleday, R., T. Sandstrom, and N. Stjernberg. 1994. Differences in bronchoalveolar cell response to nitrogen dioxide exposure between smokers and nonsmokers. *Eur Respir J* 7(7):1213-20.

Henderson, F. W., H. F. Reid, Morris R, and e. al. 1989. Home air nicotine levels and urine cotinine. *Am.Rev.Respir.Dis.* 140:197-201.

Hexter, A. C., and J. R. Goldsmith. 1971. Carbon monoxide:association of community air pollution with mortality. *Science* 172:265-267.

Heyder, J. L., J. Gebhart, G. Rudolf, and e. al. 1986. Deposition of particles in the human respiratory tract in the size range 0.005-15um. *J Aerosol Sci* 17:811-825.

Hoek, G., B. Brunekreef, R. Meijer, A. Scholten, and J. Boleij. 1984. Indoor nitrogen dioxide pollution and respiratory symptoms of schoolchildren. *Int. Arch. Occup. Environ. Health.* 55(1):79-86.

Hoek, G., and B. Brunekreef. 1993. Acute effects of a winter air pollution on pulmonary function and respiratory symptoms of children. *Arch. Environ. Health.* 48:328-335.

Hoek, G., and B. Brunekreef. 1994. Effects of low level wintor air pollution concentrations on respiratory health of Dutch children,. *Environ. Res.* 64:136-150.

Holt, P. G. 1987. Immune and inflammatory in cigarette smokers. *Thorax* 42:241-249.

Honicky, R. E., J. S. d. Osborne, and C. A. Akpom. 1985. Symptoms of respiratory illness in young children and the use of wood-burning stoves for indoor heating. *Pediatrics* 75(3):587-93.

Horvath, E. P., H. J. Anderson, W. E. Pierce, and e. al. 1988. Effects of formaldehyde on the mucous membranes and the lungs. *J.A.M.A.* 259:701-707.

Houthuijs, D., B. Remijn, B. Brunekreef, and R. Dekoning. 1987. Exposure to nitrogen dioxide and tobacco smoke and respiratory health of children. *Indoor air* 1:463-7.

Hyndman, S. J., D. L. Brown, P. W. Ewan, T. W. Higenbottam, J. W. Maunder, and D. R. Williams. 1994. Humidity regulation in the management of asthma patients sensitized to house dust mites. *Q J Med* 87(6):367-72.

Imbus, H. R. 1985. Clinical evaluation of patients with complaints related to formaldehyde exposure. *J. Allergy. Clin. Immunol.* 76(6):831-40.

Ishizaki, T., K. Koizumi, R. Ikemori, Y. Ishiyama, and E. Kushibiki. 1987. Studies of prevalence of Japanese cedar pollinosis among the residents in a densely cultivated area. *Ann. Allergy.* 58:265-270.

Jaakkola, J. J., N. Jaakkola, and R. Ruotsalainen. 1993. Home dampness and molds as determinants of respiratory symptoms and asthma in pre-school children. *J Expo Anal Environ Epidemiol* 3(Suppl 1):129-42.

Jantunen, M., J. J. K. Jaakola, and M. Krzyzanowski. assessment of exposure to indoor air pollutants:WHO regional Publications, European series. 15-17.

Johnston, S. L., P. K. Pattemore, G. Sanderson, S. Smith, and e. al. 1995. Community study of role of viral infection in exacerbation of asthma in 9-11 year old children. *B.M.J* 310 (6989):1225-1229.

Jones, A. P. 1998. Asthma and domestic air quality. *Soc. Sci.Med* 47:755-764.

Jorres, R., and H. Magnussen. 1991. Effect of 0.25 ppm nitrogen dioxide on the airway response to methacholine in asymptomatic asthmatic patients. *Lung* 169(2):77-85.

Jorres, R., D. Nowak. F. Grimminger, W. Seeger, M. Oldigs, and H. Magnussen. 1995. The effect of 1 ppm nitrogen dioxide on bronchoalveolar lavage cells and inflammatory mediators in normal and asthmatic subjects. *Eur Respir J* 8(3):416-24.

