

Prevalence and Risk Factors of Asthma among Cleaners in the North East of England

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Abstract

Introduction

A number of epidemiological studies have shown a significant association between asthma and work as cleaner but reporting schemes and workforce surveys have identified typical features of occupational asthma in only a small minority of cleaners. This discrepancy is due either due to under-reporting by clinician; misattribution of work-exacerbated asthma or other respiratory disease by the epidemiological studies, or the development of occupational asthma with atypical symptoms that make it identifiable epidemiologically but difficult to diagnose clinically.

Hypothesis

The study hypothesis is that cleaners' asthma is induced by chronic low-level irritant exposures that gradually induce airway hyper-responsiveness but do not cause work-related airway constriction/symptoms. It is thus identified by epidemiologists but is not easily identifiable clinically.

Aim

The aim of this PhD is to identify the proportion of cleaners with feature of occupational asthma and to identify risk factors for cleaners' asthma.

Methods

The PhD consists of four phases:

Phase one: A cross-sectional respiratory symptom questionnaire was distributed to 1400 cleaners via their supervisors in 3 local hospital trusts and 2 universities in the North East of England. Those with asthma-like symptoms were invited for Phase two.

Phase two: Airway responsiveness to methacholine was measured in those with physician-diagnosed asthma, asthma symptoms or using inhaler in order to establish the diagnosis of asthma. Results of methacholine test were expressed as the provocation dose causing a 20% decline in forced expiratory volume in 1 second (PD₂₀).

Phase three: Those with measurable airway responsiveness ($PD_{20} \leq 1600\mu\text{g}$) were invited to undergo further investigations to identify the proportion of cleaners with probable occupational asthma. The investigations included a repeat measurement of airway responsiveness away from work and serial peak expiratory flow (PEF) measurements that were analysed for a work-related effect using OASYS software. Subjects further underwent clinical interview. The data collected were summarised and presented to physicians interested in occupational lung disease who were asked to score it from 0% to 100% for the likelihood of occupational asthma.

Phase four: a nested case control study. A detailed work practice questionnaire was distributed to 432 cleaners. Occupational exposures of cleaners with asthma or symptoms suggestive of asthma were compared with controls who were thought unlikely to have asthma.

Results

543 of an estimated 1400 number of cleaners (39%) returned the questionnaire. It is uncertain how many received it and so the true response rate is itself uncertain.

Asthma-like symptoms were common. 49% (264/543) cleaners reported at least one respiratory symptom: 34% reported wheezing, 36% reported cough, 10% reported breathlessness and 12% reported chest tightness.

Seventy three cleaners (14%) reported physician-diagnosed asthma. In 32% ($n=23$) the asthma developed after they started work as a cleaner with a mean interval of 8 years. The incidence of work-related asthma was 4.6/1,000 person-years.

179 subjects with respiratory symptoms were invited for clinical tests. Of these, 54 (30%) attended for methacholine challenge testing. 25 (46%) of those tested had quantifiable results.

13 subjects underwent serial methacholine measurements at and away from work. Overall, there were no significant changes in airway responsiveness. Geometric mean PD_{20} at work was 190 μg and away from work was 259 μg (Geometric mean ratio=1.4, 95%CI 0.6 to 3.2). Five (38.5%) cleaners showed a

3-fold or more increase in PD₂₀ away from work raising the possibility of significant changes in those individuals.

13 subjects completed serial PEF measurements. The mean OASYS score was 2.2. Three subjects (23%) had a score of > 2.5 suggesting a work related effect.

Asthma was significantly associated with frequent use of bleach, adjusted OR 2.9 (95% CI 1.4 to 6.1) and mixing cleaning products, adjusted OR 2.7 (95% CI 1.2 to 6.0). The proportion of cases who frequently used spray was higher than controls but the difference was of borderline statistical significance, adjusted OR 1.9 (95% CI 0.9 to 4.1).

Case summaries of ten subjects were presented to be assessed for the likelihood for occupational asthma. None of the cases presented to expert physicians were identified as having probable occupational asthma when the assessing physicians relied on clinical histories alone, i.e. the average occupational asthma probability was < 50%. Two cases were identified as probable occupational asthma (occupational asthma probability score > 50%) when the results of the investigations were considered.

Conclusion

The incidence of asthma amongst cleaners in this study is consistent with other epidemiological evidence showing that they have a 1.5 to 2.0 fold increased risk of asthma. None of the asthmatic cleaners had clinical histories that were suggestive of occupational asthma but up to five cleaners (40%) had some evidence of occupational asthma from conventional clinical diagnostic tests. The findings are consistent with the hypothesis that cleaners develop their asthma in an unusual way, possibly through a low-dose irritant mechanism.

Statement of contribution

This thesis is composed of my original work, and contains no material previously published or written by another person except in advisory capacity.

This thesis has not been submitted for the award of any other degree at any other institution.

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Abbreviations

CI	Confidence interval
COPD	Chronic pulmonary obstructive disease
ECRHS	European community respiratory health survey
FEV ₁	Forced expiratory volume in one second.
FVC	Forced vital capacity
GP	General practitioner
IgE	Immunoglobulin E
OASYS	Occupational asthma system
OR	Odds ratio
PC	Provocation concentration
PD	Provocation dose
PEF	Peak expiratory flow
RADS	Reactive airway dysfunction syndrome
RR	Relative risk
SENSOR	Sentinel event notification system
SWORD	Scheme for work-related respiratory disease
UK	United Kingdom

Chapter 1 Introduction

1.1 A brief introduction to the association between asthma and work as a cleaner

Asthma is a chronic inflammatory lung disease characterized by recurrent episodes of wheeze; breathlessness; cough; and chest tightness that is associated with airway obstruction. The cause of asthma is often unknown. In adults, asthma can be caused by certain exposures at work, and this is called occupational asthma.

Occupational asthma has become the most prevalent occupational disease in developed countries. It accounts for about 15% of all asthma in adults.¹ There are believed to be two main mechanisms: sensitiser-induced occupational asthma and acute irritant induced-asthma, also called reactive airway dysfunction syndrome (RADS). Many occupations are recognized by epidemiologists and physicians as ones where there are possible exposures to sensitisers or high doses of irritants.

In recent years, growing epidemiological evidence has reported a link between asthma and occupations in which workers are neither exposed to obvious sensitisers nor to high-levels of irritants. Instead, the main recognized occupational exposure is to low levels of irritants. This has highlighted the possibility of a new type of occupational asthma induced by chronic exposure to low level of irritant, so-called low-dose irritant-induced asthma.

One possible example of an occupation with low level exposures to irritant agents and an increased risk of asthma is cleaning. Cleaners were not known to be at higher risk of developing asthma until the 1990s when the European Community Respiratory Health Survey (ECRHS)² conducted in 11 countries showed that they had double the risk of asthma (OR=2.0) compared to office workers. Several other studies^{3, 4} have shown risk factors for asthma in cleaners between 1.5 and 1.7, and this confirmation of increased asthma incidence in cleaners suggests that some of the excess may be linked with their work. Despite the accumulated epidemiological evidence, reporting schemes have identified occupational asthma in only a small proportion of cleaners. That

suggests that either occupational asthma amongst cleaners is under-reported or they present with atypical symptoms and go undiagnosed by clinicians.

The hypothesis of this PhD is that cleaning-induced asthma is an example of low-dose irritant-induced asthma. If cleaners' asthma is induced gradually, there may be few symptoms on day to day or week basis that allow the typical work-related features to be recognized by the physicians.

1.2 Aims and objectives

The study aims were:

1. To identify the proportion of cleaners that have evidence of an occupational cause of their asthma; and
2. To identify risk factors for their asthma.

Objectives were:

1. To assess the prevalence of asthma and other respiratory symptoms in cleaners.
2. To investigate the association between atopy and smoking status and the risk of developing asthma among the cleaners.
3. To identify the clinical features of possible occupational asthma among cleaners.

1.3 A brief description of the presentation of the thesis

The thesis is organized into 8 main chapters:

Chapter 1 "introduction" addresses the importance of studying asthma amongst cleaners and provides the reader with an overview of the organisation of the thesis.

Chapter 2 "scientific background" comprises two main sections. The first section describes the identification of asthma in both clinical settings and in epidemiological research. The second section discusses types of work-related asthma and the basic guidelines for clinical and objective evaluation. This is followed by a discussion of diagnosing occupational asthma in the United Kingdom (UK). The end of this section describes two approaches often used to

study occurrence of occupational asthma, namely epidemiological studies and monitoring schemes.

Chapter 3 “critical review of epidemiologic literature on asthma among cleaners” reviews detailed evidence about asthma in cleaners and the studies that investigated possible risk factors.

Chapter 4 presents the study’s hypothesis, aims and objectives.

Chapter 5 “methods” describes the design of the study in five sections. It starts with describing the preparatory phase for the study, e.g. meeting with managers and work visit surveys. This is followed by a description of the four main phases of the study: a cross sectional survey; a clinical study for verification of asthma diagnosis; the investigation for probable occupational asthma; and the identification of risk factors of asthma using a case-control design. The methods for subject recruitment; the research tool(s); and data analysis are described for each phase.

Chapter 6 “results” presents the findings of the different phases in the study. It starts with a general description of the study subjects. This is followed by detailed results of the cross-sectional survey, the clinical and the case control studies.

Chapter 7 “discussion” discusses the findings under three main headings:

“Did this study demonstrate a higher than expected prevalence of respiratory symptoms and asthma in cleaners?”, “Do the clinical features and/or the results of the investigations allow a diagnosis of occupational asthma to be established in any of the individual cleaners ? If so, is that the number of cleaners that would be expected to have occupational asthma in this cohort?”, and “Do the results indicate a specific cause of occupational asthma in cleaners?” This is followed by discussion of the limitations and strengths of the study, and its implications.

Chapter 8 “conclusion” and recommendations” provide an overall conclusion of the thesis and recommendations for future studies and policy makers.

Chapter 2 **Scientific background**

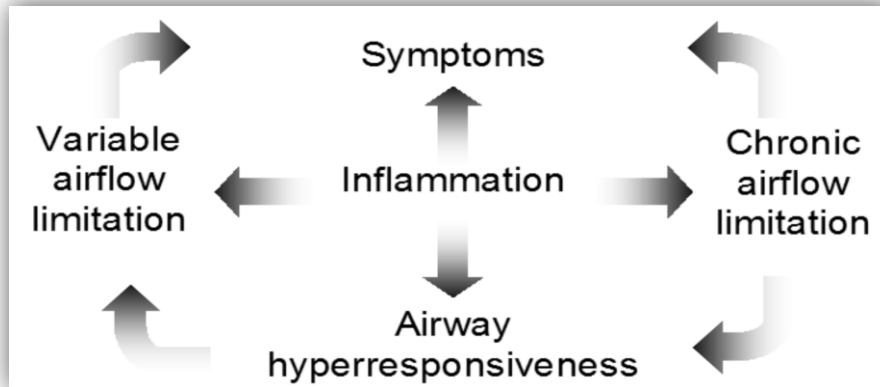
2.1 Introduction

This chapter comprises two main sections. The first starts by presenting a brief review of asthma research. This is followed by a discussion of approaches for identifying asthma in clinical settings as well as in epidemiological research. The second section gives particular emphasis of one type of asthma, i.e. work-related asthma. This section starts by describing the types of work-related asthma and discussing the different diagnostic tools which are used. The second part of the section describes the different sources of information relating to the study of occupational asthma and its risk factors. It discusses, in particular, epidemiological approaches and monitoring schemes.

2.2 Asthma

Asthma is a chronic respiratory condition encountered clinically in both children and adults. It is an inflammatory disease of the airways the cause of which is usually unknown though sometimes it can be induced by identifiable exposures such as sensitizing chemicals. The inflammatory reaction leads to the release of cellular mediators which stimulate airway smooth muscle contraction and mucus production. These changes lead to the physiological hallmarks of asthma which are variable airflow limitation and increased airway responsiveness. The latter is a state characterized by the tendency of the airway to narrow easily in response to various stimuli. Clinically, patients present with recurrent episodes of difficulty in breathing, wheeze, chest tightness and cough, the cardinal features of asthma, figure 2-1.

Figure 2-1 The interplay between airway inflammation and the clinical symptoms and the physiology of asthma⁵

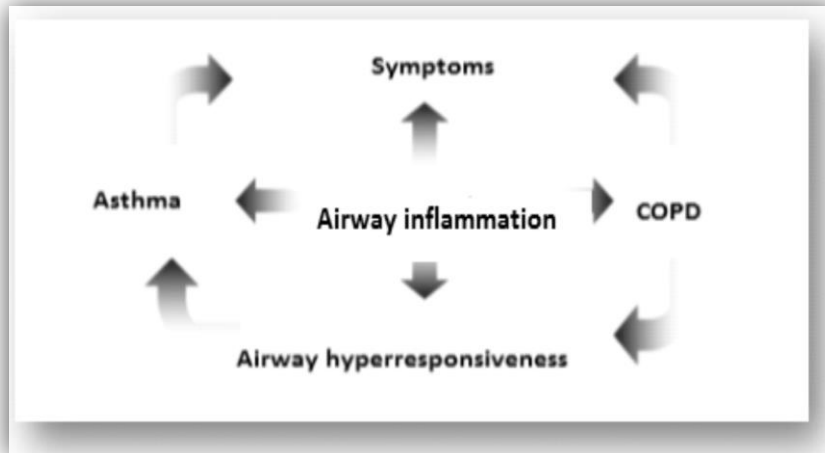


Despite the presumed interdependency of these elements (inflammation; physiological abnormality and symptoms), there is no direct relationship between them. This is illustrated by many studies which have failed to identify a relationship between the extent of airway inflammation, as assessed by cellular infiltration, and the degree of airway responsiveness.^{6,7} Moreover, several studies have demonstrated a poor correlation between asthma symptoms and the level of airway obstruction.^{8,9}

Asthma encompasses a wide range of severity and patients differ markedly in their clinical manifestations, the extent of lung dysfunction, and in the underlying inflammatory process. Asthma also varies within individuals over time. Clinicians recognize several asthma phenotypes and acknowledge that asthma is a heterogeneous disease. Both genetic and environmental factors play a role in asthma diversity. This wide spectrum of disease severity and the underlying pathological and pathophysiological features create difficulties in both defining and diagnosing asthma.

Further diagnostic difficulty occurs because other airway diseases, such as chronic obstruction pulmonary disease (COPD), overlap with asthma in relation to their pathophysiology and have many symptoms in common, figure 2-2.⁵

Figure 2-2 The overlap between asthma and chronic obstructive airway disease in mechanism⁵



Recent consensus documents define asthma by merely describing the disease:

“A chronic inflammatory disorder of the airways that causes episodes of wheezing, breathlessness, chest tightness, and coughing that are usually associated with variable airflow obstruction. The inflammation also causes an increase in the bronchial hyper-responsiveness”¹⁰

This definition neither reflects asthma heterogeneity nor differentiates it from other airway diseases, and, most importantly, it does not give clear criteria for deciding whether an individual has asthma or not.⁵

In the absence of a universally accepted definition, many guidelines have been published to help clinicians in recognizing asthma.^{11, 12} Central to all guidelines is the identification of the characteristic symptoms, the demonstration of reversible airway obstruction and/or airway responsiveness, as well as the exclusion of other conditions.

2.2.1 Clinical definition of asthma

An initial assessment of an individual with suspected asthma generally includes a medical history, physical examination and pulmonary function testing.

A comprehensive history should cover chest symptoms (duration, time of onset, triggers); potential risk factors (history of atopic disease, family history of asthma, work history) and smoking habit.¹³

The purpose of the clinical examination is mainly to detect expiratory wheeze, other allergic diseases such as eczema, and to exclude any co-existing conditions.¹⁴

If the symptoms raise the possibility of asthma, demonstrating airflow obstruction and its reversibility help in establishing the diagnosis. Spirometry is the recommended tool to evaluate airflow obstruction.^{12, 15} It measures two parameters: 1) forced vital capacity (FVC), defined as maximum volume of air that can be forcibly expelled from the point of deepest inspiration, and 2) forced expiratory volume in one second (FEV₁) which is the volume of air exhaled in the first second of FVC. An obstructive abnormality is indicated by a reduced FEV₁/FVC ratio of less than 70%.¹⁶ Reversibility of airway obstruction is the improvement in FEV₁ by 20% after the administration of a short-acting bronchodilator compared with the pre-bronchodilator value.¹² However, because of the episodic nature of asthma, it is not uncommon for an individual to have normal spirometry at the time of testing.

If the symptoms suggest asthma but airflow obstruction and/or reversibility are not demonstrable, then measuring airway responsiveness may help to validate the diagnosis. In asthma, airways narrow excessively in response to non-specific stimuli at a level that would not affect non-asthmatics. This is known as airway hyper-responsiveness.¹⁷ Airway responsiveness is quantified by a airway challenge test with a chemical (e.g. methacholine, histamine) or a physical (e.g. exercise) stimulus that provokes short-lived bronchoconstriction.¹⁸ Asthmatics respond to the stimulus with a greater degree of obstruction, usually measured by FEV₁, than non-asthmatics.¹⁹ Provided that the test is carried out properly the absence of airway hyper-responsiveness indicates that asthma is unlikely. There are, however, a number of factors that confound the measurement of airway responsiveness. The use of medications such as corticosteroids or bronchodilators can reduce airway hyper-responsiveness or antagonise the effects of bronchoconstrictors and can produce false-negative tests.

Equally, a positive airway responsiveness measurement is not a specific test diagnostic for asthma because other conditions, e.g. COPD, are also associated with airway hyper-responsiveness.²⁰ Hence, there is no one test that

can always and reliably identify asthma and an overall assessment of the combined information obtained is needed to make a final clinical diagnosis.

A major difficulty in defining a case of asthma is that the parameters used to establish the diagnosis, i.e. FEV₁ and airway responsiveness, have a continuous distribution in the general population.^{21, 22} There is not a clear discriminatory cut-off point separating asthmatic from non-asthmatic individuals. Therefore, any cut-off point selected to define an abnormal test is arbitrary and may misclassify asthma status of some individuals.

In the United Kingdom (UK), almost all asthma is diagnosed in general practice and traditionally there was under-use of spirometry to confirm the diagnosis as suggested by reports in the 1990s.^{23, 24} Bellamy *et al*,²³ for example, found that of 582 randomly selected UK general practices, spirometers were available in 186 (32%), and open access to spirometry services were available for only 103 (11%) of those without spirometers. This encouraged reliance on the medical history alone which is likely has led to misdiagnosis of asthma.^{25, 26} In 2004, however, guidelines and incentives were introduced to promote and improve asthma diagnosis using objective tests. Reports showed that, since then, spirometry has been more often available²⁷ and is increasingly used to confirm an asthma²⁸ diagnosis. Availability of spirometry however does not necessarily ensure an accurate diagnosis if the quality of data produced is poor or if the professional is not qualified to interpret the data.^{27, 29} Bolton *et al*²⁷ for example, investigated the availability; use; and the interpretation of spirometry in 227 practices in Wales after 2004. The authors found that most practices (82%) had spirometry and used it (86%), but only 58% of them were confident in its use and 34% in the interpretation of the results. These two issues suggest that there are still questions about the validity of asthma diagnosis in the UK. Furthermore, airway responsiveness is not considered a routine test in the UK and has not been introduced in primary care or even in some hospitals.

Given that patients' medical records are a common source for studying or monitoring disease prevalence and trends, misdiagnosis has implications for the validity of record-based outcomes. An example of this is the study carried out by Hansell *et al*³⁰ in which the epidemiology of asthma and COPD was examined using four different sources of routine data, such as hospital admissions and

primary care consultations. These sources are usually used for surveillance purposes in the UK. The study demonstrated inconsistent asthma rates across data sources and that was partly attributed to disease misdiagnosis. Uncertainties about asthma prevalences based on analyses of medical records or surveillance schemes are increased by the failure of a substantial proportion of potential asthmatics to report their symptoms to their general practitioners (GPs).^{25, 31} Under-reporting to GPs can be attributed to several factors including poor access to medical services,³² having mild and infrequent attacks, or attributing symptoms to other factors particularly smoking. Furthermore, some individuals with probable asthma may not seek medical help if they do not perceive or only perceive poorly the sensations associated with the airway narrowing of asthma. This is demonstrated by Van Schyack *et al*²⁵ who found that subjects who did not notice dyspnea during histamine airway challenge test (n= 9 of 47) were less likely to present with asthma symptoms to their GPs in spite of their impaired lung function. A few studies have investigated factors influencing perception of asthma symptoms.³³⁻³⁵ Barraclough *et al*,³³ for example, assessed the perception of bronchoconstriction of 615 subjects, aged 20-44 years. These subjects underwent methacholine tests and were asked whether they were aware of any abnormal respiratory sensation at the point of maximal bronchoconstriction at the end of the methacholine test and whether it had ever been experienced before. The authors found that being female and younger were predictors of the ability to perceive methacholine-induced bronchoconstriction. In another study by Brand *et al*,³⁵ female sex and younger age were also shown to be predictors of good perception as were atopy and severe baseline airway responsiveness. The mechanism of poor perception of breathlessness is not fully understood. Connolly and co-workers suggested aging to be the main cause,³⁶ while others consider it an adaptive response to persistent severe bronchial constriction.³⁷

In summary, asthma is a disease with a wide range of presentations. Although a systematic approach is possible to help establish a reliable clinical diagnosis, treating physicians still have to rely on some degree of judgment when assessing symptoms, lung function and possibly measures of airway responsiveness to arrive at a final interpretation. There is always a possibility for misdiagnosis, and that increases when the history alone is relied on. While both

under- and over-diagnosis are possible outcomes, under-diagnosis is more likely in the general population because patients often do not seek medical help.²⁵

To gain more insight into the burden of asthma, this hidden proportion of patients needs to be identified. This can be carried out in epidemiological studies which investigate the general population instead of focusing only on individuals labelled with a disease. However, given the lack of a clear definition of clinical asthma, the question now becomes “how should asthma be defined in population studies?”