Karol, M. H. 1991. Allergic reactions to indoor air pollutants. *Environ Health Perspect* 95:45-51.

Keller, M. D., R. R. Lanese, R. Mitchell, and R. W. Cote. 1979. Respiratory illness in house houlds using gas and electricity for cooking.I. Survey of incidence. *Environ. Res.* 19:495-503.

Kerr, H. D., T. J. Kulle, M. L. McIlhany, and P. Swidersky. 1979. Effects of nitrogen dioxide on pulmonary function in human subjects: an environmental chamber study. *Environ Res* 19(2):392-404.

Kilburn, K. H., R. Warshaw, and C. T. Boylen. 1983. Toxic effects of formaldehyde and solvents in histology technicians. *J. Histochem.* 6:73-6.

Kleeberger, S. R., J. Kolbe, C. Turner, and E. W. Spannhake. 1989. Exposure to 1ppm ozone attenuates the immediate antigenic response of canine perpheral airways. *J. Toxicol. Environ. Health.* 28:349-362.

Kleinman, M. T., R. M. Bailey, W. S. Linn, K. R. Anderson, J. D. Whynot, D. A. Shamoo, and J. D. Hackney. 1983. Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics. *J. Toxicol. Environ. Health* 12(4-6):815-26.

Knox, R. B. 1993. Grass-pollen, thunderstorms and asthma. *Clin. Exp. Allergy* 23:354-359.

Koenig, J. Q., T. V. Larson, Q. S. Hanley, and e. al. 1993. Pulmonary function changes in children associated with fine particulate matter. *Environmental Research.* 63:26-38.

Koo, L. C., J. H. Ho, C. Y. Ho, H. Matsuki, H. Shimizu, T. Mori, and S. Tominaga. 1990. Personal exposure to nitrogen dioxide and its association with respiratory illness in Hong Kong. *Am Rev Respir Dis* 141(5 Pt 1):1119-26.

.Koren, H. S., G. E. Hatch, and D. E. Graham. 1990. Nasal lavage as atoolin assessingacute inflammationin response to inhaled pollutants. *Toxicology* 60:15-25.

Koren, H. S., D. E. Graham, and R. B. Devlin. 1992. Exposure of humans to a volatile organic mixture. III. Inflammatory response. *Arch Environ Health* 47(1):39-44.

Kramps, J. A., L. T. C. Peltenburg, P. R. M. Kerklaan, and e. al. 1989. Measurement of specific IgE antibodies in individual exposed to formaldehyde. *Clin.Exp. Allergy.* 19:509-514.

Krzyzanowski, M., J. J. Quackenboss, and M. D. Lebowitz. 1990. Chronic respiratory effects of indoor formaldehyde exposure. *Environ Res* 52(2):117-25.

Kuller, L. H., and E. P. Radford. 1983. Epidemiological bases for the cuurent ambient carbon monoxide standards. *Environ. Health. Perspect.* 52:13-9.

Lau S, W. U. 1990. Indoor environments and the development of allergy. *ACI* 2:179-182.

Lindfors, A., G. Hedlin, H. Rietz, L. Nordwall, and M. Wickman. 1994. Indoor risk factors in young children with asthma. *J. Allergy.Clin. Immunol* 93:290.

Linn, W. S., J. C. Solomon, S. C. Trim, C. E. Spier, D. A. Shamoo, T. G. Venet, E. L. Avol, and J. D. Hackney. 1985. Effects of exposure to 4 ppm nitrogen dioxide in healthy and asthmatic volunteers. *Arch. Environ. Health.* 40(4):234-9.

Lipfert, F. W. 1997. Air pollution and human health:perspectives for the '90s and beyond. *Risk analysis* 17:137-146.

MacNee, W., X. Y. Li, P. S. Gilmour, and K. Donaldson. 1997. Proinflammatory effect of particulate air pollution in vivo and vitro. *Ann. Occup. Hyg* 41(1):7-13.