2.2.2 Asthma identification in epidemiological studies

As noted above, asthma is a heterogeneous condition that is not easy to define or diagnose. Considerable efforts have been made to overcome this and develop methods for identifying asthma among participants in population studies. In general, three main methods have been used: 1) self-reported asthma and asthma symptoms; 2) physiological measurements of airway responsiveness; and 3) a combination of both.

Epidemiological studies rely heavily on questionnaires to detect the presence of asthma since they are practical and cost efficient screening tools.

A question about asthma confirmed by a doctor is often used to identify cases. Since almost all people without asthma would not report having asthma in the questionnaire, it is specific question.³⁸ The main problem with this measure however is that it has been shown to underestimate asthma prevalence, i.e. it is not sensitive.^{39, 40} Under estimation could be due to under-diagnosis of asthma. For instance, in a study by de Marco and colleagues,³⁹ panels of respiratory physicians assessed 811 adults for current asthma based on their response to a respiratory questionnaire and on the results of respiratory and immunological tests. They showed that 34% of adults in whom the results were thought to be highly suggestive of asthma were not previously diagnosed with asthma. Another possible reason for underestimating asthma prevalence using this question is under-reporting of asthma by the subjects who have been diagnosed with asthma. In another longitudinal study,⁴⁰ 289 adults were diagnosed with adult-onset asthma at the baseline based on history and

objective tests, and were classified based on their medication into severe or mild asthma. Ten years later, when they were mailed an asthma questionnaire, 13% reported never having had asthma. All were mild asthmatics.

Another issue with this definition of asthma, i.e. doctor-diagnosed, is that it is highly dependent on the physicians' diagnostic experience. This is illustrated by a study in which airway responsiveness measurements were performed for 304 adults reported to have physician-diagnosed asthma.⁴¹ It was found that 27% of these adults had normal spirometry and airway responsiveness.

Therefore, rather than simply relying on reports of a previous diagnosis of asthma, epidemiologists have focused on developing questionnaires based on symptoms that characterise asthma (wheeze; chest tightness; breathlessness and cough). This has the advantage of collecting information similar to those obtained in a clinical consultation, yet from a larger number of subjects. This approach allows the recognition of asthma in those never diagnosed before. Hence, a number of studies using symptoms questionnaires have often found the prevalence of asthma symptoms to be substantially higher than the prevalence of physician-diagnosed asthma.⁴²⁻⁴⁵ The ability of self-reported asthma symptoms to identify true asthmatics was tested by comparing it with the results of airway responsiveness measurements or clinical assessment by a specialist.⁴⁶ An important point to emphasize here is that there is no 'gold standard' for the diagnosis of asthma. Nonetheless, both airway responsiveness measurements and clinical assessment were considered appropriate for the purpose. Studies that have compared asthma symptoms to these gold standards found that of all asthma symptoms, self-reported wheeze has been repeatedly shown to be a highly sensitive question.⁴⁷ Thus, respiratory questionnaires in general focus on wheeze in different circumstances (after exercise, at night and so on).

Asthma symptoms have lower specificities than questions about physician-diagnosed asthma since they occur in other conditions (e.g. COPD and heart disease). Therefore, using them to identify asthma inevitably gives rise to false positive diagnoses. A combination of symptom-based items rather than individual symptoms has been shown to improve questionnaires' ability to distinguish asthmatics from non-asthmatics.⁴⁸ Venbles *et al*⁴⁹ found that the

false positive rate can be reduced from around 25-30% to 6-8% if asthma is defined by reporting three or more symptoms instead of relying on one symptom.

The accuracy of the data obtained by questionnaires is dependent on subjects' lay understanding.^{50, 51} In a study by Devereux and colleagues,⁵⁰ 876 adults answered an asthma symptom questionnaire and underwent measurements of airway responsiveness. At the end of the test when the subjects were bronchoconstricted, they were asked to describe their chest symptoms using the terms: 'wheeze', 'tightness' or 'breathlessness' if appropriate. Little agreement was found between the symptoms reported on the questionnaire and the symptoms used to describe their chest sensations. This is consistent with a study in which 601 adult were asked to answer a standardized ECRHS asthma questionnaire.⁵¹ In a second visit, the investigators explained and demonstrated asthma symptoms and then asked the subjects to answer a different questionnaire related to the symptoms which had been demonstrated including wheezing at rest and exercise-induced wheezing. The authors found a poor agreement between the asthma symptoms reported on the standard questionnaire and symptoms reported following a demonstration of the actual asthma symptoms. Indeed, there was a 30 to 60% reduction in asthma symptom prevalence following the demonstration compared to those obtained from the standard questionnaire.

Cultural beliefs might also influence subjects' responses. In Brazil, for example, Macaira and co-workers⁵² observed a low frequency of positive responses to asthma questions among subjects with physician-diagnosed asthma. It was found that the local community preferred using the term 'bronchitis' to describe their condition as they believed that 'asthma' is an incurable disease while bronchitis is not.

Dales and co-workers⁵³ also pointed out that subjects' psychological status at the time of filling in a questionnaire would affect his/her reporting of respiratory symptoms. A significant relationship has been found particularly between anxiety/depression and self-reporting of wheeze; waking up with attacks of breathlessness and attacks of breathlessness after activity.⁵⁴

The wording of the questionnaires, the order of questions or translation can all have important influences on the responses to questions and the quality of the data collected. In one study,⁵⁵ bilingual participants were asked to answer the same questionnaire in two languages, English and French. Inconsistency was found in their response to 'wheeze' which was due to the difficulty in finding an equivalent word for it in French. Another study reported a significant difference in the prevalence of asthma symptoms after re-phrasing of the respiratory questions.⁵⁶

Because of the potential problems arising from the subjective symptoms' recognition and questionnaire wording, epidemiologists have often utilized objective measurements of airway responsiveness to identify asthma. This is because airway responsiveness can be measured safely using a standardized method and is known to be related to other measures of asthma activity such as medication use.⁵⁷

Airway responsiveness tests using methacholine or, to a lesser extent, histamine are widely used to document the presence or absence of airway responsiveness and to quantify it. To start the test, a subject is evaluated for eligibility including having an adequate baseline FEV₁, usually defined as FEV₁ greater than 60% or 70% of the predicted value.⁵⁸ Subjects then are exposed to an aerosol of the provocation agent in incremental doses. FEV₁ is measured shortly after inhalation of each dose and the test stops if there is a fall in FEV₁ of a predetermined percentage (usually 20%) compared to the baseline, or if the chosen maximum concentration of the agent is reached. The provocation concentration (or dose) that causes 20% reduction in FEV₁, is used to indicate the level of airway responsiveness i.e. PC₂₀, or PD₂₀. Subjects are considered asthmatic if the value of PD₂₀ is less than a predetermined value. Whether the results of the challenge are expressed in terms of concentration (PC₂₀) or dose (PD₂₀) depends on the method used to administer the methacholine.

A major limitation of airway responsiveness measurements is that many technical factors affect the precision of the results including factors related to the nebulizer output,⁵⁹ measurements of response (i.e. FEV₁); preparation, handling of methacholine solutions and the breathing pattern of the subjects.⁶⁰ Although guidelines have been published by the American Thoracic Society to

ensure control of these factors, the test results are highly dependent on adherence to the guidelines and managing the equipment properly, particularly with regard to the calibration and maintenance of nebulizers as these have important influences on aerosol output.

At present, there are two main protocols for the administration of the methacholine, namely the 2-minute tidal breathing method and five-breath dosimeter method.¹⁸ In the first technique, aerosol is generated by a nebulizer over a period of 2 minutes and the subject inhales this via a face mask or mouth piece during tidal breathing.¹⁸ Since the dose delivered during inhalation depends on breathing rate; tidal volume; and the nebulizer output, which has been found to vary over time,¹⁸ the exact delivered dose is not readily quantified and so the results are expressed as the concentration of methacholine rather than dose, i.e. (PC₂₀).

In the five breath dosimeter method, the nebulizer is attached to a dosimeter to ensure accurate dose delivery of the methacholine aerosol.¹⁸ The subject inhales aerosol in a single slow deep breath for five seconds and the inspiratory maneuver is repeated five times before measuring the FEV₁. Using a dosimeter makes it possible to estimate the actual dose of methacholine provoking a 20% decrease in FEV₁ and hence the result is expressed as provocation dose (PD₂₀) rather than concentration. This method has been found to measure airway responsiveness more precisely than the tidal breathing method. This is illustrated by the Beach *et al* study⁶¹ which investigated the importance of the precision of methacholine delivery and the technique of assessing FEV₁ on the repeatability of the airway responsiveness measurements. In the study, 20 asthmatic subjects performed four methacholine tests: two tests used the dosimeter method and two the tidal breathing method. The authors used two different methods to assess the FEV₁ at each time, the lower of two measurements, which was the recommended method, and the mean of the best three of six measurements, which was their preferred technique. The duplicate tests were compared and the precision of the PD₂₀ or PC₂₀ was evaluated. It was found that by using the dosimeter method coupled with the best 3 of 6 FEV₁ assessments the airway responsiveness measurements were repeatable within ± 1.5 doubling doses. On the other hand, the repeatability of measurements using the tidal breathing nebulizer method was within ± 5

doubling doses. The use of very different techniques with different sensitivities and repeatabilities makes much of the literature on the airway responsiveness difficult to interpret.

As noted earlier, the degree of airway hyper-responsiveness is unimodally distributed in the general population.²² Therefore, there is a continuum of airway responsiveness in the normal population that overlaps with that in the asthmatic population with no sharp dividing line between asthmatics and non-asthmatics subjects.^{21, 22} However, in most population studies, participants are dichotomised in to those “with” and those “without” airway hyper-responsiveness using different cut-off doses which are all arbitrarily defined.⁵⁸ Changes in the cut-off level mean that the test’s ability to detect asthma can vary substantially. This has been demonstrated in a study of 300 adults, including asthmatics, defined as having asthma symptoms and reversible airway obstruction, and non-asthmatics, who performed a methacholine test. While a cut-off point of ≤ 15 mg/ml identified 86% of the asthmatics, choosing a cut-off point of 2.5 mg/ml identified only 36%.⁶²

Airway responsiveness measurements are neither wholly sensitive nor specific for asthma.^{20, 63} Indeed, early evidence found that airway hyper-responsiveness is associated with other medical conditions, some of which are common such as the common cold.²⁰ In addition, several community studies of adults have shown that airway hyper-responsiveness is significantly associated with atopy, particularly in young adults, and with smoking.^{64, 65} Moreover, airway hyper-responsiveness is not uncommon among subjects who are apparently healthy with no respiratory symptoms.⁶⁶ For instance, one study found that around half of all adults with airway hyper-responsiveness had no other features of asthma when they were assessed carefully by a trained respiratory physician.⁶³

A negative challenge test also does not fully exclude asthma. Lung function can return to normal if the individual stays away long enough from the relevant stimulus such as specific occupational exposures or pollens.^{67, 68} This can be illustrated by Mapp *et al*⁶⁹ who investigated the time course of airway responsiveness induced by isocyanates. In the study, 6 subjects who had asthma caused by work exposures to isocyanates were exposed in a laboratory setting to isocyanates. Their airway responsiveness was assessed before

isocyanates exposure and then re-assessed at 8 hours, 1 day, 1 week and one month after exposure. It was found that airway responsiveness increased shortly after exposure but recovered completely within 1-4 weeks after cessation of exposure. In addition, using medications that antagonise methacholine, e.g. antidepressants and antipsychotics, can lead to false-negative tests.⁶⁸ Prolonged use of inhaled corticosteroids among asthmatics can also dramatically improve methacholine-induced airway hyper-responsiveness.^{70, 71} Furthermore, it has been reported that challenges with methacholine or histamine can be negative in cases of exercise-induced asthma, particularly among athletes.⁷²

Despite all these caveats, measuring airway responsiveness is still likely to be a useful adjunct particularly if researchers are assessing changes in the prevalence of asthma symptoms in a population.⁷³ For example, an increase in asthma symptoms and diagnosed asthma over 10 years was documented in the UK, but the prevalence of the measured airway responsiveness remained almost the same over the same period. This observation suggested that the trend was caused by reasons other than a real increase in asthma.³³

Since airway responsiveness measurements by themselves can produce false positive results, it has been proposed that combining them with asthma symptoms would be the most useful definition of asthma for epidemiological studies.⁷⁴

The effectiveness of this definition in identifying asthma has been studied in two general population surveys.^{39, 63} Both found that combining airway responsiveness measurements with asthma symptoms was highly specific for asthma but achieved a low sensitivity. In Jenkins *et al* study,⁶³ for example, 91 adults aged 28-44 years and 168 children aged 13-14 years answered standardized asthma questionnaires and carried out airway responsiveness measurements. In addition, they were assessed by a respiratory physician who was blinded to the results of other investigations. The physician's assessment was considered the diagnostic gold standard. Airway hyper-responsiveness plus asthma symptoms was highly specific for asthma among adults (99%) and children (94%) but had low sensitivity (39% and 47% respectively). This was thought to be explained by asthmatic subjects having negative airway

responsiveness measurements due to factors including medications or being away from asthma triggers. The absence of a true gold standard asthma diagnosis is a major limitation to this approach. Although clinical assessment is often used, it is affected by diagnostic habit and there is always the possibility of misdiagnosing cases. Therefore, the true sensitivity of this definition of asthma, i.e. asthma symptoms + airway responsiveness, is uncertain.

To use symptom questionnaires and airway responsiveness testing efficiently, researchers have developed a strategy in which a questionnaire survey is performed first in a large number of people, phase-I, followed by an intensive examination of airway responsiveness and lung function in a subsample (phase-II).⁷⁵ This approach has been used by the ECRHS⁷⁶ which has made a considerable contribution to asthma epidemiology, particularly in adults. The ECRHS is the largest survey conducted among adults aged 20-44 years in 11 mainly European countries. In phase-I, screening respiratory questionnaires were distributed among adults from pre-determined geographical areas in each of the participating countries. In phase-II, more detailed questionnaires and further tests including airway responsiveness measurements and allergy tests were performed for two samples: 1) a random sample that was selected from the responders to the screening questionnaire, and 2) an additional sample consisting of all subjects who answered positively to asthma related questions in the screening questionnaire in phase-I. The first ECRHS study (ECRHS-I) was conducted in 1990-1995, mainly to estimate the prevalence of asthma. Eight years later, ECRHS-II was conducted to estimate the incidence and the risk factors for asthma.

Asthma in this survey was defined as “woken by an attack of shortness of breath”; “having an asthma attack” or “taking asthma medication” in the last 12 months. Although wheeze has a high sensitivity for identifying asthma, it was not used in ECRHS as it is related to age and sex, and it was thought to risk introducing bias in a comparison between populations with different demographic structure.⁴² Therefore, questions about shortness of breath and attack of asthma were used because these have a reasonable sensitivity and specificity⁴⁷ and were found to introduce the least bias when used to compare populations.⁴² Asthma medication use, equally,⁴² is found to be strongly related to being woken up by shortness of breath.⁴²

The ECRHS has drawn the world's attention to the considerable variation of asthma prevalence between countries. This ranged from 2.0% to 11.9%⁷⁷ with a median of 4.5%.⁴⁵ The variation in prevalence appeared to be a real finding as airway hyper-responsiveness prevalence was found to vary geographically in the same pattern as asthma symptoms.

To summarize, symptom-based questionnaires appear to be the survey tool with the highest sensitivity to identify asthma epidemiologically, and previously established diagnosis is the most specific. However, these two are influenced by perception of symptoms and diagnostic trends. Airway responsiveness measurements, on the other hand, have the advantage of being objective and not influenced by these factors but have lower sensitivity. An approach has been suggested by epidemiologists that researchers should combine questionnaires with airway responsiveness measurements. This strategy was thought to give a more reliable picture about asthma prevalence and trends.

It should be emphasized that the aim of a particular epidemiological study is the key issue when considering the choice of survey tools. If the aim, for example, is to estimate the risk of developing asthma, then a definition with as high specificity as possible would be the most useful as false positives would dilute the risk estimate. However, if the researcher's aim is to identify as many cases as possible, such as in screening a workplace for potential cases of asthma, then sensitive questions such as those about "wheeze" are needed.

2.3 Work-related asthma

There has been growing evidence over the last few decades that asthma prevalences have changed globally in a too short a period of time to be explained by changes in genetic factors. Researchers, thus, have directed their interest toward identifying environmental risk factors for asthma. Occupational exposures provide some of the most potent environmental asthma risks. Indeed, in an early paper published using the ECRHS data, Kogevinas *et al* (1996),⁷⁸ identified work exposures as a substantial risk factor being associated with around 15% of adult onset asthma.¹ Work-related asthma is currently the most prevalent occupational lung disease in industrialized countries.

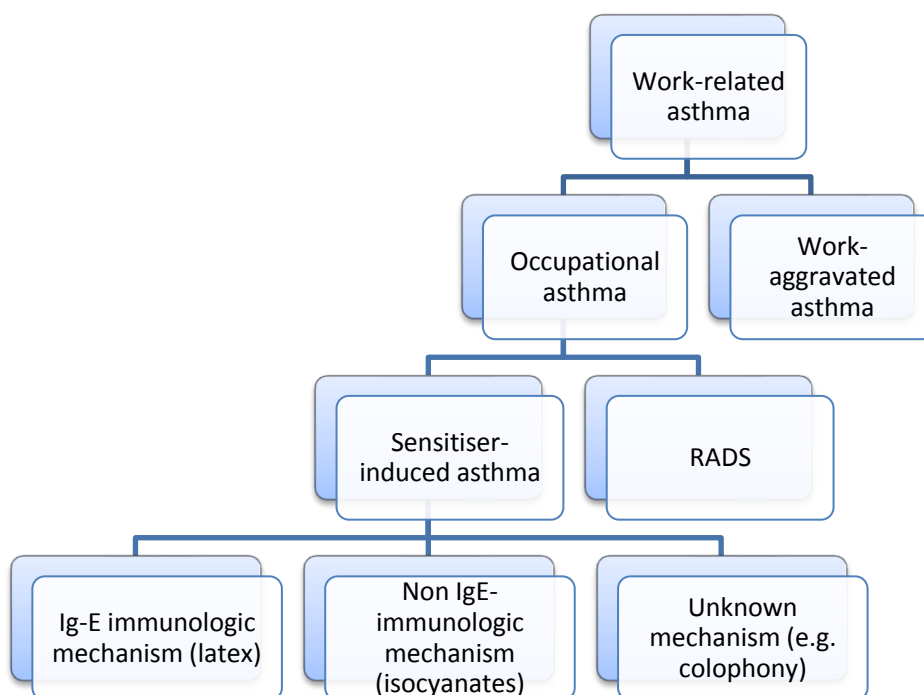
Work-related asthma is a broad term that encompasses work-exacerbated asthma and occupational asthma.

Work-exacerbated asthma is a transient worsening of pre-existing or coincident new onset adult asthma and/or an increased need for asthma medication due to non-specific exposures at work such as dust; fumes; dry air and exercise.⁷⁹ Occupational asthma, on the other hand, is a distinct subset of work-related asthma that was defined by a UK-based expert panel (2006) as “*asthma induced by exposure in the working environment to dust; vapours or fumes with or without pre-existing asthma*”.⁸⁰ While most occupational asthma is “*de novo*” disease induced by work,⁸¹ this definition highlights the possibility of having a deterioration in pre-existing asthma due to new sensitization to an agent in the workplace, i.e. non-occupational asthma overlaid by occupational asthma .

The most common type of occupational asthma is that due to an allergic response to a specific agent.⁸² It appears after a latency period of asymptomatic exposure, which can range from weeks to years. The worker during this period acquires sensitization to the causal agent, so that re-exposure to the agent at a level that was previously tolerable causes asthma symptoms. Agents causing sensitization can be divided into two categories: high molecular weight agents and low molecular weight agents.⁸¹ While high-molecular weight agents (e.g, animal protein and latex) cause sensitization by a classic Immunoglobulin E (IgE)-mediated immunologic reaction, most low molecular weight agents (e.g. isocyanates, wood dust) act through elusive allergic mechanisms.⁸³

Less commonly, asthma can develop in the minutes or hours after an unintentional exposure to high concentration of irritating gas; smoke or vapour (e.g. with spillages).⁸⁴ This condition was described in 1985 by Brooks *et al* who designated it as “reactive airway dysfunction syndrome” (RADS).⁸⁵ It is characterised by an increase in airway responsiveness which might be demonstrated for years after the initial inhalation episode. The lack of a latent period suggests that sensitization does not occur as that process generally takes at least several weeks. Also, re-exposure to a low level of the same irritant is usually tolerable further indicating the absence of hypersensitivity.⁸⁶ According to UK consensus statements,⁸⁰ occupational asthma encapsulates these two types: sensitiser-induced asthma and RADS. The latter has recently been renamed acute irritant-induced asthma, see figure 2-3.

Figure 2-3 Work-related asthma



Cases of asthma developing after repetitive high- or moderate- levels of irritants are well documented^{87, 88} particularly in pulp and paper mill workers.^{89, 90} Asthma resulting from RADS or multiple high level exposures are collectively called “irritant-induced asthma”.⁸¹

Asthma caused by chronic exposures to lower level of irritants has attracted more and more attention over the last few years. This is at least partly because of growing evidence of an increased risk of asthma in occupations such as cleaners² and swimming-pool lifeguards⁹¹ where frequent low-dose respiratory irritant exposures are expected. However, this entity, “low-dose irritant-induced asthma”, is not yet well established for several reasons. Firstly, low-dose irritant-induced asthma, inevitably, is associated with a latent period, thus, if it develops, it would have one of the important features of sensitiser-induced asthma and might be difficult to distinguish from it,⁸⁴ particularly in workers who are exposed to mixtures of irritants and so might have some work-related symptoms. Secondly, due to poor understanding of the exact underlying mechanism, there is no test that might help in identifying this type of asthma.⁹² Thirdly, exposures to irritants might have adjuvant effects in promoting allergen sensitization⁹³ and asthma developing after chronic irritant exposures might be due to sensitization to an allergen rather than the irritant itself. Lastly, non-occupational asthma is relatively common among adults and when workplace exposures to irritants cause exacerbations of coincidental new onset adult asthma, that form of work-exacerbated asthma would appear like low-dose irritant-induced asthma.⁹²

A panel of experts in occupational lung disease in the UK who attempted to agree on a working definition of occupational asthma found the issue of whether or not low-dose irritant-induced asthma exists debatable.⁸⁰ There is thus a need for further studies that investigate the issue. Also, if low-dose irritant-induced asthma does exist, studies investigating its functional characteristics are required. This might help in establishing a standard diagnostic guideline.

Regardless of the aetiology, occupational asthma has serious socioeconomic consequences if it goes unrecognized by the clinician.⁹⁴ This is because asthma might deteriorate and affect workers’ productivity.⁹⁵ Also many studies have reported higher rates of loss of income and unemployment among workers with occupational asthma than those with non-occupational asthma.^{96, 97} On the other hand, early recognition of occupational asthma and subsequent avoidance of further exposure to the initiating cause can have a dramatic effect with possible restoration of normal lung function.

Therefore, international standards have emphasized considering a diagnosis of work-related asthma in all working-age individuals who present with new onset asthma symptoms or with worsening control of pre-existing asthma.^{81, 86}

2.3.1 Review of tools used for diagnosing work-related asthma

To diagnose work-related asthma, it is crucial (1) to confirm the diagnosis of asthma (this was discussed in the previous section) and (2) to document a temporal relationship between asthma and workplace exposures. To achieve this, a stepwise approach is suggested with a history; serial PEF measurements; serial airway responsiveness measurements; immunological tests; and specific provocation tests.

Diagnosing occupational asthma

History taking

A detailed history is required when assessing a worker with suspected occupational asthma. It should include: occupational history; effect of work on asthma symptoms and presence of other affected co-workers.

A detailed occupational history must cover both current and previous jobs.⁹⁸ Information to be considered includes industry; duties; exposures occurring at the time when asthma started or worsened at work; and any recent changes in the manufactory process or in industrial products. The aim is to allow the recognition of an inducer of asthma. Failure to recognize a cause is possible if the exposure is indirect (in that it emanates from a nearby process); if it is intermittent (in case of maintenance workers); or if the potential agent is newly introduced in the market (and has not yet been identified as an asthma inducer).^{86, 99} A history of exposure to spills, fires or other high-level irritant exposures in the workplace that preceded the onset of asthma symptoms should also be queried since it might suggest RADS.¹⁰⁰

It is very important for the clinician to identify a temporal relationship between symptoms and work exposure by asking whether symptoms improve on weekends and holidays. A positive response to this question is considered to be suggestive of occupational asthma.⁸¹ Indeed, this criterion is reported by around 62-88% of patients with confirmed occupational asthma.^{101, 102} However, this pattern might be absent if the worker has occupational asthma in an advanced

stage when symptoms usually persist on holidays or even indefinitely after leaving work.⁹⁸ Furthermore, a worker may not notice any distinctive improvement away from work if the causative exposure at work is intermittent.¹⁰³

Evidence should also be sought as to whether other co-workers complain of similar symptoms. In one study,¹⁰⁴ pulmonologists reported that having seen other workers affected at the same workplace was one of the most important factors triggering considering occupational asthma as a possible diagnosis.

Additional questions about a history of rhino-conjunctival symptoms are important. They commonly precede or co-exist with sensitiser-induced occupational asthma due to high molecular weight agents. They occur less frequently with low molecular weight agents.¹⁰⁵

Although the history is sufficient to identify occupational asthma in 71% of cases,¹⁰² there is evidence that the occupational history is largely overlooked by health care providers. For instance, when Shofer and co-workers¹⁰⁶ reviewed the medical notes of 197 patients with newly diagnosed adult asthma, occupational exposure was considered in only 11% of the patients. This might be because clinicians generally have limited or no knowledge of work processes and the related exposures. In a study in the UK, 60% of GPs reported that their difficulty in exploring patients' work-related problems was attributable to their limited occupational health knowledge.¹⁰⁷

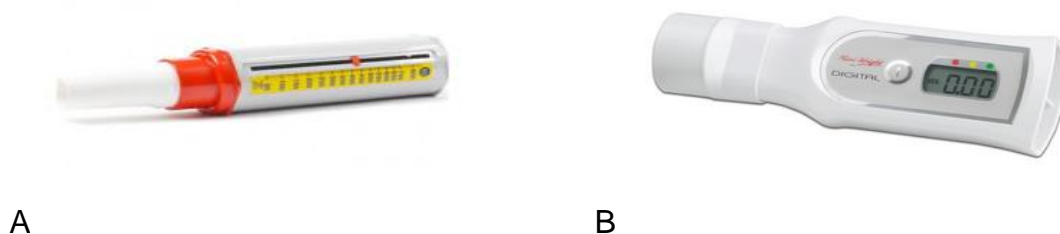
The clinical history alone was found to incorrectly diagnose 30% of suspected cases of occupational asthma.¹⁰² Thus, all consensus statements,^{81, 86, 108} recommended that a diagnosis of occupational asthma is confirmed with objective tests even in cases with a high probability of an occupational cause.

Serial PEF measurements

PEF is the maximal flow of air achieved during forced expiration starting after a full inspiration. It is measured in litre/minute.¹⁰⁹ For the purpose of investigating work-relatedness, a worker is asked to measure PEF daily on work days and when away from work. If there is an effect of work exposures, lower PEF readings would be expected during the work periods than when the worker is away from work, or is not exposed to the offending agent.¹¹⁰ PEF is usually

measured using a small portable device, figure 2-4. One commonly used device, Mini-Wright meter (A), measures PEF only, and subjects have to record the reading beside the date on a written diary record. In a new digital version of the device, digital Mini-Wright meter (B), both FEV and FEV₁ are measured and saved along with the time and date of the measurements. In either case, the worker should be carefully instructed on the correct use of the device and, most importantly, on how to perform the forced expiratory maneuver properly.¹¹¹

Figure 2-4 Devices used to measure PEF (A) Mini-Wright (B) digital Mini-Wright



The PEF record can be assessed visually. In this case, Malo and co-workers suggested that the worker should record FEV₁ measurements for four weeks, two weeks at work and two weeks away from work.¹¹² The collected PEF is presented graphically by plotting the minimum, mean and maximum PEF readings of each day on a chart. This method of assessment is found to be efficient particularly when there is a greater PEF variation on working days than days off work.¹¹³

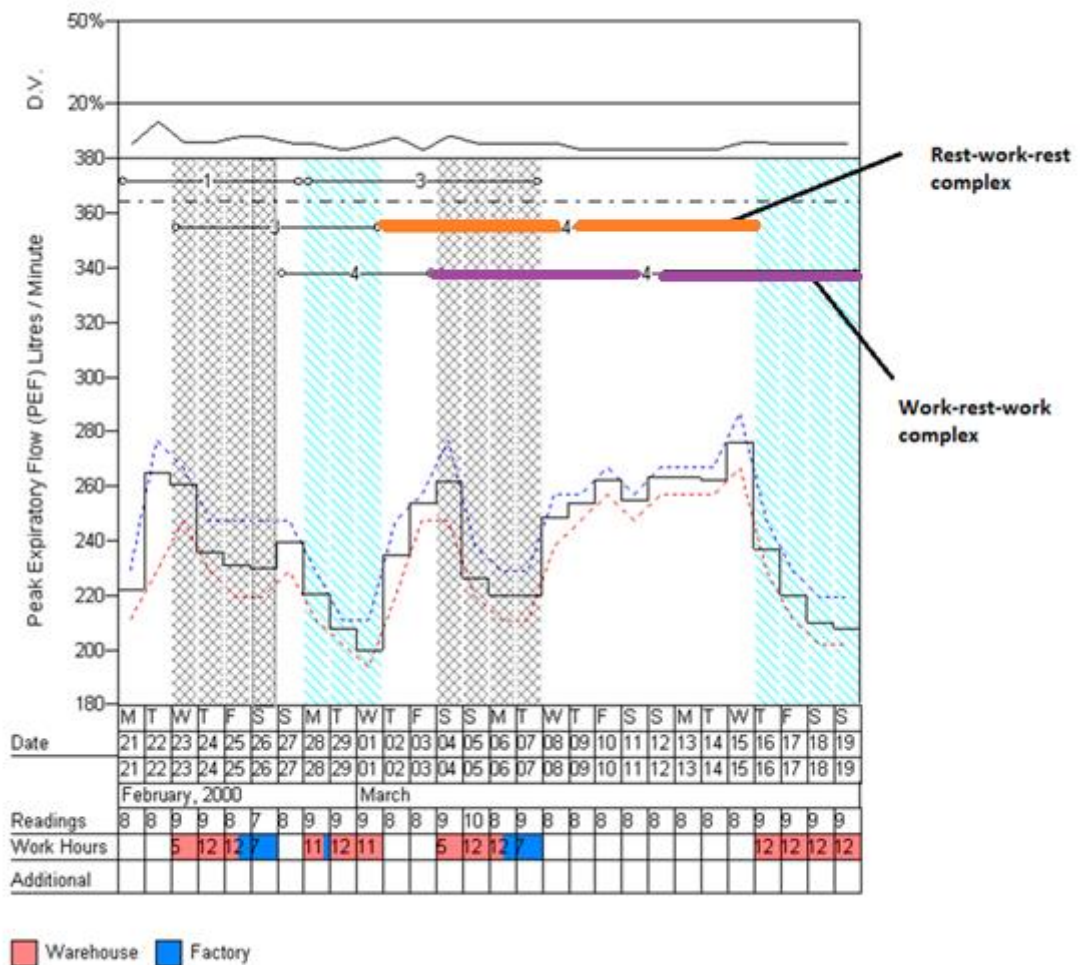
Many objective criteria have been suggested for determining whether a trace is positive for occupational asthma or not but none is widely accepted.¹¹³ While Cote *et al*,¹¹⁴ for example, required PEF measurements in two working weeks to be lower than those on weekends to show a work effect, others considered a fall in PEF measurement of 20% or more in one day to be a sufficient criterion.¹¹⁵ Accordingly, observers might have different interpretations for the same PEF trace.^{116, 117}

This inter-observer variability was the drive for Burge and colleagues,¹¹⁸ in the UK, to develop a computer-based PEF analysis tool known as OASYS

(Occupational Asthma System) in which the analysis, unlike observers' assessments, is completely reproducible. A point to be considered is that OASYS does not diagnose occupational asthma. Instead, it analyses PEF traces to detect any pattern indicative of a work effect. For this purpose, OASYS was tested using the records of a wide range of workers with occupational asthma confirmed by other tests. The analysis generates an overall score between 1 and 4. In general, PEF traces are classified into positive records, i.e. show a significant work-related effect, or negative records, i.e. show no or unremarkable work-related effect, based on a cut-off value of 2.5. Seventy five percent (75%) of the records of patients with true occupational asthma have a score > 2.5, and 94% of those with no occupational asthma have a score ≤ 2.5.¹¹⁹

It is recognized that OASYS detects work effects best if the PEF data fulfill certain criteria.¹²⁰ Malo *et al*¹¹² and Anees *et al*¹²⁰ agree that having four readings per day taken evenly throughout the day, such as when waking up in the morning; noon; supper time; and before going to bed, is adequate to diagnose occupational asthma in 72%-82% of patients. The worker is required to record the four PEF measurements for a minimum of 2.5 weeks. During this period, working days should alternate at least 3 times with rest days. This is a fundamental requirement since OASYS basically analyses 'complexes' comprising either work-rest-work or rest-work-rest periods. In order to accentuate the difference between work and rest periods, it is recommended to have three or more consecutive work days in any work period, figure 2-5.

Figure 2-5 OASYS analysis



Serial PEF, whether assessed visually or using OASYS, is generally found to be a satisfactory tool that can identify up to 86% of patients with confirmed occupational asthma (sensitivity) and identify its absence in up to 90% of those without occupational asthma (specificity).^{114, 121, 122} However, this performance is only achieved when the PEF data meet the minimum requirements discussed above. This is a problem as, on average, only 61% of patients return PEF records with acceptable data.¹²³ The accuracy of even these records is debatable given the possibility of fabricating readings. In a study by Malo and co-workers,¹²⁴ 21 subjects, 8 of whom had occupational asthma, were asked to measure PEF every two hours for a mean of 36 days using a VMX meter that logged the measurements and times. Subjects were asked to record the times and PEF values on a sheet of paper although these were stored electronically in the device. There were a total of 4839 readings, of which only 52% were both

logged by the meter and recorded precisely by the subject. Twenty eight percent (28%) were hand recorded but not stored suggesting that they were fabricated. Quirce *et al*¹²⁵ applied a comparable method on 17 subjects under investigation for occupational asthma. There was agreement between the hand-written and VMX measurements in only 55.3% of records, and 20% of readings were thought to be most likely invented. This inaccuracy of data recording further increases the possibility of misdiagnosing workers with occupational asthma.¹²⁶

To overcome this problem, it has been suggested to replace non-electronic meters with electronic ones that can assess and store data.¹¹¹ This would eliminate false readings and should improve the quality of the returned data. No study has been identified that has investigated the effect of using digital meters on compliance by subjects who are aware of their data-saving property. Non-compliance is not a straightforward issue, with many influences related to workers' socioeconomic status and medico-legal aspects¹²⁴ when a worker is asked to do PEF for the sake of compensation. Until strategies are developed to improve workers' adherence, non-compliance will be the weakest point in serial PEF testing.¹²⁶

Having a large number of PEF measurements is not sufficient to guarantee good data quality. Accuracy of performing the manoeuvres is another crucial component. Unsupervised PEF readings have been shown to be significantly lower than readings taken after the patient received further training and encouragement by a respiratory function technician.¹²⁷

Two other potential sources of error are: variation of anti-asthmatic treatments and respiratory infections.^{128, 129} Using more bronchodilators at work would minimize PEF changes resulting from work exposure. Respiratory infection, on the other hand, can cause a large reduction in PEF which would obscure improvements on rest days. Fortunately, it is possible to control for the effect of these in part. The worker should be kept on the same treatment during the entire period of the test, and be advised to make readings before taking bronchodilator inhaler.⁸⁶ In addition, the worker should maintain a diary record of respiratory infection, exposures and medications. This information can be

used to identify parts of the record affected by factors other than work and exclude them before the final analysis.¹¹³

An important point that must be considered is that serial PEF shows work effects whether these are due to sensitization or to irritation. Subjects with work-exacerbated asthma suffer worsening of their asthma at work so it is highly likely that they have an increase in PEF variability during work compared to periods away from work. Accordingly, serial PEF may not be able to differentiate occupational asthma from work-exacerbated asthma. This is demonstrated in a study by Chiry and co-workers¹³⁰ in which clinicians were asked to interpret PEF graphs of 15 subjects with work-exacerbated asthma and 19 subjects with confirmed occupational asthma. It was found that clinicians could not differentiate occupational asthma from work-exacerbated asthma whether they relied on visual interpretation or on OASYS analysis.

On occasions, PEF records may not reveal a clear pattern of work-relatedness. This can happen if the exposure is intermittent or if the worker is unable to take readings evenly due to, for example, wearing protective equipment during the whole work shift. In these cases, interpretation of the PEF records could be improved if additional information is obtained from other objective measures, such as monitoring airway responsiveness.

To summarize, serial PEF tests closely monitor airway calibre over typical working and resting days. Theoretically, this would readily uncover work effects if data are collected satisfactorily. In practice, there are many factors that compromise its performance. Of these, workers' commitment is the most important as falsification and inaccuracy has been shown to affect around 50% of measurements.¹²⁴ Despite that, it still has been found to identify work-effects correctly in a minimum of 69% of cases.¹²⁹

[Serial measures of airway responsiveness](#)

An increase in airway responsiveness due to workplace exposures in those with occupational asthma may decrease or even return to normal if the worker is no longer exposed to the offending agent.¹³¹ Based on that, guidelines suggest measuring airway responsiveness at more than one time, preferably towards the end of a working week and at the end of a holiday (≥ 10 days).⁸¹ A significant improvement of PD₂₀ while off work, defined as an increase of 1.5

double doses or more compared to the PD₂₀ measured during work would support the diagnosis of occupational asthma.¹¹⁰ The reason for choosing a cut-off point of 1.5 double doses is that the airway responsiveness measurements have been found to be repeatable within ± 1.5 double doses⁶¹ and hence changes in airway measurements beyond this should generally be considered significant, depending on the methodology used for obtaining the measurements.

In contrast to serial PEF, the validity of this test in identifying occupational asthma has been little investigated. In a systematic review of the diagnosis of occupational asthma, Beach *et al*¹³² (2007) found six studies only that had investigated the sensitivity and specificity of serial airway responsiveness tests compared with specific inhalation tests. One study found that sensitivity and specificity of serial airway responsiveness tests was 100% while the remaining five studies had pooled sensitivity of 50% to 68% for mixed and low molecular weight exposures respectively. This could be because the speed of improvement in airway responsiveness and hence the magnitude of changes over a relatively short period depends on many factors such as duration of exposure to the causative agent at the time of the diagnosis, the degree of airflow obstruction and the degree of hyper-responsiveness,¹²⁸ Hence, it is likely that more than 50% of subjects do have improved airway-responsiveness away from work but less than 1.5 double doses, i.e. within the repeatability of the measurement and insufficient to be diagnostic in any individual.

Another limitation of serial airway responsiveness is that factors other than occupational exposure are likely to affect the measurements and confound the results. For example, exposure to non-specific allergens and viral respiratory infections encountered while off work might mask a potential improvement in airway sensitivity. Conversely; taking asthma medication while at work could obscure deterioration of airway responsiveness.^{86, 128}

Overall, paired airway responsiveness tests are considered to provide additional helpful information.¹³³

As noted above, PEF testing can demonstrate work-relatedness but it cannot differentiate occupational asthma from work-exacerbated asthma as both may lead to worsening at work. Concurrent measurements of airway responsiveness

would suggest work-exacerbated asthma if no, or small, changes are revealed between the work period and when off work, and there are documented respiratory irritants at work.^{86, 133} The converse is more likely, i.e. large changes in airway responsiveness suggest occupational asthma.

PEF and airway responsiveness tests do not always give a definite diagnosis.¹³⁰ Each sometimes gives false negative or false positive results^{116, 134} and the measurements may be conflicting. It is possible, also, that neither of these tests can be undertaken if the worker has severe asthma and, hence, cannot return back to the implicated work exposure, or if the worker requires medication that could mask any work-related airway changes.⁹¹ In these uncertain conditions, specific inhalation tests are an alternative option.

Specific inhalation challenge tests

With specific inhalation challenge tests, the worker, who is suspected to have occupational asthma, is exposed in a challenge chamber or closed-circuit apparatus to the suspected agent. Alternatively, the worker can simulate a work task in a monitored laboratory environment.¹³⁵ If the test demonstrates a direct relationship between exposure to the test agent and an asthmatic reaction, then that suggests the diagnosis of occupational asthma.

Although specific challenge is considered the “gold standard” for the diagnosis of occupational asthma, there is a possibility, as with any other test, for false-negative¹³⁶ and, to a lesser extent, false positive results.^{137, 138} In general, most of the false results occur either because of technical errors (wrong agent, wrong level of agent) or because of poor preparation of the patient before the test (instability of lung function, using asthma medication prior to the test).¹³⁵ Erroneous results can be minimized with careful patient assessment, both before and after the test, and by proper conduct of the test.

Although specific inhalation challenge testing is a valuable diagnostic test; it is not used routinely in the UK. This is mainly because only competent staff in highly specialized centres can do the test, and these are relatively few.¹³⁹

Specific inhalation challenge in some countries, e.g. Finland and Canada, is most commonly used in situations such as for medico-legal purposes (e.g. compensation), particularly when it is difficult to differentiate occupational

asthma from work-exacerbated asthma, and if asthma in the latter condition started after entering the worksite of interest and is worsened at work.¹⁴⁰ However, this is unlikely to be applied in the UK.

In the tests discussed so far (serial PEF; serial airway responsiveness and specific inhalation challenge), the basic concept for diagnosing occupational asthma is demonstrating changes in the airway calibre in relation to a workplace exposure. An alternative method of identifying occupational asthma is demonstrating a worker's sensitization to a suspected agent at his workplace by immunological testing.

Specific immunological testing

Immunological tests for detecting specific IgE are performed either by skin prick tests or by serological testing. These are mainly done for high molecular weight agents since they cause occupational asthma through IgE-mediated immunological mechanism.⁹⁸ However, there are two main limitations of these tests. First, positive immunological results are not uncommon among asymptomatic workers,¹⁴¹ therefore, a positive test to an agent adds to the likelihood of diagnosis of occupational asthma if a worker is exposed to that agent at work and is presenting, at the same time, with a history suggestive of occupational asthma.⁸⁶ Second, there is lack of commercially available reagents and of standardized extracts with known allergen content for many occupational allergens.⁸² Hence, it is recommended to further demonstrate the work association by the objective tests mentioned earlier.