Maples, K. R., T. Sandstrom, Y. F. Su, and R. F. Henderson. 1991. The nitric oxide/heme protein complex as a biologic marker of exposure to nitrogen dioxide in humans, rats, and in vitro models. *Am. J. Respir. Cell. Mol. Biol.* 4(6):538-43.

Martin, C. J., S. D. Platt, and S. M. Hunt. 1987. Housing conditions and ill health. *Br. Med. J. (Clin Res Ed)* 294(6580):1125-7.

Mattenheimer, H., and U. Mohr. 1975. Ciliotoxicity of cigarette smoke and adenylate kinase. *Z.Klin.Chem.Biochem.* 13(7):325-326.

McConnochie, K. M., and K. J. Roghmann. 1985. Predicting clinically significant lower respiratory tract illness in childhood following mild bronchiolitis. *Am.J.Dis.child.* 139:625-31.

Meijer, G. G., D. S. Postma, S. van der Heide, D. M. de Reus, R. J. Roorda, G. H. Koeter, and W. M. van Aalderen. 1996. Exogenous stimuli and circadian peak expiratory flow variation in allergic asthmatic children. *Am. J. Respir. Crit. Care. Med.* 153(1):237-42.

Melia, R. J., C. D. Florey, D. G. Altman, and A. V. Swan. 1977. Association between gas cooking and respiratory disease in children. *Br. Med. J.* 2(6080):149-52.

Melia, R. J., C. V. Florey, and S. Chinn. 1979. The relation between respiratory illness in primary school children and the use of gas for cooking. 1. Results from a national survey. *Int. J. Epidemiol.* 8:333-8.

Melia, R. J., C. d. V. Florey, R. W. Morris, B. D. Goldstein, D. Clark, and H. H. John. 1982. Childhood respiratory illness and the home environment. I. Relations between nitrogen dioxide, temperature and relative humidity. *Int J Epidemiol* 11(2):155-63.

Melia, R. J., C. d. V. Florey, R. W. Morris, B. D. Goldstein, H. H. John, D. Clark, I. B. Craighead, and J. C. Mackinlay. 1982. Childhood respiratory illness and the home environment. II. Association between respiratory illness and nitrogen dioxide, temperature and relative humidity. *Int. J. Epidemiol.* 11(2):164-9.

Melia, R. J., S. Chinn, and R. J. Rona. 1988. Respiratory illness and home environments of ethnic groups. *B.M.J.* 296:1438-41.

Mohamed, N., L. Ng'ang'a, J. Odhiambo, J. Nyamwaya, and R. Menzies. 1995. Home environment and asthma in Kenyan schoolchildren: a case-control study. *Thorax* 50(1):74-8.

Mohsenin, V. 1987. Effect of vitamin C on NO2-induced airway hyperresponsiveness in normal subjects. A randomized double-blind experiment. *Am Rev Respir Dis* 136(6):1408-11.

Monto, A. S., and B. M. Ultman. 1974. Acute respiratory illness in an american community. *JAMA* 227:164-169.

Morris, k., M. Morganlander, J. L. Coulehan, S. Gahagen, and V. C. Arena. 1990. Wood burning stoves and lower respiratory tract infection in American Indian children. *Am.J.Dis.Child* 144:105-108.

Morris, R. D., E. N. Naumova, and R. L. Munasinghe. 1995. Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities [see comments]. *Am J Public Health* 85(10):1361-5.

Mukala, K., J. Pekkanen, P. Tiittanen, S. Alm, R. O. Salonen, M. Jantunen, and J. Tuomisto. 1996. Seasonal exposure to NO2 and respiratory symptoms in preschool children. *J Expo Anal Environ Epidemiol* 6(2):197-210.

Muranaka, M., S. Suzuki, K. Koizumi, S. Takafuji, T. Miyamoto, R. Ikemori, and H. Tokiwa. 1986. Adjuvant activity of diesel -particulates for the producyion of IgE antibody in mice. *J. Allergy. Clin. Immunol.* 77:616-623.

Murray, A. B., and B. J. Morrison. 1986. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J Allergy Clin Immunol* 77(4):575-81.

Murray, A. B., and B. I. Morrison. 1988. Effect of passive smoking on asthmatic children. *Chest* 94:701.

Murray, V., K. Venables, T. Laing -Morton, M. Partridge, J. Thurston, and D. Williams. 1994. Epidemics of asthma possibly related to thunderstorms. *BMJ* 309:131-132.

Mustafa, M. G., and D. F. Tierney. 1978. Biochemical and metabolic changes in the lung with oxygen, ozone, and nitrogen dioxide toxicity. *Am Rev Respir Dis* 118(6):1061-90.

Nafstad, P., L. Oie, R. Mehl, P. I. Gaarder, K. C. Lodrup-Carlsen, G. Botten, P. Magnus, and J. J. Jaakkola. 1998. Residential dampness problems and symptoms and signs of bronchial obstruction in young Norwegian children. *Am J Respir Crit Care Med* 157(2):410-4.

National Heart Lung and Blood Institute. 1995. Global Intiative for asthma. National Heart Lung and Blood Institute, Bethesda, Maryland.

National Research Council. 1977. Committee on Medical and biological effects of environmental pollutants, Subcommittee on carbon monoxide. Carbon monoxide. National Academy of sciences, Washington.

Neas, L. M., D. W. Dockery, J. H. Ware, J. D. Spengler, F. E. Speizer, and B. G. Ferris, Jr. 1991. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. *Am J Epidemiol* 134(2):204-19.

Neas, L. M., D. W. Dockery, J. H. Ware, and e. al. 1994. Concentration of indoor particulate matter as a determinant of respiratory health in children. *Am. J. Epidemiol* 139(11):1088-1099.

Neas, L. M., D. W. Dockery, J. H. Ware, J. D. Spengler, B. G. Ferris, Jr., and F. E. Speizer. 1994. Concentration of indoor particulate matter as a determinant of respiratory health in children [see comments]. *Am. J. Epidemiol.* 139(11):1088-99.

Nicolai, T., S. Illi, and E. von Mutius. 1998. Effect of dampness at home in childhood on bronchial hyperreactivity in adolescence. *Thorax* 53(12):1035-40.

Norback, D., M. Torgen, and C. Edling. 1990. Volatile organic compounds, respirable dust, and personal factors related to prevalence and incidence of sick building syndrome in primary schools. *Br J Ind Med* 47(11):733-41.

Norback, D., E. Bjornsson, C. Janson, J. Widstrom, and G. Boman. 1995. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. *Occup Environ Med* 52(6):388-95.

Nordman, H., H. Keskinen, and M. Tuppurainen. 1985. Formaldehyde asthma--rare or overlooked? *J. Allergy. Clin. Immunol.* 75(1 Pt 1):91-9.

Ogston, S. A., C. D. Florey, and C. H. Walker. 1985. The Tayside infant morbidity and mortality study:effects on health of using gas for cooking. *B.M.J.* 290:957-60.

ONS. 1996. Family spending: A report on the 1995-1996 family expenditure survey. Office for National statistics, London.

Orehek, J., J. P. Massari, P. Gayrard, C. Grimaud, and J. Charpin. 1976. Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. *J. Clin. Invest.* 57(2):301-7.

Ostro, B. D., M. J. Lipsett, J. K. Mann, M. B. Wiener, and J. Selner. 1994. Indoor air pollution and asthma. Results from a panel study [see comments]. *Am J Respir Crit Care Med* 149(6):1400-6.

Packe, G. E., and J. G. Ayres. 1985. Asthma outbreak during a thunderstorm. *Lancet* ii:199-204.

Packe, G. E., and J. G. Ayres. 1986. Aeroallergens in an asthma outbreak. *Lancet* i:1333-1334.

Palmieri, M., G. Longobardi, G. Napolitano, and D. Simonetti. 1990. Parental smoking and asthma in childhood. *Eur.J.Paediatr.* 149:738-740.

Patel, J. M., and E. R. Block. 1986. Effect of NO2 exposure on antioxidant defense of endothelial cells. *Toxicology* 41(3):343-52.