Diagnosing work-exacerbated asthma

There are two scenarios for workers with work-exacerbated asthma:¹⁴⁰ a) they already have asthma before employment in the current work and they present with worsening of their asthma with exposure to a new irritant work environment, or b) they developed asthma while working in current work and they present with new work-related asthma symptoms. While work-exacerbated asthma can be readily suspected in the first scenario, it can be very difficult to differentiate work-exacerbated asthma from occupational asthma in the second. Since occupational asthma can complicate non-occupational asthma, physicians should consider possible occupational asthma even in cases with a presentation that is suggestive of work-exacerbated asthma.

To diagnose work-exacerbated asthma, a detailed history should be taken followed by objective tests.

History taking

The history should aim first to confirm the diagnosis of asthma and then to assess the relationship between asthma and work. The details that should be ascertained are the same as those described above for occupational asthma.

Objective tests

Serial PEF, as mentioned earlier, demonstrates a work effect whether it is induced by sensitization or by irritation mechanisms, thus, positive PEF records could indicate either occupational asthma or work-exacerbated asthma. Therefore, additional investigation with serial airway responsiveness tests is recommended.⁸⁶ If no changes in airway responsiveness are demonstrated when away from work compared to periods at work, this supports the diagnosis of work-exacerbated asthma. However, since improvement in airway responsiveness may require a long time off work, negative results do not absolutely rule out occupational asthma.

Diagnosing low-dose irritant-induced asthma

The concept of low-dose irritant-induced asthma has been proposed recently after observing an increased risk of asthma among workers who are exposed to irritants such as cleaners² and swimming-pool lifeguards.¹⁴²

There are limited studies that suggest the possible mechanism(s) underlying low-dose irritant-induced asthma.¹⁴³ It has been proposed that exposure to irritants can induce bronchial epithelial disruption and facilitate the penetration of allergens which induces the asthma.¹⁴³ This implies that atopic workers would be at greater risk of low-dose irritant-induced asthma than non-atopics but previous studies of workers exposed to irritant gases or fumes could not demonstrate an association between atopy and asthma.^{144, 145} This indicates that irritants most likely induce asthma through non-allergic pathways that are as yet unknown.

In parallel, there are few studies that have described the physiological abnormalities associated with exposures to irritants at moderate exposures.^{146, 147} These suggest that repeated exposures to moderate levels of potentially irritant gas might be able to preferentially increase airway responsiveness without affecting airway calibre.

In Gautrin *et al* study (1995),¹⁴⁶ 239 workers in a metal production plant underwent pulmonary function and methacholine testing. Air monitoring showed that they were exposed to low levels of irritant gases, mainly chlorine, most of the time. Some workers (n=35) reported occasional higher chlorine gassing incidents. It was found that spirometric pulmonary function tests (FEV₁ and FEV₁/FVC) were within the normal range even after gassing incidents. However, the frequency of positive methacholine tests (PD₂₀ < 16 mg) among workers who reported gassing incident (25%) was higher than those who never experienced such events (9%). Among workers who ever experienced gassing events, increased airway responsiveness (PD₂₀ < 16 mg) was observed even if the workers did not experience respiratory symptoms. One limitation of the Gautrin *et al* study is the absence of baseline lung function assessment since some individuals may have had pre-existing airway hyper-responsiveness even before the gassing events.

In a later study, Leroyer *et al* (1998)¹⁴⁷ studied the same group of workers. They used the pulmonary function and methacholine data collected by Gautrin *et al*¹⁴⁶ as a baseline and followed up the workers for four years. Workers who reported chlorine incidents underwent lung function assessment and airway responsiveness three weeks after the incident and then monthly until full recovery was obtained. Thirteen workers reported chlorine incidents during the four year follow up. Of these, two (15%) demonstrated increased airway hyper-responsiveness, i.e. < 16 mg/ml, despite having baseline airway responsiveness within the normal range. Their methacholine tests returned to normal after three to four months of follow-up. Airway calibre (FEV₁ and FEV₁/FVC) was slightly reduced in one case but remained within the normal range.

These two studies suggested that airway responsiveness would be temporarily increased into the asthma range after moderate irritant exposures even if the affected workers did not have asthma symptoms.

There is only one study that directly assessed airway responsiveness among workers exposed to more continuous low levels of irritants. Massin *et al*¹⁴⁸ investigated the relationship between spirometric pulmonary function tests (FEV₁ and FEV₁/FVC) and airway responsiveness of 234 swimming-pool lifeguards and chloramine concentrations. It was observed that the severity of airway responsiveness increased with the degree of exposure among female lifeguards. The measured spirometric function tests, on the other hand, were within the normal range regardless of the measured chloramine concentrations.

Taken altogether, the evidence presented above is at least consistent with the possibility that low-dose irritant exposures may preferentially affect airway responsiveness with little short term effect on lung function (and hence work-related symptoms). Thus, it can be hypothesized that chronic irritant exposures might slowly increase airway responsiveness to a level within the asthma range without causing any typical features of occupational asthma.

Since the concept of low-dose irritant-induced asthma has only recently emerged and little is known about it, no guidelines have been developed in relation to diagnose and few authors have discussed the diagnostic difficulties.^{84, 92} The main issues raised have been: 1) whether or not it exists,

and if it exists 2) how to differentiate it from sensitiser-induced asthma since both develop after a latency period, and 3) how to differentiate it from work-exacerbated asthma, particularly in a worker who develops new asthma unrelated to work but who works in an irritant environment. However, based on the available information, there could be additional challenges in this type of asthma:

1. Absence of work-related symptoms

Workers with low-dose irritant-induced asthma may not present with work-related asthma symptoms. Indeed, it was observed in the above mentioned studies among pulp mills workers and life guards that moderate and low level exposures to irritants did not induce work-related airway obstruction¹⁴⁶⁻¹⁴⁸ and that some workers developed increases in airway responsiveness after repetitive exposures to modest levels of irritants yet did not report symptoms.¹⁴⁷

2. Negative serial PEF

In keeping with the absence of work-related symptoms, serial PEF, which demonstrates whether work exposures affect airway calibre, might be negative in low-dose irritant-induced asthma.

Therefore, in cases of low-dose irritant-induced asthma, serial airway hyper-responsiveness test might be more sensitive than serial PEF for diagnosis.

Before moving on, it should be emphasized that these points are hypothesized based on few studies.

Summary

The possibility of occupational asthma should be considered in all workers with new-onset asthma. Because of the possibility of false positive or negative results from any of the available tests, every effort should be made to gather information from a combination of tests before finalizing the diagnosis.

For sensitiser-induced occupational asthma, demonstrating a temporal association between workplace exposure and airway limitation, mainly by serial PEF and serial airway responsiveness measurements, is the cornerstone of diagnosis.

To diagnose acute irritant induced-asthma (RADS), it is sufficient to have a positive history of a high-level accidental exposure, in addition to objective demonstration of airway hyper-responsiveness three months from the date of the event, in a previously healthy worker.

Work-exacerbated asthma can be identified merely from a history of short-term worsening of pre-existing asthma and the exclusion of occupational asthma.

A complex situation of occupational asthma superimposed on non-occupational asthma should be considered if a patient's asthma worsens despite the compliance with asthma medication, particularly if there is a recent change in the work such as introducing a new chemical. In this case, further confirmation is required such as for sensitiser-induced asthma.

Low-dose irritant-induced asthma can be considered if the occupational history indicates exposures to irritants rather than to sensitisers. Work-relatedness might be demonstrated by measuring airway responsiveness at work and when away from work. The effectiveness of serial PEF in diagnosing irritant asthma is questionable.

These are summarised in table 2-1 in the next page.

Table 2-1 Diagnosis of occupational asthma, reactive airway dysfunction syndrome and work-exacerbated asthma

Work-related asthma	History	Serial PEF	Serial airway responsiveness	Specific inhalation test	Immunological tests
Sensitiser-induced occupational asthma	Improvement of symptoms when away from exposure History of exposure to a known sensitiser	Worse during work period than when off work	Worse at end of a work week than at end of a holiday period.	Positive response when challenged with the suspected agent	Positive response
RADS	History of exposure to high level of irritant	Not relevant	Not relevant	Not relevant	Not relevant
Work-exacerbated asthma	Improvement when away from work	Worse during work period than when off work	No difference between work periods and when off work	Negative response	Not relevant
Low-dose irritant asthma	History of exposures to irritants	? may not show work-related changes in airway calibre	? Worse at end of a work week than at end of a holiday period	? not relevant	Not relevant

Limitations of the diagnostic process of occupational asthma in the health care scheme of the UK

In the UK health care system, the GP is the first point of contact for the majority of workers. Several national guidelines, for example the British Thoracic Society Standard of Care for Occupational Asthma,¹⁵⁰ have been developed to improve nurses' and physicians' practice, particularly those based in primary care.¹⁴⁹ However, a study by Barber and co-workers¹⁵⁰ showed that 72% of GPs are unaware of these guidelines and hence may not adequately consider occupation as a possible cause when adults with new-onset asthma are encountered. Indeed, in a recent audit (2012)¹⁵¹ of four primary care practices in West Midlands, UK, 400 medical records of working-age asthmatics were reviewed. It was found that occupations were recorded in only 14%, and inquiring about work effects was documented in only 2%. This could delay occupational asthma diagnosis. Fishwick *et al*¹⁵² traced the history of 97 workers referred to secondary centres for possible occupational lung disease. He found that 67% had their first contact with the GP on average four years before they were referred for further assessment in secondary centres. Eight workers had waited for more than 10 years.

Even in secondary care centres, patients are not necessarily seen by a specialist in occupational respiratory diseases as other respiratory consultants often assess and investigate possible occupational asthma. The diagnostic process is not standardised.¹⁵³ This is illustrated by a study¹⁵⁴ among 100 non-specialist respiratory consultants who were asked about their diagnostic approach to a case scenario of a patient with possible occupational asthma. The study found a marked disparity in the diagnostic approaches which was sometimes poorly related to the recommended best practice in the guidelines.

Although non-specific provocation challenge testing, specific IgE to occupational allergens; and OASYS style PEF software are considered essential facilities when assessing possible occupational asthma, there is limited access to these in respiratory departments in the UK. A study of 34 respiratory departments across the UK found that 50% of departments did not have facilities for non-specific airway responsiveness testing.¹³⁹ Similarly, testing for specific IgE to common occupational allergens in the blood was

absent in 46%. Only 12% of departments had access to OASYS software although it is particularly useful for respiratory clinicians who may not be expert in visually assessing PEF records for work effects.¹⁵⁵ These limitations would further compromise the performance of non-specialised clinics. Despite the presence of tertiary centres which are fully equipped with all of the required tests to diagnose asthma, referral to them is restricted by the long travelling distances in some areas of the UK.¹³⁹

There is thus a considerable potential for misdiagnoses of occupational asthma at both primary and secondary care levels. This causes major concern not only at individual patient level, but also at a community level because health policy makers generally depend on clinicians' reports to monitor disease prevalence and plan preventive measures.

2.3.2 Approaches used to study occurrence of occupational asthma

Information about the distribution and determinants of occupational asthma comes from two main sources: 1) epidemiological studies; and 2) disease surveillance or monitoring schemes.

1. Epidemiological approaches for the studying of occupational asthma

While the epidemiological definition of asthma has to some extent been unified internationally after the development of the ECRHS, the definition of occupational asthma in epidemiological studies varies according to the purpose of the study and its design.¹⁵⁶ Some epidemiological studies, for example, rely on self-reporting of work-related symptoms to determine whether a subject has occupational asthma or not,¹⁵⁷ while other studies performed an additional objective test, such as serial PEF, to ascertain occupational asthma cases.¹¹⁶ This looseness of occupational asthma definition has led to terms such as "possible occupational asthma" and "probable occupational asthma".¹⁵⁸

In general, there are two main approaches adopted by epidemiologists to investigate the epidemiology of occupational asthma: population-based studies and workforce-based studies.

Population-based studies

Unlike workforce-based studies, in population-based studies a sample, or even the entirety, of a population is selected for assessment of exposure-outcome relationships. The population is often defined a priori based on the residential area and it may include workers employed in a diverse range of work sectors as well as unemployed subjects.¹⁵⁶ Most of these studies are large scale including > 1000 participants. They have generally relied on workers' self-reports to define both the outcome and the exposure.¹⁵⁹ Many of the population-based studies that investigated occupational asthma were either cross-sectional in design^{2, 160} or cohort studies.^{3, 161}

In cross sectional studies, the health outcomes under study, i.e. asthma, and information about exposures are determined simultaneously for each subject. The authors then compare the prevalence of asthma in subjects who are exposed to potential harmful exposures, i.e. fumes, dust or vapour, with the prevalence of asthma in a reference group in which subjects are presumably have no or low exposures, e.g. office workers. This type of study is considered a useful tool in generating hypotheses about the presence of new exposure-disease relationships. In the analysis of cross-sectional studies, the association is often quantified by odds ratio (OR) which is defined as the odds of getting asthma if an exposure is present divided by the odds of getting (asthma) if the exposure is not present. An OR value of more than 1 indicate the presence of a positive association, and the greater the value of OR the stronger is the association.¹⁶² However, the presence of an association between an exposure and asthma in these studies does not necessarily mean that this certain exposure is a cause of asthma. Exposures and asthma are simultaneously assessed and thus there is no evidence that the exposures under the study have preceded the occurrence of the asthma. However, in order to be able to make causal inferences from epidemiological studies, there are many other criteria that should be considered apart from the presence of a temporal relationship. These include the presence of biological plausibility, presence of dose-response relationship, consistency of the findings, and the presence of the experimental evidence though this might not be widely used in case of occupational epidemiology.¹⁶³

In cohort studies, the researcher starts with a group of exposed and non-exposed workers and then monitors the development of asthma, i.e. incident cases, is observed longitudinally over a specific period.¹⁶⁴ The asthma incidence is then compared between these two groups. This type of studies has the advantage over cross-sectional studies in that the researcher is reasonably sure that exposures preceded asthma, and is able to study the natural history of the disease. However, they have the disadvantage of missing subjects during the study due to, for example, immigration. This might affect the results if this has affected one group, i.e. exposed or non-exposed, significantly more than the other. Another disadvantage is that these studies are time consuming and costly. A cohort design could be considered appropriate if there is sufficient evidence from prior cross-sectional studies about an exposure-disease relationship that needs to be further characterised by a more robust design.

One of the most important of the population-based studies is the ECRHS. The first stage of this study (ECRHS-I)² was a cross-sectional respiratory survey among 15,637 subjects aged 20–44 in 12 industrialised countries. Of these, 9476 subjects completed an airway responsiveness measurement. It was found that occupational asthma accounted for 5%-10% of adult asthma. In addition, higher risks of asthma, defined as airway hyper-responsiveness and asthma symptoms, were shown for farmers and painters. Most importantly, the study drew attention to a high asthma risk in some occupations that were not known previously to be associated with a risk of developing occupational asthma such as cleaners. In stage two of the study,³ 6837 asthma-free adult workers were followed for approximately 9 years and investigated for new-onset asthma. It was found that the incidence of new-onset asthma attributable to occupational exposure, defined by self-reporting asthma symptoms with or without airway responsiveness, was 250-300 cases per million people per year.

Since participating workers would have worked in different industries and have been exposed to different chemical(s) in their lifetime, the main issue that faced investigators in this type of study is what relevant exposure should be considered in the exposure-outcome relationship, i.e. should they consider exposures in the last job; the longest held job; or any exposures that ever occurred in the workers' lifetime.

In recent studies, three main methods have been used to assess exposure: 1) self-reported job title; 2) self-reported exposure to vapour, gas, dust, or fumes; and 3) job exposure matrices.¹⁶⁵

The 'current job' or the 'job title' at the time when a participant changed job because of respiratory problems' is commonly used as a surrogate for exposure. Workers, whose job titles indicate seemingly similar tasks, are grouped under a common title of industry or occupation. Researchers then explore whether there is an association between asthma and any of these groups. The weakness of this approach is the assumption that workers in the same group have homogenous exposures.¹⁶⁵ This is almost certainly an oversimplification since workers' exposures vary considerably depending on work practices and control measures available.¹⁶⁶ Despite the potential for exposure misclassification, a number of population-based studies have succeeded in finding an association between asthma and previously known at-risk occupations such as baking and painting.^{3, 78, 161} More importantly, associations have been found with occupations not previously known to have a high risk of asthma such as cleaners. The ability of population studies to bring to light previously hidden risky jobs is a strength of this type of study.

An alternative approach to grouping by job title is to assess occupational exposures by asking workers individually about any work-related exposure to vapours; gas; dust or fumes, either in regard to longest-held job or to their entire working life.¹⁶⁵ The researcher then dichotomizes workers' exposures into never-exposed versus ever-exposed, and compares the proportion of asthmatic workers in each category. Despite the simplicity of the approach, it identified the exposure status correctly in 71% of exposed workers in one study.¹⁶⁷

It is worthwhile to emphasize here that since exposure is self-reported, it might be expected that asthmatic workers would recall previous exposures more than non-asthmatics in attempt to find an explanation for their condition (a recall bias).¹⁶⁵ This would probably lead to over-estimation of the association between particular exposures and asthma.

None of the above methods allows identification of the exact causative agent(s). Therefore, asthma-specific job exposure matrices have been developed to further link job titles to specific exposures relevant to occupational asthma.¹⁶⁵

One commonly used asthma-specific job exposure matrix includes 18 high molecular weight and low molecular weight agents. When the job exposure matrix was used to describe occupational exposures, asthma was found to be associated with commonly recognized agents, such as isocyanates,¹⁶⁸ as well as other agents not commonly notified in surveillance schemes. The use of job exposure matrices, therefore, has further enhanced population studies' roles in generating hypotheses about new links between occupational asthma and overlooked risky exposures. These should lead to work-force based studies to further investigate these findings.

Workforce-based studies

These are surveys restricted to workers from the same occupation or individual workplaces.¹⁵⁹ A considerable amount of research has been conducted in some workforces (bakers, painters, farmers) and with some exposures, e.g. isocyanates. Some of these studies have been triggered by physicians' reports about clustering of occupational asthma cases in specific jobs, i.e. outbreaks.¹⁶⁹ Other workforce studies have followed from population-based studies when the results have suggested a high risk of occupational asthma in an occupation *a priori* considered to be associated with a low or even no risk of occupational asthma.¹⁵⁶

To investigate whether workers in a specific job are at higher risk of developing occupational asthma, epidemiologists compare how often asthma occurs in those workers compared with the general population or with an unexposed group of workers. Alternatively, asthma occurrence in high-exposure workers is compared with that of lesser exposure workers generating an exposure-response relationship. These comparisons also permit examination of the effect of both environmental factors, for example the exposure level, and host factors, such as atopy and smoking, on the susceptibility of workers to asthma.¹⁵⁶

Many of the workforce-based studies, particularly recent ones, have used objective tests such as serial PEF;¹⁷⁰ airway responsiveness measurements¹³⁴ and to a lesser extent specific inhalation challenge tests¹³⁸ to define occupational asthma. This seems to be more feasible than in population-based studies, as the investigator can perform the airway responsiveness test and encourage PEF testing in situ instead of asking workers to visit an investigator's

clinic in their spare time. Such a request might be inconvenient and lead to lower response rates.

Most of the existing workforce-based studies are cross-sectional in design.¹⁵⁸ They thus include only current workers and might miss workers who have already been transferred to less exposed jobs, or left work because of their asthma, i.e. survivor effect. Indeed, Le Moual *et al*¹⁷¹ analyzed 13 occupational asthma studies from 1995 to 2006 and found that persons with asthma were more likely to quit or change their job than non-asthmatic workers. Alternatively, workforce studies might be affected if workers were not hired or avoided jobs with exposure because of their health condition, i.e. healthy hire effect.¹⁷² Both survivor and hire effects have been found to cause under-estimation of the association between asthma and exposure. An example of the possible bias introduced by a survivor effect is the Zock and co-workers' study.¹⁷³ This study aimed to investigate the respiratory effects of exposure to dust and endotoxins in the potato processing industry. Workers completed a respiratory questionnaire and performed spirometry. The levels of airborne dust and endotoxins were assessed by personal monitoring and workers were categorized into two groups, low and high exposures. The authors did not find an association between current exposure levels and respiratory health, contradicting the existing evidence. The authors believed that symptomatic workers had dropped out of the work and this explanation was supported by the finding that workers employed for ≤ 5 years reported significantly more asthma symptoms and had lower lung function than those employed for > 5 years.

2. Data on occupational asthma from national notification systems

At present, registries of occupational disease are the major source of estimating the incidence of occupational asthma in various occupations and industrial sectors.¹⁵⁹ These registers are mainly based on mandatory or voluntary physician reporting and medico-legal statistics for compensation purposes.¹⁵⁶

Notification of occupational asthma in the UK

In the UK, volunteer chest and occupational specialists report cases of occupational asthma to a national reporting scheme for work-related respiratory disease, (SWORD)¹⁷⁴ which was primarily established to gather information for preventive measures. Another independent scheme is SHIELD¹⁷⁵ which covers

the West Midlands only. Based on these schemes, a number of authors have estimated the incidences of occupational asthma and RADS in the UK, table 2-2.