Peat, J. K., R. H. Van den Berg, W. F. Green, C. M. Mellis, S. R. Leeder, and A. J. Woolcock. 1994. Changing prevalence of asthma in Australian children. *BMJ* 308:1591-1596.

Peters, A., A. Doring, H. E. Wichmann, and e. al. 1997. Increased plasma viscosity during an air pollution episode:a link to mortality. *Lancet* 349:1582-1587.

Platt, S. D., C. J. Martin, S. M. Hunt, and C. W. Lewis. 1989. Damp housing, mould growth, and symptomatic health state [see comments]. *BMJ* 298(6689):1673-8.

Platts-Mills, T. A., R. B. Sporik, L. M. Wheatley, and P. W. Heymann. 1995. Is there a dose-response relationship between exposure to indoor allergens and symptoms of asthma? [editorial]. *J. Allergy. Clin. Immunol.* 96(4):435-40.

Poloniecki, J. D., R. W. Atkinson, A. Ponce de Leon, and H. R. Anderson. 1997. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. *Occup. Environ. Med.* 54:535-540.

Pope, C. I., and D. W. Dockery. 1992. Acute health effects of PM10 pollution on symptomatic and asymptomatic children. *Am.Rev.Respir. Dis.* 145:1123-1128.

Porter, J. A. 1975. Acute respiratory distress following formalin inhalation. *Lancet* 2:603.

Proctor, P. H., and E. S. Reynolds. 1984. Free radicals and disease in man. *Physiol. Chem. Phys. Med. Nmr.* 16:175-195.

Pryor, W. A., and J. W. Lightsey. 1981. Mechanisms of nitrogen dioxide actions, initiation of lipid peroxidation and the production of nitrous acid. *Science* 214:435-437.

Rennie, D., Y. Chen, and J. Dosman. 1994. Damp housing as a risk factor of chronic wheeze and asthma in a community study. *Am. J. Respir. Crit. Care. Med.* 149:A247.

Riedel, F., M. Kramer, C. Scheibenbogen, and C. H. L. Rieger. 1988. Effects of SO2 exposure on allergic sensitization in the guinea pig. *J. Allergy. Clin. Immunol.* 82:527-534.

Rona, R. J., and S. Chinn. 1993. Lung function, respiratory illness, and passive smoking in british primary school children. *Thorax* 48:21-25.

Rowlands, J. R., and E. M. Gause. 1971. Reaction of nitrogen dioxide with blood and lung components. Electron spin resonance studies. *Arch. Intern. Med.* 128(1):94-100.

Rubinstein, I., B. G. Bigby, T. F. Reiss, and H. A. Boushey, Jr. 1990. Short-term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway responsiveness to sulfur dioxide in asthmatic subjects. *Am Rev Respir Dis* 141(2):381-5.

Ruffin, J., V. Evans, S. Banerjee, and U. Banerjee. 1984. A preliminary study of the allergenicity of red oak (Quercus rubra) pollen extract after contamination with some common atmospheric pollutant (e.g. NO2, SO2 and CO). *J Palynol* 20:17-30.

Ruffin, J., M. Y. Liu, R. Sessoms, S. Banerjee, and U. C. Banerjee. 1986. Effects of certain atmospheric pollutants (SO2, NO2 and CO) on the soluble amino acids, molecular weight and antigenicity of some airborne pollen grains. *Cytobios* 46(185):119-29.

Sakula, A. 1975. Formalin asthma in hospital laboratory staff [letter]. *Lancet* 2(7939):816.

Salvaggio, J. E. 1991. The impact of allergy and immunology on our expanding industrial environment. *Journal of allergy and clinical Immunology* 85:689-699.

Samet, J. M., I. B. Tager, and F. E. Speizer. 1983. The relationship between respiratory illness in childhood and chronic airflow obstruction in adulthood. *Am.Rev.Respir.Dis* 127:508-532.

Samet, J. M., M. C. Marbury, and J. D. Spengler. 1987. Health effects and sources of indoor air pollution. Part I. *Am Rev Respir Dis* 136(6):1486-508.