Table 2-2 Estimated incidence of occupational asthma by reporting schemes in the UK

Reference	Reporting scheme	Period	Incidence/million/year
Occupational asthma			
176	SHIELD	1990-1997	41.2
174	SWORD	1992-1997	38
177	SWORD	1992-2001	22
178	SHIELD	1991-2005	42
RADS			
179	SWORD	1990-1993	11

Having isolated figures may not be meaningful because of the large number of potential biases that influences detection and reporting but comparing occupational asthma annual incidence over years can be more informative. A recent report from the Health and Safety Executive (Statistics, 2011/2012)¹⁸⁰ suggests that there has been an overall decline in occupational asthma in the UK in the last decade, figure 2-6, based on the information reported by specialist physicians to SWORD.

Figure 2-6 Trend in occupational asthma during 1998-2011 in the UK



This decline may be the result of regulations on the control of exposures in high risk occupations, or a reduction in the size of the manufacturing sector in the UK. On the other hand, the observed trend may not reflect a true change in the annual number of new cases of occupational asthma, but rather it could be due other factors such as reporter fatigue, or the introduction of new chemicals that may cause occupational asthma and are not yet well known and so the associated asthma goes unrecognized.¹⁸¹ Data from SWORD indicated that isocyanates and flour exposures were the cause of the largest proportion of the new cases of occupational asthma for five consecutive years 2005-2010.¹⁸⁰ Although this consistency over a period could be true, it could also be due to the higher tendency of clinicians to report what is well known to cause occupational asthma than unfamiliar causes.

Another limitation of reporting schemes is that they depend largely on the readiness of the affected individual to present their symptoms to a clinician. Workers with work-related disease in general and occupational asthma in particular may not ask for medical help, because of fear of losing their job; missing overtime or promotion opportunities; stigmatization; fear of loss of work-

based friendships and support; or due to difficulty accessing medical facilities at convenient times.^{182, 183}

Despite the acknowledged limitations, reporting schemes are the most convenient means by which public health providers can monitor occupational asthma incidence. Therefore, many European and non-European countries have established surveillance programmes similar to SWORD.

Notification system of occupational asthma in other European countries

Registers in other countries are also based on notification by physicians. In contrast to the UK's SWORD system, some reporting schemes, particularly those established for medico-legal and compensation purposes, have standardized criteria to confirm occupational asthma diagnoses. One example is the reporting scheme in Finland, FROD.¹⁸³ The estimated annual incidence of occupational asthma by different reporting schemes is shown in table 2-3.

Table 2-3 Estimated incidence of occupational asthma by international reporting schemes

Reference	Country	Name of surveillance system	Period	Incidence/million /year
161	Finland	FROD	1989-1995	174
184	Canada	PROPULSE	1991-1992	Men 70 Women 42
185	Australia	SABRE	1997-2001	30.9
186	Belgium	BWCB	1993-2002	29.4
187	France	ONAP	1996-1999	24
188	South Africa	SORDSA	1996-1998	13.1

There is a notable difference in the reported annual incidences between these countries with a range from 13.1 (South Africa) to 174 (Finland) per million workers per year. These figures are not directly comparable since there are

variations between countries in the diagnostic criteria used and in reporting guidelines. For instance, nurses can participate in SORDSA.¹⁵⁹ The high detection rate of the Finland scheme could be because reporting is required of doctors by law; and the scheme covers more than 90% of the working population in the whole of Finland.¹⁸³

Similar to SWORD, these reporting schemes show that a few agents are responsible for 50%-90% of reported occupational asthma cases. These include isocyanates; flour; latex; enzymes; and wood dusts. In parallel, occupations where these substances are used are also identified as at high risk, e.g. spray painters, bakers and health care workers.

Overall, reporting schemes are important sources of information for policy makers to monitor occupational asthma and to evaluate the effectiveness of implemented interventions in achieving targets to reduce the disease. However, estimates from reporting schemes probably do not reflect the true size of the occupational asthma problem as underreporting is inevitable and is contributed by both clinicians and workers. Reporting practice itself can be modified by factors such as clinicians' motivation; training; and changes to policies as well as current evidence.¹⁸⁹⁻¹⁹¹

In summary, epidemiological studies have advantages over monitoring schemes in that: 1) they provide data that allow a better estimate of the burden of occupational asthma. This can be seen when the incidence of occupational asthma estimated by the ECRHS, 250-300 per million people per year, is compared to that estimated by reporting schemes, for example in the UK, the estimated incidence was 87 per million workers per year, and in Finland, which has the most complete surveillance system, the incidence was 176 per million workers per year. 2) They draw attention to workforces and agents that were conventionally not considered to pose risks. The newly emerging occupational asthma-exposure link increases awareness of the medical community to consider occupational asthma in previously overlooked workforces/chemicals. This is illustrated by the recent emergence of cleaning agents as a cause of adult onset asthma in the registries-based studies.^{175, 192, 193}

Until relatively recently cleaners and cleaning agents were only infrequently reported, or not even mentioned in registry studies. However, in the last 20

years, a number of population-based studies have showed a significant association between adult onset asthma and exposure to cleaning agents.¹⁹⁴⁻¹⁹⁷ This growing evidence has caught clinicians' interest and in recently published papers based on registry data, cleaning agents were among the commonest suspected agents reported by physicians.^{175, 192, 193} An example would be the UK SHIELD scheme which is run by specialist clinicians working in a tertiary centre for occupational asthma.¹⁷⁵ The reports of these schemes from 1999 to 2008 found isocyanates to be the most common cause of occupational asthma in most of the years and cleaning agents were either not on the list or the number of the reported cases was small. However, for years 2009-2011, cleaning products were among the commonest cited agents causing occupational asthma. There is good epidemiological evidence that cleaner's asthma has been common for several decades now and there is no evidence that it has become more common recently. This suggests that the changes in reporting frequency are probably due to increased awareness and/or diagnostic experience.

Chapter 3 **Critical review of the epidemiologic literature on asthma in cleaners**

3.1 Introduction

Professional cleaners constitute 3% of the occupationally active population in the UK,¹⁹⁶ about 5% in Finland⁴ and 2% in the USA.^{198, 199} They were not recognized to be at risk of occupational asthma until the beginning of the 1990s when an increasing volume of literature identified them to be at higher risk of suffering from or developing asthma compared with reference populations (e.g. office and administrative workers).^{2, 78, 197, 200}

This chapter starts with a detailed discussion of the evidence linking asthma and cleaners starting with epidemiological studies followed by registry-based studies. This is followed by with a brief description of some of the general hazards encountered in cleaning work that may cause asthma. The last section focuses on the available evidence on the association with specific cleaning tasks and products. It places emphasis on chlorine bleaches and the possible mechanism of chlorine-induced asthma.

To find relevant papers for the literature review, two methods of searching were used: first, Scopus, Web of Knowledge, Medline and Google Scholar were searched using free text searches and using the following terms: asthma, work related asthma, cleaner, respiratory effect, cleaning agents, occupational exposure. Second, the reference lists of the main papers were hand searched for additional papers of interest. The search was limited to publications in English from 1980 till June 2013.

Fourteen key studies were identified: eleven population-based studies^{2, 3, 144, 160, 194, 197, 200-204} and three work-force based studies^{4, 205, 206} that investigated the association of asthma in cleaners. In addition, five registry-based studies^{161, 174, 187, 192, 193} were identified and included in the review as they discussed the incidence of work-related asthma or occupational asthma in cleaners.

Further searching was carried out to identify studies that investigated the tasks and products used in cleaning that are associated with asthma. Six studies

were identified.^{145, 205-209} The studies reviewed in this section are demonstrated in figure 3-1 and figure 3-2.

Figure 3-1 Flow chart of the reviewed studies on the risk of asthma in cleaners stratified by design

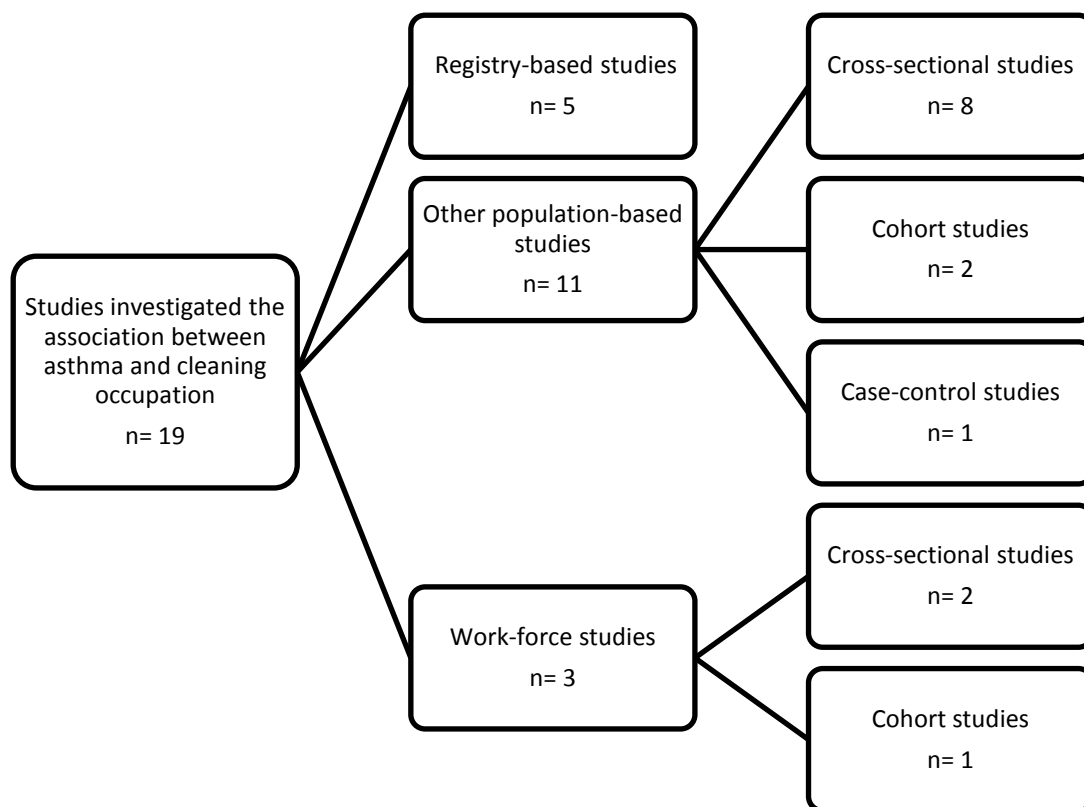
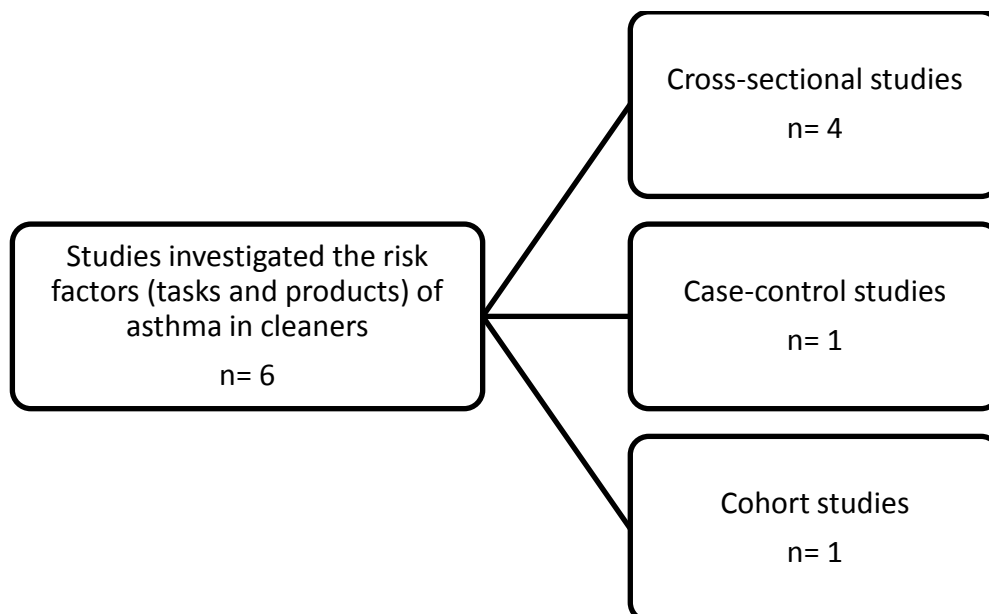


Figure 3-2 Flow chart of the reviewed studies of risk factors (tasks and products) stratified by design



3.2 Evidence of a high risk of asthma among cleaners

3.2.1 Population-based and workforce-based cross-sectional studies

One of the first epidemiological studies which called attention to the association between asthma and cleaning was the ECRHS-I study conducted by Kogevinas and colleagues.² This was a large scale study in which randomly selected members of the population aged 20-44 years (n=were contacted in 12 European and non-European countries. The aim was to identify which occupations were associated with a high risk of asthma. In the first stage, the contacted participants were asked to complete a short respiratory questionnaire. In the second stage, a 20% randomly selected sample and all participants who reported respiratory symptoms but were not selected in the random sample (total n= 26 848) were re-contacted to answer a detailed questionnaire that included information on smoking and occupations and to undertake respiratory function tests. Only 15 637 completed the second detailed questionnaire (response rate 58%), and the authors excluded 832 people because they were occupationally inactive and 224 because of missing data. The analysis thus included 14581workers. Of the eligible participants, 9476 performed the airway responsiveness measurement.

Occupation was defined by self-reported current job or the job when breathing problems occurred. Asthma was defined as reporting asthma symptoms or using asthma medication alone or combined with a positive airway responsiveness measurement.

The adjusted OR for asthma, defined as airway hyper-responsiveness and asthma symptoms or medication, for 443 current cleaners was elevated at 2.0 (95% confidence interval (CI) 1.3 to 2.9) when compared with professional, clerical and administrative workers across most of the participating countries. The association remained positive when asthma was defined by self-reported symptoms or medication use alone (OR 1.8, 95% CI 1.4 to 2.3). Of the 16 studied occupational groups, cleaning was the occupation with fourth highest risk of asthma after farmers, painters and plastic workers.

One limitation of this study is the use of current job title as a surrogate for exposure. People with the same job title may have different exposures

depending on the companies' activities. For example, a clerk in a factory may be exposed to emission sources unlike a clerk who is not working in a production area, e.g. in a separate office. Accordingly, a number of asthma cases among office workers might be attributed to exposures not related to their own work. These might dilute the risk estimates.

Another paper published by Zock and co-workers¹⁴⁴ used the same ECRHS data to evaluate the clinical, immunological and functional characteristics of asthma in cleaning workers and compare it with those in other occupational groups.

The authors used the data of 12336 subjects who responded to the detailed occupational questionnaire. The authors used more than one method to assess exposures. Initially, subjects were aggregated into three main exposure groups based on the job title of the current job [cleaners (n=397), workers exposed to high molecular weight agents (n=409) and workers exposed to low molecular weight agents n=1383) and a group of unexposed reference workers selected from professional, clerical and administrative workers (n=10147)]. The authors then applied a job exposure matrix and asked subjects about previous exposures to gas, dust or fumes. Subsequently, 4998 office workers were excluded because they were exposed to dust/gas or fumes in their current office work or in a previous job. This step may have excluded a number of asthma cases among office workers that were caused by exposures to dust/fumes rather from their current office job. Additionally, 9 workers exposed to high or low molecular weight agents were excluded due to possible exposures to cleaning agents. A worker was considered asthmatic if he/she reported asthma attacks; being woken up by shortness of breath, or had used of asthma medications in the last 12 months.

To evaluate the risk of asthma for cleaners compared with the office workers, the authors used the data of subjects in the random sample (cleaners n= 302, office workers n= 4492). The risk of asthma for cleaners was found to have a higher risk of current asthma compared to office workers, OR of 2.5 (95% CI 1.7 to 3.6). The functional characteristics of asthma that developed among cleaners were not different from the asthma that developed among workers employed in high-risk occupations. The estimated OR (2.5) was higher than that estimated

by Kogevinas *et al*² (OR 1.8) and may be explained by the further assessment done by Zock *et al* minimizing exposure misclassification which would have diluted the asthma-exposure relationship.

Medina-Ramon and co-workers¹⁶⁰ conducted a population-based cross sectional study in Spain in 2000-2001 with the aim of assessing the risk of asthma in women domestic cleaners. A random sample of 5120 women aged 30-64 with less than eight years of education was identified using census data. They were posted a questionnaire with follow up phone call for non-responders. Four thousand five hundred ninety two (n=4592) women returned the questionnaire (response rate 90%). Seventy one questionnaires were excluded from further analysis because of missing data, and 4521 completed questionnaires were used for the final analysis. Cases were defined as: a) reporting an asthma attack; b) being woken up by breathlessness; or c) taking asthma medication in the last 12 months. Using these criteria, an increased risk of current asthma was observed among those reporting ever having been employed in cleaning (n=2259), OR 1.7 (95% CI 1.4 to 2.1), compared to women who never worked in cleaning (n=2262). The OR of 1.7 is comparable to Kogevinas *et al*² (OR 1.8) but is lower than Zock *et al*¹⁴⁴ (2.5) yet the confidence intervals overlap.

There are some methodological issues in Medina-Ramon *et al* study. The response rate of 90% was exceptionally high for a survey of this type, a feature that is not explained or commented on in the paper. The authors reported that subjects were selected randomly, but the proportion of subjects working in cleaning was unusually high (almost exactly 50% of the study population) so it is likely that some other selection method was used. That is not described in the paper and raises questions about the reliability of the results.

In New Zealand, Eng and co-workers²⁰¹ used a survey to identify occupations associated with increased risk of asthma. The authors randomly selected a sample of 10,000 adults, aged 20-64 years, from the Electoral Roll and sent them an invitation letter to complete a telephone survey. Of the 10,000, 1846 were considered ineligible (e.g. deceased, no longer living in New Zealand). Invitation letters were sent up to three times for the remaining 8154 subjects but only 3003 agreed to take part in the telephone interview (response rate 37%). Data was missing for 100 subjects, thus, the final analysis included 2903 subjects. The authors classified a participant as a cleaner if he/she ever had this job in his/her life and considered all workers who never worked in this occupation as the reference group. Asthma prevalence, identified based on the ECRHS definition, was found to be 26% among cleaners with an OR of 1.6 (95% CI 1.1 to 2.4). The estimated OR is lower than ORs estimated in some other studies^{2, 144} though is comparable to that estimated by Medina-Ramon *et al* study (1.7).¹⁶⁰ This could relate to the exposure classification “ever cleaner versus never cleaner” rather than ever cleaner versus a low risk reference group. The referent group of non-cleaners might include subjects who worked in high-risk occupations other than cleaning. Thus a larger number of asthmatics might be found in the referent group and this would under-estimate cleaning-asthma association.

The response rate was low in Eng *et al* study (37%), however, the authors examined the characteristics of non-responders and its effect on the outcome estimation in a follow-up paper.²¹⁰ They showed that non-response bias was unlikely.

In the United States, Arif and co-workers investigated the association between work-related asthma and 40 pre-determined occupations.²⁰² They used data from National Health and Nutrition Examination Survey III, which was conducted among 40,000 Americans between 1988-1994. They defined work-related asthma as a positive response to the questions “*has a doctor ever told you that you has asthma*” and “*whether lower respiratory symptoms (e.g. wheeze) or upper respiratory symptoms (e.g. itchy nose and watery eyes) were brought on by their work environment*”. Based on the response to the survey, the authors identified 188 workers with work-related asthma. These were classified into the 40 occupations based on the longest held job.

Cleaners (n=4) had a higher risk of work-related asthma, OR 2.4 (95% CI 0.5 to 10.6), compared to the referent group of management; secretarial and clerical occupations but it did not reach statistical significance. Equipment cleaners (n=3) were found to have the highest prevalence of work-related asthma (14%) with an OR of 10.6 (95% CI 1.5 to 27.5).

There are two limitations in Arif *et al* study: first, the estimated ORs were based on small numbers of cleaners and thus the precision of the estimated risk is low as reflected by the wide confidence intervals. Second, the definition used for work-related asthma included also upper respiratory symptoms and this implies that subjects with work-related symptoms of congested nose or red eyes might also have been included under the label of work-related asthma.

A study from France reached the same conclusion, demonstrating an association between asthma and cleaning. Le Moual and colleagues¹⁹⁴ investigated the association between asthma and occupations in 14 151 adults aged 25-59 enrolled in the air pollution and chronic respiratory diseases survey in 1975. For the analysis, occupational exposure was assigned on the basis of job titles which were grouped *a priori* into 29 high risk occupations, and asthma was assessed using three definitions: 1) ever asthma which was considered if the subject reported having ever had an asthma attack or wheeze, 2) asthma with airflow limitation which was considered present if the subject reported “ever asthma” and was found to have airway obstruction as assessed by spirometric measures, and 3) adult onset asthma which was defined as developing asthma after the age of 14 or after the start of the current job. Comparing cleaners (n=404) to a referent group of administrative and service workers (n=8428), this study found an increased risk among cleaners when asthma was defined using spirometric measures or as adult onset-disease with OR ≥ 2 . The 95% CI was not specified but the authors reported that cleaners were among other occupations that showed an increased risk of asthma that was significant or of borderline statistical significance. When the authors used the asthma-specific job exposure matrix, they found a significant association between the use of industrial cleaning agents and adult onset asthma with an OR of 2.5 (95% CI 1.4 to 3.3). The associations were weaker when asthma was defined as ever having had an asthma attack or wheeze, adjusted OR 1.04 (95% CI 0.7 to 1.5). This lack of association may be due to the inclusion of ever wheeze in the definition as it is a non-specific symptom and many office workers may have reported having this symptom.

There are two workforce-based cross-sectional studies that investigated asthma risks among cleaners:

In a cross-sectional study, Vizcaya and colleagues²⁰⁵ asked 1018 cleaning service companies to participate in a study evaluating associations with asthma. Of these, 286 companies had stopped their cleaning activities and were excluded and, of the remaining, only 37 agreed to participate. The investigators distributed 4993 self-administered questionnaires to the employees via representatives assigned by the participating companies. The questionnaire collected information about respiratory symptoms and exposures to cleaning products based on information provided by the companies. Only 950 of 4993 subjects returned the questionnaire and 33 were excluded because of missing data. Therefore, the final analysis was of 917 participants only (response rate 18%). Seven hundred and sixty one (n= 761) participants were cleaners at the time of the study, while the remaining were either former cleaners (n= 86) or had never worked as cleaners (n=70), i.e. were managers or office staff.

Current asthma in this study was defined as having had one of the following in the last 12 months: woken up by an attack of shortness of breath; had an attack of asthma or used asthma medicines such as inhalers or tablets. The prevalence of asthma among current cleaners (n=761) was 11% compared to 6% in never cleaners (n=70) with an OR of 1.9 (95% CI 0.6 to 5.5).

The other work-force based study was conducted in Canada. Obadia and colleagues²⁰⁶ compared work-related asthma symptoms among cleaners with those of other building workers. The authors contacted two local unions aiming to recruit 1500 cleaners and 1500 non cleaning reference workers such as clerical staff; maintenance workers and security personnel. These were sent a questionnaire about respiratory symptoms and cleaning activities and, after one week, were sent a reminder letter. Non-responders were mailed the questionnaire a month later. Of the 3000 questionnaires distributed, 566 cleaners, mainly working in schools, (response rate 38%) and 587 non cleaning workers (response rate 39%) returned the questionnaire.

In this study, asthma was defined by either self-reported physician-diagnosed asthma or by having three or more positive responses to the nine respiratory symptoms adapted from a validated respiratory questionnaire created by

Venables *et al.*⁴⁹ Work-related asthma was diagnosed if a worker reported improvement in these symptoms when away from work.

Male cleaners (n= 447) reported physician-diagnosed asthma (10.5%) twice as often as the referent group (5.8%) leading to an OR of 2.1 (95% CI 0.9 to 4.8). No association for physician-diagnosed asthma was apparent in female cleaners (n=87), OR 1.1 (95% CI 0.6 to 2.1). However, female cleaners reported respiratory symptoms significantly more frequently than the reference group, OR 2.6 (95% CI 1.6 to 4.3). Work-related asthma was more common among male (15%) and female cleaners (21%) than in the reference group (10.5% and 6% respectively) giving an OR of 1.6 (95% CI 0.8 to 3.0) for men and 3.9 (95% CI 2.1 to 7.4) for women.

Although the educational level of the women cleaners was significantly lower than that in the reference group, the authors did not adjust for this factor. Studies of socioeconomic status and asthma have shown inconsistent results. Some studies found increased asthma prevalence in lower socioeconomic groups²¹¹⁻²¹³ while others reported no association.²¹⁴ Possibly the most robust study to investigate the association between asthma and socioeconomic status was carried out by Basagana *et al.*²¹² using data of the ECRHS. In this study, 10 971 adults, aged 20-44, underwent interviewer-led questionnaires about asthma symptoms and lifestyle. The study found that asthma prevalence was higher among subjects in lower socioeconomic groups whether defined by social class (OR1.51, 95% CI 1.2 to 1.9) or educational level (OR 1.28, 95% CI 1.0 to 1.6).

Another limitation of the study is including maintenance workers in the reference group which may be inappropriate since their job may involve activities such as grinding, drilling that could cause exposure to dust/particles that would affect their chest.²¹⁵

The response rates in the above studies, with the exception of Medina-Ramon *et al.*,¹⁶⁰ were relatively low with a median of 38% ranging from (18%-58%). Non-response may bias the estimated risk if the non-responders differed from responders in factors associated with asthma symptoms. Most of the studies did not obtain any information about the characteristics of non-responders for reasons such as ethical considerations so the extent of any bias in these studies is not known.

It has been reported that smoking, being a male, and having low socioeconomic status are commonly associated with poor participation in studies.²¹⁶ The likelihood of participation is also affected by subjects' perception of the importance of the study to their life. For example, several studies observed that those with diagnosed asthma or respiratory symptoms were more likely to respond to respiratory health surveys than healthier subjects.^{217, 218} Subjects' final decisions about whether or not to participate is based on all these factors.²¹⁶

For people of high socioeconomic status who are usually well educated, participation in scientific studies is perceived to be important and, in general, they show willingness to respond to health surveys.²¹⁰ In contrast, persons with lower socioeconomic status have lower education and usually experience stressful lives that make their participation in studies much less likely²¹⁹ unless the study is concerned with an issue related to their life.²¹⁶

Knowing that cleaners are of low socioeconomic status and that smoking is reported to be common in this group, it is reasonable to expect that some cleaners who participated in the epidemiological studies may have been motivated to participate by having asthma or respiratory symptoms. Accordingly, the observed prevalences might have been over-estimated. However, in a review of participation rates in epidemiological studies not necessarily related to asthma, Galea *et al* reported that there is little evidence of a substantial bias from non-participation.²¹⁶ This is illustrated by a New Zealand study where the prevalence of ever asthma (22%) among responders was found to be comparable to that of non-responders (21%) despite the low response rate (37%).²¹⁰ In summary, the epidemiological studies which showed increased risk of asthma among cleaners had suffered from low response rates, which might have slightly over-estimated the estimated prevalence though the magnitude of any effect is not likely to be large.

In contrast to these findings, there are studies that did not show an association between asthma and cleaning.

Fishwick and colleagues used the New Zealand arm of the ECRHS study to investigate the effect of current occupations on respiratory symptoms. In this study, 1609 subjects completed the questionnaires (response rate 64%) and 1126 (response rate 70%) underwent an airway responsiveness measurement.²⁰³ Occupational exposure was defined by the current job or by a previous job when respiratory problems started. When defining asthma as having a positive airway responsiveness measurement, cleaners (n=26) had no excess risk of asthma compared with referents of professional and administrative workers (n=1085) (OR 0.6 95% CI 0.2 to 2.1). Similar results were obtained for other asthma definitions such as wheeze alone (OR 1.0, 95% CI 0.4 to 2.0) or wheeze and airway hyper-responsiveness (OR 0.6, 95% CI 0.1 to 2.4).

The study did not show an association between asthma and cleaning possibly because of the low sample size compared with other studies. Indeed, the study also failed to show the association between asthma and other occupations which are well known to be associated with asthma such as spray painters and bakers as the number of these subjects was also small.

In the United States, an analysis of the National Health and Nutrition Examination Survey III data from 2001-2004 was performed to assess the relation between physician-diagnosed asthma and current occupation for working adults aged 20-59.²⁰⁴ Working in cleaning was not associated with an increased risk of asthma with an OR of 0.8 (95% CI 0.2 to 3.2). Unlike other studies, the authors selected construction workers as a referent group. This represents a major limitation since several studies have reported an increased risk of asthma among construction industry workers.^{220, 221}

An important point is that studies have used different classification systems for occupations such as the International Standard Classification of Occupations and the Standard Occupational Classification in the United States. Some countries such as France have developed their own system of occupational coding. Cleaners across countries have different titles, such as cleaner; housekeeper; and caretaker and are employed in different sectors.

Consequently, they might be classified differently either as a separate group or combined with other occupations having similar activities. This may introduce exposure misclassification which may partly contribute to the inconsistency between studies. Another related issue is that data about occupation in the epidemiological studies was collected and coded by interviewers who may also have introduced misclassification if they were not trained enough about the structure and the rules of the coding system.²²²

Summary of the cross-sectional studies

Table 3-1 presents an overview of the discussed cross-sectional studies.

Evidence from eight cross sectional studies showed that the prevalence of asthma in cleaners ranged from 11-28% compared with 6-17% among workers in the reference groups giving a range of ORs values ranging from 1.6 to 2.5 in the studies that showed an association. There were two studies that did not find an association between cleaning and asthma. This most likely was due to systematic errors or to insufficient statistical power of the studies.

There are notable limitations to the cross-sectional epidemiological evidence: low response rate, insufficient sample size, inappropriate reference groups, and possible exposure misclassification. These may have biased the results either by overestimating or underestimating of the estimated ORs.

None of the cross sectional studies investigated the temporal relationship between asthma development and working in cleaning. Temporal relationship is required to make a strong claim about the existence of a causal relationship between these variables. This could be possible if the information about the time of both asthma diagnoses and start of cleaning job was available. This missing piece of information in the cross-sectional studies makes it difficult to determine whether the increased risk of asthma in cleaning jobs was attributable to newly developed asthma or to aggravation of a pre-existing asthma.

Cohort studies are needed to establish a temporal relationship.

Table 3-1 Overview of cross-sectional studies of asthma in cleaners

First author, year	Location	Study Population	Assessment of asthma	Assessment of exposure	Results OR (95% CI) Cleaners Vs reference group	Note
Kogevinas, ² 1999	28 centres in European and non-European countries	15 637 adults Aged 20-44 years	- Questionnaire: asthma attack or awaking by shortness of breath in past 12 months or current use of asthma medication - Airway hyper-responsiveness	- Job title of current occupation or occupation when respiratory symptoms occurred - Grouped into 30 sets - Reference: professional, clerical and administrative	Asthma defined by questionnaire +airway responsiveness measurements OR 1.97 (1.3 to 2.9) Asthma defined by questionnaire OR 1.8 (1.4 to 2.3)	OR adjusted for age, sex, smoking, study centre
Zock, ¹⁴⁴ 2002	30 centres in European and non-European countries	6301 adults Aged 20-44	Questionnaire: asthma attack or awaking by shortness of breath in past 12 months or current use of asthma medication	Job title of current or most recent job Reference: professional, clerical and administrative	Asthma defined by questionnaire OR 2.5 (1.7 to 3.6)	OR adjusted for age, sex, smoking, study centre

Table 3-1 (continued) Overview of cross sectional studies of asthma in cleaners

First author, year	Location	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI) Cleaners Vs reference group	Note
Medina-Ramon, ¹⁶⁰ 2003	Spain	4521 women Aged 30-65 years	Questionnaire: asthma attack or awaking by shortness of breath in past 12 months or current use of asthma medication	Ever worked in cleaning (domestic and non-domestic) Reference: never worked in cleaning	OR 1.7 (1.4 to 2.1)	OR adjusted for age, smoking
Eng, ²⁰¹ 2010	New Zealand	2903 adults Aged 20-64	Questionnaire: asthma attack or awaking by shortness of breath in past 12 months or current use of asthma medication	Ever worked in cleaning Reference: never worked in cleaning	OR 1.6 (1.10 to 2.4)	OR adjusted for age, sex, smoking , deprivation

Table 3-1 (continued) Overview of cross-sectional studies of asthma in cleaners

First author, year	Location	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI) Cleaners Vs reference group	Note
Arif, ²⁰² 2003	United States	6551 adults over the age of 20 years	Questionnaire: ever diagnosed with asthma or have wheeze in the last 12 months Work-related asthma defined as positive answer to any of the above plus reporting worsening of respiratory symptoms at work.	Job title of the longest held job Grouped into 40 occupations Reference group: management, sectorial and clerical occupations	OR 2.4 (0.5 to 10.6)	OR adjusted for age, sex, atopy and smoking status
Le Moual, ¹⁹⁴ 2004	France	14 151 adults aged 25-59 years	Questionnaire: ever asthma, asthma with airflow limitation or asthma after the age of 14 years (adult-onset asthma).	Job title of the current or most recent job Categorized into 29 occupational groups Reference group: administrative and service employees	Asthma defined as ever asthma: OR 1.04 (0.7 to 1.5) Asthma defined as adult onset asthma or asthma with airflow obstruction: OR 2	OR adjusted for age, sex and smoking habits

Table 3-1 (continued) Overview of cross sectional studies of asthma in cleaners

First author, year	Location	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI) Cleaners Vs reference group	Note
Obadia, ²⁰⁶ 2009	Canada	566 Cleaners working in schools and racetrack public building Reference: 587clerical, maintenance, and security personnel	Questionnaire: 1.physician-diagnosed asthma 2. reporting three or more respiratory symptoms	Job title: current cleaners Reference group: never cleaner	Physician-diagnosed asthma: Male: OR 2.1 (0.9 to 4.8) Female: OR 1.1 (0.6 to 2.1) Reporting three or more respiratory symptoms Male: OR 1.2 (0.7 to 1.9) Female: OR 2.6 (1.6 to 4.3)	OR adjusted for age and smoking but not for socioeconomic status
Viscaya, ²⁰⁵ 2011	Spain	761 Current cleaners in different sectors 86 Former cleaners Reference: 70 never worked as cleaners	Questionnaire: asthma attack or awaking by shortness of breath in past 12 months or current use of asthma medication	Job title: current cleaners Reference group: never cleaner	OR 1.9 (0.6 to 5.5)	OR adjusted for age, sex, nationality, smoking

Table 3-1 (continued) Overview of cross sectional studies of asthma in cleaners

First author, year	Location	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI) Cleaners Vs reference group	Note
Fishwick, ²⁰ ³ 1997	New Zealand	1906 subjects aged 20-44 years	Questionnaire: asthma defined as reporting wheeze in the past 12 months Airway responsiveness measurements	Job title of current occupation or most recent job - Grouped into 21 sets - Reference: professional, clerical and administrative	Asthma defined as wheeze: OR 0.9 (0.4 to 2.0) Asthma defined as airway hyper-responsiveness 0.6 (0.2 to 2.1)	OR adjusted for age, sex and smoke
McHugh, ²⁰⁴ 2010	United States	4,585 subjects aged 20- 59	Questionnaire: physician-diagnosed asthma	Job title of current occupation or most recent job - Grouped into 22 sets - Reference group: construction workers	OR 0.8 (0.2 to 3.2)	OR adjusted for sex, body mass index and socioeconomic status.

3.2.2 Population-based case-control study

In Finland, Jaakkola and co-workers assessed the relation between occupation and the risk of asthma in a population-based incident case-control study.²⁰⁰ The study targeted adults 21-63 years of age living in a geographically defined area of south Finland. Cases were defined as adults with newly diagnosed asthma in the period between 1997-2000. The diagnostic criteria were: having at least one asthma-like symptom such as wheeze; cough; exercise induced dyspnea; and demonstrating reversibility of airway obstruction by objective tests. A total of 362 cases (response rate 90%) were identified from health care facilities specializing in pulmonary medicine. The authors also recruited 159 asthmatic patients registered in the National Social Insurance Institution during the period 1997-1999 (response rate 78%). In total, 521 cases fulfilled the study criteria. Cases were asked to report the job held at the time when asthma or respiratory symptoms started. Controls (n=1500) were randomly selected from the community using the national registry. Recruitment of controls was done by posting invitation letters up to three times and by making telephone calls to those who had a landline. One thousand and sixteen individuals responded but 84 possible controls were excluded because of previously having asthma; being older than 63 years; or missing questionnaire data. Thus, a total of 932 controls were included in the study giving a response rate of 62%. Comparing cases with controls showed that women cleaners had an increased risk for asthma with an OR adjusted for age and smoking of 1.42 (95% CI 0.8 to 2.5) compared to a reference category of administrative, professional and clerical personnel.

The estimated OR of 1.4 estimated was lower than those of the cross-sectional studies (1.8-2.5). This may be because the authors in most of the cross sectional studies relied on the questionnaires only to define asthma. Therefore, they may have identified those with mild asthma or with other respiratory conditions such as COPD. The latter may falsely inflate the number of asthma cases leading to over-estimation of the risk. On the other hand, the stricter criteria used in defining asthma in Jaakkola *et al*²⁰⁰ study were more likely to identify asthma accurately, but confined cases to levels of moderate to high in severity.

3.2.3 Population-based and workforce-based cohort studies

Kogevinas and colleagues³ conducted a prospective community-based study in order to estimate the relative and attributable risks of new onset asthma in relation to occupations and work exposures. Subjects (n=15716), aged 20-44 years, who participated in the ECRHS-I (1990-1993) were re-contacted after approximately ten years (1998-2003) and invited to participate in a second phase of the study, ECRHS-II. In this phase, 9175 subjects responded to the asthma questionnaire (response rate 43%) and among these, 8476 subjects took part in a detailed face-to-face interview about each job that was held for at least 3 months between ECRHS-I and ECRHS-II. Since the study was targeting asthma cases developing during the follow-up period, the authors excluded all subjects who reported asthma like symptoms at baseline (n= 1639). Hence, the analysis was restricted to 6837 participants. Of these, 4438 participants were tested for airway responsiveness by methacholine challenge. Occupational exposures were classified either by using a pre-determined list of occupations known to have a high risk of asthma; or by an asthma-specific job exposure matrix which linked each occupation to a specific exposure. The latter step was carried out by experts who were blinded to the asthma status of the subjects.

When asthma was defined as having an asthma attack or taking asthma medication in the last 12 months, those working in cleaning and caretaking (n=358) had a higher risk of developing asthma compared with a reference group of professional, clerical, and administrative workers with an adjusted (age, smoke and sex) relative risk (RR) of 1.7 (95% CI 0.9 to 3.2). Applying the job exposure matrix, it was found that participants exposed to cleaning products (n=410) had a higher risk of developing asthma with a relative risk of 1.8 (95% CI 1.0 to 3.2) compared with unexposed participants. This study had the advantage of using multiple measures when assessing exposure which are likely to have minimized exposure misclassification.

In the UK, a large population-based birth cohort study was conducted recently by Ghosh *et al*¹⁹⁷ (2013) with the aim of identifying occupations and occupational exposures associated with asthma in the British adult population. In this study, 17 638 babies born in the UK between 3 and 9 March, 1953 in addition to immigrants (n= 920) that were born in the same week were followed up and interviewed at the ages of 7, 11, 16, 33 and 42 to identify newly developed asthma. Subjects at the age of 33 and 42 years were also asked about jobs that were held for at least one month, and these were coded to the International Standard Classification of Occupations-88. Job titles were then used to determine individuals' work-related exposures using an asthma specific job exposure matrix. At the end of the follow up, 2082 subjects were excluded because there was a parental report of asthma or wheezy bronchitis at the age of 7, 11 or 16. The reason for exclusion of both groups is that It would have been difficult to distinguish asthma from bronchitis in the age group < 16 years so to ensure that subjects with childhood asthma were not studied both groups were excluded. Therefore, the study included 7406 subjects who did not have asthma in childhood, of whom 639 (9%) reported ever having had asthma at the age of 33 or 42 years, i.e. adult onset asthma.

The study found that ever having worked as helpers and cleaners in hotels and offices (n= 516) was more frequently associated with adult-onset asthma compared with those who worked in office-based occupations, adjusted OR (1.8, 95% CI 1.4 to 2.5).

Although the study started with 18558 subjects, the analysis included only 7406 subjects, i.e. 40%. Losing subjects during follow up study is a potential problem in cohort studies in general and may occur due to, for example, migration, withdrawal or death. The characteristics of those who were lost during follow up were not reported in the study. These might have influenced the association if they differed in asthma status or work exposure from the participants.

The OR (1.8) obtained and the RR (1.7) estimated in the ECRHS-II study indicate that cleaners had an excess risk of asthma. However, it is noticed that the proportion of subjects taking part who were cleaners in both the ECRHS (9%) study³ and Ghosh *et al* (11%)¹⁹⁷ was unexpectedly high bearing in mind that cleaners generally form only 2-4% of the working population. The figure for

those who ever worked as a cleaner - the criteria for the ECRHS-II and the birth cohort studies - will inevitably be greater than 2-4% but the very high figures for participation of cleaners in these studies at least raises the possibility of exposure misclassification. In the ECRHS-II and the birth cohort studies, subjects were asked about occupational histories and specific tasks, after which the information was coded by experts using either national or international classifications. The reliability of the coding thus depends on two main factors: 1) the accuracy of the occupational information collected from subjects; and 2) the reliability of the translation process of this information into a single code.²²² So if the subjects failed to recall a job title; deliberately falsified a job title; or provided a vague description of the tasks,²²³ exposure misclassification may have occurred. Equally, if the person who was responsible for assessing exposures did not receive adequate training on the coding system, misclassification would be inevitable. Such errors might have influenced the estimates.

In a Finnish study, Karjalainen and colleagues investigated the risk of asthma among 53,708 Finnish cleaners.⁴ The authors identified three consecutive census cohorts of women cleaners aged 25-59 years who did not have pre-existing asthma (total n= 53 708) and three cohorts of administrative workers (n=202 751). Each cohort was followed for asthma during one of these periods: 1986-1990, 1991-1995, or 1996-1998 respectively. During follow-up, the investigators identified new cases of asthma by reviewing the Medical Reimbursement Register and identified occupational asthma by reviewing the Finnish Register of Occupational Diseases. In Finland, the patient is reimbursed for asthma medication if the diagnosis is confirmed by objective tests showing airway reversibility and certified by a specialist doctor. Moreover, if the asthma is suspected to be work-related, the patient is sent to a specialized centre in order to verify work-relatedness by objective tests such as serial PEF and specific inhalation tests. Patients with positive results are registered in the Finnish Register of Occupational Diseases for compensation.

2414 cases of asthma were identified among cleaners with an estimated annual incidence of 3.4/1000 cleaners. During the same period, 5235 administrative workers developed asthma with an incidence of 2.0/1000 worker per year. The age adjusted RR was 1.5 (95% CI 1.43 to 1.57) in cleaners.