Samet, J. M., W. E. Lambert, B. J. Skipper, A. H. Cushing, W. C. Hunt, S. A. Young, L. C. McLaren, M. Schwab, and J. D. Spengler. 1993. Nitrogen dioxide and respiratory illnesses in infants. *Am Rev Respir Dis* 148(5):1258-65.

Samet, J. M., and F. E. Speizer. 1993. Assessment of health effects in epidemiologic studies of air pollution. *Environ. Health. Perspect.* 101 Suppl 4:149-54.

Sandstrom, T., N. Stjernberg, A. Eklund, M. C. Ledin, L. Bjermer, B. Kolmodin-Hedman, K. Lindstrom, L. Rosenhall, and T. Angstrom. 1991. Inflammatory cell response in bronchoalveolar lavage fluid after nitrogen dioxide exposure of healthy subjects: a dose-response study. *Eur Respir J* 4(3):332-9.

Schenker, M. B., J. M. Samet, and F. E. Speizer. 1983. Risk factors for childhood respiratory disease. The effect of host factors and home environmental exposures. *Am Rev Respir Dis* 128(6):1038-43.

Schwartz, J., U. Ackermann-Liebrich, K. Blaser, G. Bolognini, J. P. Bongard, and e. al. 1994. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). *Am.J.Respir.Crit.Care.Med.* 150:1222-1228.

Schwartz, J. 1997. Air pollution and hospital admissions for cardiovascular disease in Tucson [see comments]. *Epidemiology* 8(4):371-7.

Sexton, K. 1984. Personal exposure to respirable particles:a case study in Waterbury, Vermont. *Atmospheric environment* 18:1385-1398.

Sheps, D. S., M. C. Herbst, A. L. Hinderliter, and e. al. 1990. Production of arrythmias by elevated carboxyhemoglobulin in patients with coronary artery disease. *Ann. Intern. Med.* 113:343-351.

Shumway, R. H., A. S. Azari, and Y. Pawitan. 1988. Modeling mortality fluctuations in Los Angeles as functions of pollution and weather effects. *Environ. Res.* 45:224-242.

Smedley, J. 1996. Is formaldehyde an important cause of allergic respiratory disease? [editorial]. *Clin. Exp. Allergy.* 26(3):247-9.

American Thoracic Society 1996b. Health effects of outdoor air pollution (State of the art). *Am. J.Respir.Care.Med* 153(part 1):3-50.

Somerville, S. M., R. J. Rona, and S. Chinn. 1988. Passive smoking and respiratory conditions in primary school children. *J Epidemiol Community Health* 42(2):105-10.

Speizer, F. E., B. Ferris, Jr., Y. M. Bishop, and J. Spengler. 1980. Respiratory disease rates and pulmonary function in children associated with NO2 exposure. *Am. Rev. Respir. Dis.* 121(1):3-10.

Spengler, J. 1991. Sources and concentrations of indoor air pollution. *In* S. J. Samet J., editor. Indoor air pollution, a health perspective. John Hopkins University Press, Baltimore. 33-67.

Spengler, J., L. Neas, and S. Nakai. 1994. Respiratory symptoms and housing characteristics. *Indoor Air* 4:72-82.

Strachan, D. P. 1988. Damp housing and childhood asthma: validation of reporting of symptoms [published erratum appears in BMJ 1988 Dec 10;297(6662):1500]. *BMJ* 297(6658):1223-6.

Strachan, D. P., M. J. Jarvis, and C. Feyerabend. 1990. The relationship of salivary cotinine to respiratory symptoms, spirometry,and exercise induced bronchospasm in seven year old children. *Am.Rev.Respir.Dis.* 142:147-151.

Stresemann, E., and G. Von Nieding. 1980. The acute effects of 5ppm of nitrogen dioxide on the resistence of the human respiratory tract to breathing. *Staub. Reinhalt. Luft.* 30(6):259-260.

Sutherland, A., and A. P. Hall. 1994. Thunderstorms and asthma admissions. *Lancet* 344:1503-1504.

Tager, I. B., S. T. Weiss, A. Muno, B. Rosner, and F. E. Speizer. 1983. Longitudinal study of maternal smoking and pulmonary function in children. *N.Eng.J.Med.* 309:699-703.