One possible criticism of this Finnish study is the lack of adjustment for smoking because of the unavailability of this information from the registry. This is important given that ECRHS-I with data on 14565 adults in 11 European countries demonstrated that cleaning was among the occupations associated with higher levels of smoking with a prevalence of 50.7% in women and 48.1% in men in comparison with 33.6% and 35.4% among groups of professional; administrative; clerical and service workers.²²⁴ Several studies have suggested that smoking might increase the risk of asthma.^{225, 226} For example, Piipari *et al*²²⁵ conducted an incident case-control study in which 521 new clinically diagnosed asthma cases were compared to 932 controls. The authors found that current smokers had a 30% increased risk of developing asthma, (95% CI 1.0 to 1.7). On the other hand, there are studies that have failed to show an association between developing asthma and smoking and the effect of smoking on asthma in adults is uncertain.^{227, 228} Smoking might have amplified the estimated relative risk of asthma associated with cleaning in the Karjalainen *et*

a/ study.⁴ However, since all other epidemiological studies found an increased risk of asthma among cleaners after adjustment for smoking, and as that the relation of smoking with asthma is still controversial, smoking is not likely to explain the increased risk of asthma in cleaners.

Summary of longitudinal studies

The reviewed prospective cohort studies revealed that there is high incidence of asthma among cleaners that ranged from 3.4-4.8/1000 person-years compared with an incidence of asthma (1.2-2.6/1000 person-years) among a reference group of administrative workers. This was reflected in an elevated measures of association (RR and OR) which ranged from 1.5 to 1.8. This is generally lower than the range of the risk estimates reported in cross-sectional studies (1.8-2.5).

Cohort studies have the advantage over the cross-sectional in that they provide a clear temporal sequence of exposure (cleaning job) and disease (asthma). The strength of some of the reviewed studies in particular was in defining asthma cases by combining symptoms with objective tests. This would minimize misclassifying non-asthmatic subjects as being asthmatics, however, this may make the studies biased toward more severe asthma. Nevertheless, the reviewed studies did not study the attribution of host factors such as atopy and smoking on the development of asthma.

Overall, the findings from longitudinal studies confirmed the observation of the earlier cross-sectional studies by demonstrating the temporal relationship between asthma development and working in cleaning. It is not uncommon to have cohort studies initiated by the results of cross-sectional studies. This can be illustrated by the asthma among laboratory animal workers which was first suggested by cross-sectional studies. However, the exposure-disease relationship was only confirmed by subsequent cohort studies.

The summary of the case-control and cohort studies are presented in table 3-2 and table 3-3.

Table 3-2 Population-based case-control studies

First author, year	Location	Study period	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI)	Note
Jaakkola, ²⁰⁰ 2003	Finland	1997- 2000	1453 adults Aged 21-63 years	Symptoms +clinical tests for airway reversibility	Job title of current occupation or occupation when respiratory symptoms occurred Grouped into 29 sets Reference: professionals, clerks, administrative	Women cleaners vs reference OR 1.4 (0.8 to 2.5)	OR adjusted for age and smoking

Table 3-3 Cohort studies of asthma in cleaners

First author, year	Location	Study period	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI)	Note
Kogivenas, ³ 2007 ECRHS-II	28 centres in 13 European and non-European countries	Phase-I 1990-1995 Phase-II 1998-2003	6837 adults	Questionnaire : asthma attack in past 12 months or current use of asthma medication	Occupational history by interview, workers classified in to priori at risk occupations by experts Asthma specific job exposure matrix Reference: professional, clerical and administrative	Cleaning and caretaking vs reference RR 1.7 (0.9 to 3.3) Cleaning products RR 1.8 (1.0 to 3.2)	RR adjusted for age, sex, study centre, smoking
Ghosh, ¹⁹⁷ 2013	UK	Birth cohort 1958 up to the age of 42	7406 cohort members with no asthma or wheezy bronchitis in childhood	Self-reported physician-diagnosed asthma at the age of >16 years	Occupational history by interview, job titles coded using the International coding system Asthma specific job exposure matrix Reference: professional, clerical and administrative	Helpers and cleaners in hotels and offices Vs reference OR 1.8 (1.4 to 2.5)	OR adjusted for sex, smoking, father's social class at birth, region and hay fever

Table 3-3 (Continued) Cohort studies of asthma in cleaners

First author, year	Location	Study period	Study Population	Assessment of asthma	Assessment of exposure	Results (95% CI)	Note
Karjalainen, ⁴ 2002	Finland	1986- 1995	53708 Women cleaners Reference: 202751 Women administrative workers	Symptoms +clinical tests for airway reversibility	- Job title of the current occupation - Reference: professionals, clerks, administrative	Cleaners vs reference RR 1.5 (1.4 to 1.6)	RR adjusted for age

Despite the existence of a number of published epidemiological studies linking asthma and cleaners, there has been little discussion about the association from the clinical point of view. Most of published papers are individual case reports that described the development of asthma in a cleaner after exposure to specific cleaning products.^{229, 230} Few studies have focused on the characteristics of asthma in cleaners in general and those that did have produced contradictory results. For example, an early international study (2002) by Zock et al¹⁴⁴ found that asthmatic cleaners were less atopic when compared to non-occupational asthma among office workers. A recent study (2013),²³¹ on the other hand, found a significant association between asthma and atopy when asthmatic cleaners were compared with non-asthmatic cleaners.

There have been no attempts to systematically investigate whether the proportion of cleaners who have been identified to have occupational asthma by physicians matches the increased prevalence of asthma reported in epidemiological studies. If it does not, further research would be needed to investigate the possible reasons of the discrepancy between the findings of the epidemiological studies and the findings based on the clinical data. It is known that a diagnosis of occupational asthma could be missed or delayed by GPs.¹⁵² However, whether this applies to cleaners, and if so, the size of under-recognition is unknown. This issue of underdiagnosing occupational asthma is important when we consider cleaners since they constitute a large workforce population in many countries including the UK.¹⁹⁸

Nonetheless, there are several papers which estimated the prevalence of work related asthma among cleaners based on the registry notes.

3.2.4 Registry based-studies

In the United States, California, physicians are required to submit a form called Doctor's First Report if they treat an employee with work-related illness or injuries. These are the source of information for a surveillance system for work-related illness called Sentinel Event Notification System for Occupational Risk programme (SENSOR). Reinisch and co-workers¹⁹² reviewed SENSOR data from 1993 to 1996 to identify potential cases of work-related asthma. Of 9478 respiratory reports, the authors identified 945 with the diagnosis of asthma or RADS. After case identification, the researcher conducted telephone interviews to assess occupation and work-relatedness of symptoms. Only 444 subjects agreed to participate and were included in the final analysis. It was shown that janitors and cleaners had the highest annual rate of work-related asthma, 625/million employed workers, based on 32 cases.

Based on the same surveillance system (SENSOR), Rosenman and colleagues¹⁹³ reviewed Doctor's First Report forms submitted in 1993-1997 in four states: California; Massachusetts; Michigan and New Jersey. They identified 1915 cases of work-related asthma for which they conducted telephone interviews to inquire about occupation. Janitors (n=52) were the largest of 11 occupational groups, constituting 22% of all of reported occupations. The incidence of work-related asthma in the four states was found to be 43/million workers. It is important to note that this estimate is substantially lower than that estimated by Reinisch *et al*¹⁹² in California alone (625/million workers) using the same surveillance system, i.e. SENSOR, in the same period. This discrepancy in the incidence estimates could be because there is no standardized method for reporting to SENSOR in the different states. While it depends on a limited number of clinics in Massachusetts, there is a comprehensive administrative system in California where a large number of physicians can report. Therefore, the number might not be representative of the population in certain states.

The incidence of occupational asthma, rather than work-related asthma, in cleaners was reported in three published papers, table 3-4.

Table 3-4 Estimated annual Incidence of occupational asthma per million cleaners based on reporting-schemes

Reference	Country	Surveillance system	Period	Incidence (95% CI) per million cleaners
174	UK	SWORD	1992-1997	18 (8 to 39)
187	France	ONAP	1996-1999	55 (42 to 68)
161	Finland	FROD	1989-1995	80 Female (60 to 120) 40 Male (0 to 250)

Apart from FROD, there were no confirmatory pulmonary tests.

One important question is whether these figures reflect the real size of the cleaning-related asthma problem. The best way to answer that is to compare incidence estimated by the reporting schemes to what has been estimated by population-based studies.

The Finnish study of Karjalainen *et al*⁴ is the most robust of the epidemiological studies. It included a relatively large cohort of cleaners (n=53,708) and administrative workers (n= 202,751), it had a longitudinal design, and it used a strict asthma definition based on questionnaires and objective tests. During the follow-up period, 2414 cleaners developed new onset asthma with an incidence of 3350/million/year which was higher than that among administrative workers (1980/million/year) giving a RR of 1.5 (95%CI 1.4 to 1.6). This RR implied that one third of the cases (n=805) were most likely associated with work which would yield an estimated incidence of 1117/10⁶/year. This estimate is higher than that estimated by the reporting schemes presented in the table above (range 18-80/million/year). This suggests that while 1117 per million cleaners develop new occupational asthma yearly, physicians recognize at most 80 cases only. Thus, a great proportion of cleaners with occupational asthma go unrecognized as having work-related disease, i.e. labelled with asthma only, or may be misdiagnosed as other disease, e.g. COPD.

There are two possible explanations for this discrepancy: either population based studies have over-estimated the risk of asthma in cleaners or clinicians have failed to recognize the occupational asthma.

Over-estimation of the asthma risk in population-based study may have occurred by including mild asthma cases or other conditions with asthma-like symptoms such as COPD. Nevertheless, this is unlikely given the consistency of the findings obtained by many studies, some of which have used stringent criteria to define asthma and, yet, have found a positive association between cleaning and asthma.

The other explanation is that occupational asthma in cleaners goes under-recognized by physicians. It is possible that cleaners develop sensitiser-induced asthma with typical work-related symptoms but clinicians fail to recognize it for various reasons. GPs, who are usually the first contact, do not often consider occupational history during clinical consultations.¹⁵¹ Even if they inquire about occupational history, GPs in general are only aware of the most common occupations related to occupational asthma and cleaners have only recently been identified as a high-risk job. It is also possible that GPs are not willing to report the case as occupational asthma since this would have negative impact on the cleaner's job and income.¹⁰⁴

Under-recognition could also be caused by cleaners themselves if they do not present their symptoms to the GPs. Previous studies found that workers in general often do not often report work-related illness for many reasons such as fear of management reprisal and of losing their job.¹⁸² One study among 941 hotel cleaners found that 30% reported work-related illness during the previous 12 months although over 90% experienced work-related pain or discomfort.²³²

Alternatively, cleaners' occupational asthma might have different features from typical occupational asthma and that make it difficult to recognize by physicians. Cleaning-related asthma may develop gradually due to exposure to low level irritants without having symptoms related to work, the feature that is required to diagnose occupational asthma clinically.

3.3 Description of general occupational hazards experienced by cleaning workers that may be associated with asthma

Cleaners work in a variety of industrial and non-industrial sectors in different work environments, both indoors and outdoors (e.g. schools, hospitals and factories). They are exposed to numerous types of chemicals and particulate compounds that might be responsible for cleaning-related asthma. These exposures come not only from cleaning tasks but also from the environment in which the cleaning is carried out.

Dusting and vacuum cleaning often cause re-suspension of dust which can contain mites or toxins that might induce asthma.²³³ In a recent study (2013), Viscaya *et al*²³¹ compared the functional and biological characteristics of 42 cleaners with asthma and/or respiratory symptoms to those of 53 healthy cleaners. Atopy evaluated by measuring specific Ig-E to 10 common aeroallergens and sensitization to dust mites was found to be more prevalent among cases (42% and 31% for atopy and dust mite respectively) than controls (10% and 4%).²³¹ However, when Zock *et al*¹⁴⁴ analysed the ECRHS data to investigate the characteristics of cleaners' asthma, they found that asthmatic cleaners were less atopic than asthmatic office workers. These contradictory findings indicate that the role of sensitization to common allergens is uncertain. It might contribute to some asthma in cleaners but it remains unclear by how much and it alone is unlikely to account for the very high risks identified in some epidemiological studies.

Microbial agents such as moulds can also be encountered during cleaning operations. Several epidemiological studies have reported an association between indoor dampness/moulds and asthma in adults^{234, 235} and overall, there appears to be approximately a 1.5-fold increased risk of asthma in those exposed to damp/moulds.²³⁶ That therefore might also contribute to the increased risk of asthma in cleaners. In a Finnish study, 20 female cleaners underwent comprehensive clinical investigation of their asthma including specific challenge tests. It was found that exposures to moulds caused asthmatic reactions in 11 (55%) cleaners.²³⁷ However, sensitization was found in only three cleaners which indicate that a causative relationship between moulds and asthma is unlikely unless moulds induce asthma through non-

allergic mechanism, a possibility that is suggested by one study.²³⁴

Furthermore, the proportion of mould-associated asthma (55%) in the Finnish study appears to be exceptionally high and may not be generalizable. Damp and mould problems are common in many countries²³⁸ and affect properties such as houses and schools. Nevertheless, there are no reports of epidemics of mould-induced asthma either among the general population or workers such as teachers.

Cleaners particularly in industrial sectors may also encounter agents known to cause occupational asthma e.g. flour dust. In Karjalainen *et al's*⁴ study in Finland, about 50,000 cleaners were followed up for ten years and 2414 developed asthma. A diagnosis of occupational asthma was established in 25 cleaners mostly due to industry-specific exposures such as isocyanates and flour dust.⁴ Given that epidemiological studies^{3, 4} suggest that 30%-40% of asthma in cleaners is work-related, the 25 cleaners in whom a specific previously-recognized cause of occupational asthma was identified represents only a very small proportion of the overall burden. The bulk of the disease has some other as yet unidentified cause or causes.

Rubber gloves have been widely used among cleaners in different settings such as hospitals and the food industry. When gloves are made of natural rubber latex, they introduce a risk of latex sensitization and asthma.²³⁹ Latex-induced asthma was a major problem in the early 1990s when powdered latex gloves were widely used in healthcare settings to prevent the transmission of blood borne pathogens but substitution of powdered latex gloves with low protein or non-latex gloves has markedly reduced the prevalence of latex-induced asthma since the early 2000s. In an earlier registry-based study, latex was the second most frequently reported cause of work-related asthma among health care workers including cleaners.²⁴⁰ A recent study (2013) among non-domestic cleaners found that 7% of cleaners had latex sensitization defined by the presence of specific IgE antibodies.²³¹ However, being sensitized to latex does not mean that the subject will necessarily develop occupational asthma. This can be illustrated by Vendenplas *et al's*²⁴¹ study in which 273 health care workers were investigated for latex induced asthma. They underwent skin prick testing, airway responsiveness measurements and specific challenge with latex.

Five percent (5%) showed positive skin reaction to latex. Of these, half (2.5%) only developed significant airway responses to latex gloves exposure.

Clearly, there are several potential causes of typical sensitiser-induced occupational asthma in cleaning work. They might be the cause in some cases of asthma but they do not fully explain the observed increased asthma risks in cleaners. Since cleaners are employed in different sectors and have different exposures, the causative factors are most likely inherent to cleaning itself rather than due to industry-specific or previously established causes of occupational asthma.

3.4 Literature investigating work-related risk factors (tasks and products) for asthma in cleaners

In order to ascertain the mechanism(s) of asthma in cleaners, many workforce-based studies have investigated potential risk factors for cleaning-related asthma.

Zock and colleagues telephoned 78 cleaners who participated in the 1992 Spanish limb of the ECRHS study.²⁰⁷ Their aim was to determine the specific cleaning activities and cleaning products associated with asthma. Five cleaners were excluded because they reported never having worked as a cleaner and five refused to participate. The authors thus interviewed 68 cleaners in 1998 to obtain detailed information about their cleaning work (location, duration, activities, frequency, and the products used) six years previously. After interview, one cleaner was excluded because he was the only one who worked outdoors while the remaining were indoor cleaners and carried out similar tasks. This group was further subdivided into those exposed and unexposed for each activity and product. Asthma prevalence was compared to that of a reference group of office workers. Asthma prevalence was found to be higher for kitchen cleaning, prevalence ratio of 3.9 (95% CI 2.2 to 7.0); vacuuming; cleaning furniture; cleaning sanitary facilities, all with the same prevalence ratio of 3.8, (95% CI 2.1 to 6.8). With regard to cleaning products, it was found that polishes, prevalence ratio of 4.1 (95% CI 1.6 to 10.00), and oven sprays, prevalence ratio of 4.3 (95% CI 2.2 to 8.7) had the highest risk estimates.

In the study, cleaners were required to remember the cleaning tasks they were doing 6 years earlier. Recall of exposures that took place a long time ago might produce inaccurate information. Indeed, studies have shown that human memory retrieves less than 50% of details of a recognizable event after five years.²⁴²

Medina-Ramon and co-workers investigated which agents and tasks in domestic cleaning were related to asthma and chronic bronchitis using a case-control design.¹⁴⁵ Detailed information on the frequency of 23 cleaning tasks and the use of 22 different agents was collected in face-face interviews with 40 cases, defined as domestic cleaners with asthma or chronic bronchitis, and 150 controls who were cleaners with no respiratory symptoms. The investigators

also asked about a history of inhalation accidents when using single or mixtures of cleaning products.

Of the 23 cleaning tasks, mopping the floor, OR of 2.8 (95% CI 1.2 to 6.8), and cleaning kitchens, OR of 2.2 (95% CI 1.0 to 5.3), were the only tasks with significant or borderline associations with asthma or chronic bronchitis. In addition, the use of undiluted bleach, OR 2.4 (95% CI 1.0 to 6.1), undiluted ammonia, OR 3.1 (95% CI 1.2 to 8.0), and degreasing sprays, OR 2.6 (95% CI 1.1 to 6.0) in high frequency were reported more by cases than controls. Having inhalation accidents was independently associated with asthma with an adjusted OR of 3.0 (95% CI 1.0 to 14.0).

The studies were restricted to domestic cleaners who have been shown to often lack the training and knowledge required to perform cleaning work in a safe manner, such as not mixing incompatible chemicals, compared with cleaners in other settings, e.g. industrial cleaners.²⁴³ Therefore, poor practices among the domestic cleaners may have partly contributed to their higher risk of respiratory symptoms in these studies, making their generalizability to cleaners as a whole questionable.

Macaira and co-workers identified 11 320 cleaning workers employed in different companies in Brazil.²⁰⁸ Their aim was to measure rhinitis and asthma prevalences and to analyse the associated risk factors. The authors excluded cleaners employed in locations with possible exposures to dust, fumes or gases unrelated to cleaning activities, such as transportation, ending up with only 5051 eligible workers. Of these, 341 non-domestic subcontracted cleaners working in 36 locations were selected by systematic sampling. They were given questionnaires about respiratory symptoms and current non-domestic cleaning work.

The frequency of: 1) performing 6 tasks, 2) using 19 different cleaning products, and 3) the inhalation of significant quantities of gas/vapour/fume from cleaning products that caused immediate respiratory symptoms was compared between cleaners with asthma and/or rhinitis and cleaners without symptoms (reference). Among female cleaners (n=245), the tasks were performed and products used in a similar frequency between these two groups. Among the men (n=96), however, having asthma/rhinitis was associated with dusting/vacuuming/sweeping/rug beating, OR 1.6 (95% CI 0.8 to 3.3) and using bleach, OR 1.9 (95% CI 0.8 to 4.3), though none of these associations was statistically significant. There was a marginally significant association between asthma/rhinitis and using a degreaser, OR 2.0 (95% CI 1.0 to 4.0). Inhalation accidents were associated with a non-significant increased risk of asthma/rhinitis among both male and female cleaners, OR 1.5 (95% CI 0.7 to 3.1).

Viscaya and co-workers²⁰⁵ recruited cleaners from companies with heterogeneous activities with the aim of studying associations between the use of cleaning products, particularly irritant products, and asthma. The authors asked 761 cleaners to complete a questionnaire about respiratory symptoms and occupational exposures to a list of 12 irritant products including bleach, degreasers and air fresheners. The reference group (n=161) comprised subjects who had never been cleaners, and current cleaners who had not been exposed to the cleaning products under study in the year preceding the study. Most of the products (9 of 12) were associated with an excess risk of current asthma but not significantly so: hydrochloric acid, OR 1.8 (95% CI 0.8 to 3.8); bleach, OR 1.7 (95% CI 0.8 to 3.5) and ammonia, OR 1.4 (95% CI 0.6 to 3.2).

The confidence intervals in Macaira *et al's*²⁰⁸ and Viscaya *et al's*²⁰⁵ studies generally overlapped 1 so no significant associations were demonstrated. One of the reasons for not demonstrating a statistically significant association may relate to the study population who were subcontracted cleaners. These cleaners usually rotated through different premises and worked under conditions that changed from one day to another. Consequently, their cleaning products and tasks may have changed so frequently that they could not recall accurately what they used or performed and for how long.

Obadia and co-workers²⁰⁶ investigated the association of work-related asthma symptoms and cleaning tasks among male cleaners (n=463) who worked in school and racetrack buildings. The association was highest for wax-stripping, OR 2.45 (95% CI 1.2 to 5.2); carpet spot cleaning, OR 2.2 (95% CI 1.3 to 3.8) and oiling furniture, OR 2.7 (95% CI 1.3 to 5.6).