Takafuji, S., S. Suzuki, K. Koizumi, K. Tadokoro, T. Miyamoto, R. Ikemori, and M. Muranaka. 1989. Diesel-exhaust particulates inoculated by the intranasal route have an adjuvant activity for IgE production in mice. *J.Allergy. Clin. Immunol* 90:1-7.

Thomas, T., Jr., and R. A. Rhoades. 1970. 14C-1-palmitate incorporation by rat lung: effect of nitrogen dioxide. *Proc. Soc. Exp. Biol. Med.* 134(4):1181-3.

Touloumi, G., E. Samoli, and K. Katsouyanni. 1996. Daily mortality and ' winter type' air pollution in Athens, Greece - a time series analysis within the APHEA project. *J. Epidemiol. Community. Health* 50(Suppl 1):S47-S51.

Tunnicliffe, W. S., P. S. Burge, and J. G. Ayres. 1994. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet* 344(8939-8940):1733-6.

Turner, C. R., S. R. Kleeberger, and E. W. Spannhake. 1989. Pre-exposure to ozone blocks the antigen-induced late asthmatic response of the canine perpheral airways. *J.Toxicol. Environ. Health.* 28:363-371.

Tuthill, R. W. 1984. Woodstoves, formaldehyde, and respiratory disease. *Am. J. Epidemiol* 120(6):952-5.

Walshaw, M. J., and C. C. Evans. 1987. The effect of seasonal and domestic factors on the distribution of Euroglyphus maynei in the homes of Dermatophagoides pteronyssinus allergic patients. *Clin Allergy* 17(1):7-14.

Wantke, F., C. M. Demmer, P. Tappler, M. Gotz, and R. Jarisch. 1996. Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children. *Clin. Exp. Allergy.* 26(3):276-80.

Ware, J. H., D. W. Dockery, A. d. Spiro, F. E. Speizer, and B. G. Ferris, Jr. 1984. Passive smoking, gas cooking, and respiratory health of children living in six cities. *Am. Rev.Respir.Dis.* 129(3):366-74.

Ware, J. H., J. D. Spengler, L. M. Neas, J. M. Samet, G. R. Wagner, D. Coultas, H. Ozkaynak, and M. Schwab. 1993. Respiratory and irritant health effects of ambient volatile organic compounds. The Kanawha County Health Study [see comments]. *Am J Epidemiol* 137(12):1287-301.

Weiss, S. T., I. B. Tager, F. E. Speizer, and B. Rosner. 1980. Persistent wheeze, its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. *Am. Rev. Respir.Dis.* 122:6697-707.

Weitzman, M., S. Gortmaker, D. K. Walker, and A. Sobol. 1990. Maternal smoking and childhood asthma. *Pediatrics* 85:505-511.

WHO. 1989. Indoor air quality: organic pollutants. Euro reports and studies.

Wieslander, G., D. Norback, E. Bjornsson, C. Janson, and G. Boman. 1997. Asthma and the indoor environment: the significance of emission of formaldehyde and volatile organic compounds from newly painted indoor surfaces. *Int. Arch. Occup. Environ. Health.* 69(2):115-24.

Wieslander, G., D. Norback, and C. Edling. 1997. Airway symptoms among house painters in relation to exposure to volatile organic compounds (VOCS)--a longitudinal study. *Ann Occup Hyg* 41(2):155-66.

Wilhelmsson, B., and M. Holmstrom. 1987. Positive formaldehyde RAST after prolonged formaldehyde exposure by inhalation. *Lancet*(ii):164.

Williamson, I. J., C. J. Martin, G. McGill, R. D. Monie, and A. G. Fennerty. 1997. Damp housing and asthma: a case-control study. *Thorax* 52(3):229-34.

Yanai, M., T. Ohrai, T. Aikawa, H. Okayama, K. Sekizawa, K. Maeyama, H. Sasaki, and T. Takishima. 1990. Ozone increases susceptibility to antigen inhalation in allergic dogs. *J. Appl. Physiol.* 68:2267-2273.