In one follow-up study conducted by Nielsen and co-workers²⁰⁹ among female cleaners, the risk of developing asthma and irritant symptoms when using spray products was assessed. In 1989, a questionnaire about using sprays, irritant eye and nose symptoms and asthma, defined as attacks of wheezing, was posted to female cleaners working in schools, nursing homes and offices (n=2697). Of these, 1237 (response rate 55%) answered the questionnaires after two reminders. A follow-up questionnaire was sent in 1991 which was answered by 1011 (response rate 88% of those who responded in 1989). The authors found that cleaners who continued to use spray products were at higher risk of asthma but not statistically significant, OR 3.0 (95% CI 0.9 to 10.0), and at a significant increased risk of irritating nose and throat symptoms, OR 2.1 (95% CI 1.1 to 3.8), compared with cleaners who never used sprayers. This association was also suggested for those who started using sprayers during the follow-up with an OR of 2.4 (95% CI 0.6 to 10.0) for asthma and OR of 2.0 (95% CI 0.9 to 4.1) for nose/throat irritant symptoms.

In the occupational epidemiology studies reviewed above, a point that must be taken into account when assessing exposure-response relationships is the healthy worker effect which results from either the higher tendency of workers with asthma to terminate their employment or to transfer into lower exposure areas than the healthy co-workers, or from the tendency of asthmatics to stay

away from exposed jobs. Indeed, in Ghosh *et al*¹⁹⁷ study which investigated the association of asthma with occupation in the 1958 birth cohort, asthmatic cleaners were found to spend significantly less time in cleaning jobs (one year) than non-asthmatic cleaners (3 years). This may have caused underestimation or even absence of a positive association between cleaning tasks/products and asthma. This healthy worker effect can be illustrated by Eisen *et al*²⁴⁴ study about the association of metalworking fluid with asthma. Their initial cross-sectional study of 1788 workers did not show a positive association between diagnosed asthma and exposure to metalworking fluid despite the strong evidence from clinical studies. However, when the authors re-analysed the data using the exposure status before the asthma onset, a significant association was revealed (rate ratio 3.0, 95% CI 1.2 to 8.0) which indicated that workers had moved away from the exposure area after asthma onset.

All the studies reviewed so far relied on cleaners self-reported exposures in questionnaires or interviews. The self-report method is particularly subject to recall bias. In case-control studies, such as Medina-Ramon *et al*¹⁴⁵, the recall of the relevant exposures of controls and cases might have differed. Cases may be more motivated to search their memories for exposures in an attempt to find an explanation for their asthma, and this might have caused over-estimation of the associations demonstrated. Another point that would affect the accuracy of the self-reported information is that it depends on the subjects' knowledge of their occupational exposures. In Donnay *et al*²⁴⁵ study, for example, health care workers were asked to self-report their occupational exposures. At the same time, experts were asked to assess the employees' occupational exposures. By comparing self-reported exposures to the expert assessment, it was found that cleaners underestimated their exposures to many chemicals including ammonia, and quaternary ammonium. This was thought to be because cleaners might know the common names of the products they use or their general category, for example polish and glass cleaners, but they are unlikely to know the chemical names of the products' components. This might also lead to under-estimation of the association between asthma and exposures to some of these chemicals.

All workforce-based studies are summarized in table 3-5.

Table 3-5 Summary of the main findings on the relation between respiratory morbidity and cleaning exposures

Ref	Study design	Study population	Main risk factors
207	Cross-sectional	21 domestic female cleaners, Spain	Cleaning kitchen, vacuuming, cleaning furniture and sanitary facilities, using polishes and products in spray form were associated with asthma
145	Case-control	40 case with asthma/ bronchitis 155 controls without respiratory symptoms, all domestic cleaning women, Spain	Using bleach, washing dishes, inhalation accidents and history of non-domestic cleaning was associated with asthma.
208	Cross-sectional	341 non-domestic cleaners working in cleaning service companies in Brazil.	Among men cleaners: dusting/sweeping/vacuuming and using bleach were associated with asthma/rhinitis Inhalation accidents was associated with asthma/rhinitis among male and female cleaners
205	Cross-sectional	761 cleaners working in cleaning companies in Spain.	Using irritant products including bleach, sprays (glass cleaner and air fresheners) and ammonia was associated with current asthma
206	Cross-sectional	566 cleaners 587 other building workers Canada	Waxing, carpet spot cleaning, furniture oiling and cleaning tiles were associated with work-related asthma symptoms in men cleaners
209	Cohort study	1011 cleaners working in schools, nursing homes and offices, Denmark	Using sprays was associated with asthma and irritating symptoms.

Among the investigated chemical products, bleach was repeatedly shown to be a risk factor for asthma.

Chlorine bleach is the most commonly used cleaning agent in the developed world. Commercial “household” bleach contains 5% to 10% sodium hypochlorite, a chlorine-liberating agent, as the active component. In industrial bleach, the concentration of this agent may reach 50%.²⁴⁶ It disinfects mainly through the slow release of chlorine. However, during cleaning, chlorine may interact with nitrogen compounds found for example in food or urine forming chloramine compounds. This implies that cleaners are often exposed to low levels of chlorine/chloramines when bleach is used in cleaning tasks. Exposure levels were documented in Medina-Ramon and colleague’s study¹⁴⁵ by *ad hoc* personal measurement of chlorine concentration for ten cleaners while cleaning kitchens or bathrooms. It was shown that cleaners were exposed to a median level of chlorine ranging from 0-0.4 ppm, which is lower than the occupational exposure limit (0.5 ppm).²⁴⁷

Both chlorine and chloramines are strong irritants to the respiratory system.²⁴⁸⁻²⁵⁰ Many case reports have described irritant symptoms such as cough, throat irritation and bronchospasm among people after accidental exposure to chlorine gas in domestic situations²⁵¹ or in community environments such as after spills.²⁵² In addition, several studies of industrial workers have reported similar symptoms among workers exposed to chlorine.^{146, 147} Likewise, chloramines have been found to be the main cause of upper respiratory irritation symptoms among workers in different settings such as in the food industry and in swimming pools.^{142, 148, 248} An example of this is the study carried out by Massin *et al*²⁴⁸ with the aim of investigating the respiratory effects of chloramines used in cleaning and disinfecting processes in food plants. The authors found that exposed cleaners had significantly more nose; eye; and throat irritant symptoms compared with non-exposed workers employed in other factories. The almost ubiquitous use of chlorine in cleaning and its irritant properties raises the question of whether chronic exposure to low levels of irritants could induce asthma in cleaners.

It is well known that acute high level exposure to chlorine can cause acute-irritant-induced asthma (RADS). Chlorine is considered one of the commonest irritants that cause RADS.²⁵³ Sallie and MacDonald, for instance, found that chlorine was the most frequently reported cause of RADS cases identified in the UK.¹⁷⁹ The respiratory effect of moderate level exposures of chlorine was

studied in the 1990s mainly among pulp mills workers.^{89, 147} The studies found that workers who were repeatedly exposed to moderate levels of chlorine developed persistent asthma-like symptoms and changes in airway calibre.^{90, 146} There is no parallel research for chloramines.

More recently, studies have suggested that there is a possibility that chronic exposure to low levels of chlorine/chloramines may also induce asthma. Most of the evidence comes from studies carried out among swimmers who frequently attend chlorinated swimming pools. It was found that lifeguards and trainers were at an increased risk of irritant respiratory symptoms^{142, 148, 249} and asthma⁹¹ compared with groups with lower levels of exposure such as administrative staff in the swimming pool. These observations support the hypothesis that cleaners and others might develop asthma due to low-dose irritant exposures.

The mechanism of low-dose irritant-induced asthma is unknown. It is proposed based on few studies¹⁴⁶⁻¹⁴⁸ among pulp mill and swimmer population that low-dose irritation cumulatively increases airway responsiveness without affecting airway constriction or, in parallel, without causing work related symptoms. If this is the case, the lack of work relatedness could explain why asthma among cleaners would go unrecognized by physicians.

Alternatively, cleaners might be intermittently exposed to considerable amounts of chlorine or chloramines fumes after mixing bleach with other incompatible cleaning agents. This could cause RADS as described in previous case reports among professional cleaners (n=1); and others (n=4) carrying out cleaning tasks.^{230, 254-256} The diagnosis of RADS can easily be established because of the relatively brief latency between exposure and respiratory effects and it is highly unlikely to have been missed by reporting physicians. Since so few cases of asthma in cleaners have been identified over 20 years, developing asthma through this mechanism does not seem to play a major role in cleaners' asthma and is not likely to explain the increased risks observed in the epidemiological studies.

Given that cleaners' asthma seems to develop in an unusual way that makes its diagnosis difficult, exploring the potential mechanism by which chlorine and chloramines might induce asthma could help by finding a test that would allow early detection of the occupational asthma of cleaners.²⁵⁷

Basic mechanism of chlorine toxicity

When chlorine comes into contact with water including the moist linings of mucosal surfaces and airways, it forms hydrochloric and hypochlorous acids.²⁵⁸

Chlorine-induced airway injury is mainly related to the oxidizing potential of chlorine and hypochlorous acid. The hypothetical mechanisms of airway injury are the following:

- 1) The hydrochloric and hypochlorous acids may cause injury and initiate inflammation. This would recruit activated inflammatory cells such as neutrophils and macrophages. These release reactive oxidant species, such as hydrogen peroxides; nitric oxide and superoxide that may worsen the degree of injury.²⁵⁹
- 2) Released hydrogen peroxides; nitric oxide and superoxide interact with hypochlorous acid and chlorine to form reactive intermediates capable of crossing the cell wall and causing changes in the structure of enzymes and other proteins.^{250, 260}

With exposure to low concentrations of chlorine, most will be removed in the upper airway mucosa. The formed acids will affect the sensory nerve endings causing irritant symptoms, such as rhinitis and reflexive bronchoconstriction. With continuing exposure on a day-to-day basis, damage occurring at a cellular level (point 2 above) would irritate mucosal cells causing hyper-secretion of mucus and sloughing of dead epithelial cells. This might affect the integrity of airway which further induces inflammation. The inflammation might underpin the increased airway responsiveness. In the long run, this might lead to swelling of the airway mucus which would narrow the lumen. Clinically, this would be manifested as reduced lung function, and by the perception of asthma-like symptoms such as cough and shortness of breath.²⁵⁸

Chloramine toxicity

Unlike chlorine, chloramines are relatively insoluble and thus are not absorbed in the mucous membrane of the upper airway.²⁶¹ After exposure, a great quantity will reach the distal airways and alveoli where it decomposes into ammonia and hydrochloric acid. The hydrochloric acid will induce injury by the

same mechanism as explained above. Ammonia combines with moisture forming ammonium hydroxide. This is a strong corrosive solution that causes burns and desquamation of the epithelial layer of the airways.²⁶² Together, the sloughed epithelia, oedema and inflammation caused by the acids and alkali might induce airway hyper-responsiveness and obstruction.

Chapter 4 **Study hypothesis, aims, and objectives**

4.1 Hypothesis

The hypotheses were as follows:

1. Cleaners have higher risk of asthma compared with the general population. In particular, the estimated incidence of asthma among cleaners in Newcastle will be comparable to that found in previous studies of cleaners that demonstrated higher risks of asthma among cleaners.
2. Cleaning-induced asthma is an example of low-dose irritant-induced asthma that presents with a history that is atypical of occupational asthma and so is not recognized by physicians.
3. Chlorine bleach is the principal cause of asthma in cleaners.

4.2 Aims

The aims of the study were:

1. To estimate the proportion of cleaners with evidence of occupational asthma.
2. To identify risk factors of asthma including work practices and cleaning products used.

4.3 Objectives

Specific objectives were:

1. To assess the prevalence of asthma and other respiratory symptoms in cleaners.
2. To investigate the association between atopy and smoking status and the risk of developing asthma among the cleaners.
3. To identify the clinical features of the work-related asthma among cleaners.

Chapter 5 **Methods**

5.1 Introduction

This chapter commences with a broad overview of the different phases of the study. This is followed by describing the procedures that were undertaken in a preparation for the study. The next sections then describes in details each phase of the study with regard to the method of subjects' recruitment, research tool(s) used, and methods of data analysis.

5.2 Overview of the study

The study involved four phases:

- i) Phase-I: A cross-sectional survey of asthma in cleaners

This was a cross-sectional survey. Respiratory symptom questionnaires were sent to cleaners recruited from local hospitals and educational institutions.

- ii) Phase-II: Clinical study for supporting asthma diagnosis

Responders who reported physician-diagnosed asthma, asthma-like symptoms, or using inhaler in phase-I were invited to the second phase. Participants were assessed clinically to support the diagnosis of asthma. They underwent spirometric lung function testing and airway responsiveness measurements.

- iii) Phase-III: Establishing the work-relatedness of the asthma

Cleaners with results suggestive of asthma were invited to the next phase to identify the proportion with work-related asthma. They underwent a clinical interview; serial measurements of PEF and repeat measurements of airway responsiveness after a period away from work. Serial PEF was analysed using a computer-based OASYS programme. A score for the probability of occupational asthma was given based on the interview and the results of the tests.

- iv) Phase-IV: Identifying risk factors for asthma in cleaners

This was a case-control study to explore risk factors for asthma amongst cleaners. Cases and controls were recruited from those who responded to the

respiratory survey. Cases were defined as those who have current asthma or had a minimum of three asthma-like symptoms. All others were considered controls.

5.3 Preparation for the study

5.3.1 Meeting with managers

Initial meetings were arranged with key persons in the participating organisations. Meetings were attended by two researchers who explained the aim of the study and discussed the possible logistics for recruitment:

1. It was initially hoped that a meeting could be held with all the cleaners in each centre, where the study could be explained and the questionnaire distributed. This suggestion was considered unfeasible, as some cleaners worked part time on different shifts and others worked at weekends only, particularly in hospitals. Therefore, it was agreed that the questionnaire would be distributed via the managers only.
2. It was hoped that the managers might establish a list of the employees with the aim of identifying non-responders to whom reminder letters could be send. This was considered unacceptable by managers, due to the Data Protection Act.

5.3.2 Observational surveys

Before the main study, cleaners in Newcastle University and in two hospitals, Freeman hospital and Royal Victoria Infirmary were observed in June 2010. The aim was to identify the products used and the associated cleaning tasks in two different settings.

5.3.3 Development of the questionnaire

The information obtained from the aforementioned visits was used in developing a work-practice questionnaire. The aim of this questionnaire was to collect information on cleaners' daily tasks and assess their exposures to cleaning products.

A pre-pilot study was carried out on a few cleaners (n=4) in Newcastle University. Cleaners were interviewed informally to go through the questions and discuss any issues relating to clarity, question wording and layout.

In addition, they were encouraged to suggest re-wording or additional questions about tasks that were missed by the researcher.

Amendments to the first version of the questionnaire were tested in a pilot study on 32 cleaners. The aims of this were to assess the feasibility of the recruitment process to be adopted in the main study, as well as to identify any ambiguities in the questions and the range of possible answers for each question.

The 32 questionnaires were distributed in three phases among cleaners in Newcastle Royal Victoria Infirmary and Freeman hospitals, as well as in Newcastle University. The questionnaires were sent to the managers/supervisors who were asked to forward them to their staff in the way they would do in the main study. The questionnaire was amended in response to cleaners' feedback after each phase.

At the start, the questionnaire included questions about both respiratory symptoms and work practices. This made it relatively long and it was felt that this would impact on the return rate.²⁶³ It was decided to separate these questions into two questionnaires, the respiratory and work-practice questionnaires (appendix 1, appendix 2).

A participant information sheet (appendix 3) was also piloted but no amendments were made as the cleaners stated that the information provided was adequate to explain the purpose of the study.

5.3.4 Estimating the sample size and precision

Phase-I Cross sectional survey of asthma in cleaners

The objective of this step was to obtain a precise and accurate estimate of the proportion of cleaners reporting asthma. To calculate the required sample size, the programme Epi-Info version 6.03 was used.²⁶⁴ Based on the assumption that the prevalence of asthma among adults is 5% as reported in previous studies,^{45, 265} it was found that a sample of 1800 subjects was required to estimate prevalence with a 95% confidence interval with a width $\pm 1\%$.

Since not all subjects would respond to a survey, a larger sample size was required. Based on the results of the pilot study, it was assumed that the response rate would be 80%. Thus, the final target sample size was 2250 subjects.

Phase-II [Supporting the diagnosis of asthma] and phase-III [Establishing the work relatedness of asthma]

It was anticipated that recruitment for the clinical tests would be difficult because (1) the methacholine tests can take up to 1.5 to 2 hours, and this might not be convenient for many potential participants, and (2) the test was done in one place only, Newcastle Royal Victoria Infirmary, which could involve travelling a long distance for some subjects, particularly those recruited from North Tyneside area. Although there are other more simple and rapid method for assessing airway responsiveness, such as Yan technique²⁶⁶ and by using mannitol dry powder,²⁶⁷ the method used in the current study, i.e. five breath dosimeter, is the most widely used technique and is well standardised.¹⁸ In addition, the method used in this study in particular, i.e. the Newcastle dosimeter technique, has been found to have high repeatability.⁶¹ Because of the long duration of the test, it was assumed that only one third of the subjects with physician-diagnosed asthma would attend for clinical tests. So, assuming that 1800 subjects would return the questionnaire, and that 5% would report asthma, it was expected that a minimum of 27 subjects would be available for phases two and three.

Phase-IV Risk factors for asthma in cleaners

In this phase, the second questionnaire, i.e. work-practice questionnaire, was to be posted to the participants rather than delivered via managers at the workplace. The literature on response rates to postal surveys suggests that return rates are likely to range from 40%-80%,²⁶⁸ so it was assumed that 65% of the responders in phase-I would respond to the second questionnaire. That would lead to (1170) returned questionnaires.

It was the aim of this phase to explore an association of specific factors with asthma by comparing exposure between asthmatics (cases) and non-asthmatics (controls). Assuming an asthma prevalence of 5%, there would be 58 cases, and these were to be matched with controls. The initial plan was to

invite three matched controls per asthma case to complete the second questionnaire. It was anticipated that, on average, there would be data on 2 controls per case, but the number of controls per case would vary between 1 and 3 leading to a necessarily more complex and unbalanced analysis. For the purposes of this study, only one matched control per case would be analysed allowing simpler statistical techniques to be used. It was planned that another member of the research team would carry out a more complex analysis of the full dataset.

On that basis, assuming that 5% of responders to the first survey reported asthma, and 65% of them would return the second questionnaire, this should provide data on 58 cases. Assuming that data was available on 58 cases and 58 matched controls, this should provide 80% power at the 5% level to detect a standardised difference of 0.4 using a paired t-test (i.e. a difference of 0.4 of a standard deviation). However, given the low response to the first questionnaire, it was later decided to send the second questionnaire to all those who agreed to be contacted again (whether cases or controls) and the case-control study was unmatched.

5.3.5 Lung function training

It was necessary to receive training carrying out respiratory function and airway responsiveness tests before the start of the study. Training was carried out by a specialized lung function technician. At first, the researcher observed the tests, then took part partially and lastly performed the tests independently.

5.3.6 Ethical approval

The study was sponsored by the Newcastle upon Tyne Hospitals NHS Foundation Trust, and approval was obtained from the Research and Development section of the Joint Research Office in Royal Victoria Infirmary.

The study protocol was presented to County Durham and Tees Valley Research Ethics Committee on January 2011 (REC reference number 10/ H0908/68). Two major changes to the research protocol were required before giving final approval: 1- It was mentioned in the protocol that a list of the responders was to be sent to the managers who would be asked to send reminder letters to non-responders. This was perceived to be a breach of confidentiality, and the

committee members advised that reminder letters should be sent anonymously to all the participants, 2- It was not planned to inform participants' GPs about their involvement in the study but the committee recommended that the researcher should send a letter to the GPs. This should include the clinical results since treatment and follow-up might be required particularly for subjects with results suggestive of asthma. Amendments were made and final approval was obtained in February 2011 (appendix 4).

5.4 Phase-I A cross-sectional survey of asthma in cleaners

5.4.1 Population

Subjects were drawn from 2 educational and 3 health service organisations in Newcastle upon Tyne and North Tyneside areas, and from Newcastle city council. The exact numbers of cleaning staff in the participating organisations could not be obtained. This was attributed to a high labour turnover and to some of the cleaning staff being employed by private companies and working for the participating organisation under contract. Therefore, the managers at the initial meetings provided only approximate estimates of the numbers of their cleaning staff. Other key persons (secretaries and supervisors) in three organisations (Newcastle and North Tyneside Mental Health Trust, Freeman Hospital, North Tyneside Hospital) provided estimates of the numbers of cleaners that differed from those provided by the managers. The number of the cleaners in each organisation as reported by the managers and by the other key persons is presented in table 5-1.

Accordingly, the total number of the potential participants could have ranged from 2299 to 2427 participants.

Table 5-1 Participating organisations and the number of the cleaning staff

Organisation	Number of cleaners as estimated by the managers	Number of the cleaning staff as estimated by other key persons
Newcastle upon Tyne Hospitals NHS Foundation Trust:		
1. Royal Victoria Infirmary	350	350
2. Freeman hospital	250	236
Newcastle, Tyne and Wear Mental Health Trust	130	122
North Tyneside Hospital NHS Foundation Trust	300	450
Newcastle University	208	208
Northumbria University	261	261
Newcastle City Council	800	800
Total	2299	2427

5.4.2 Questionnaire

A pre-piloted self-administered respiratory questionnaire was used in this phase (appendix 1). It was a single sheet questionnaire. On one side was an invitation to participate and brief explanation of the purpose of the study. Help was offered bearing in mind possible problems of literacy and foreign languages. The questionnaire was coded with a number from 1 to 7, each number allocated to a participating organisation.

The other side included 29 items divided in 5 sections:

Respiratory questions:

There were 15 questions adapted from previously validated asthma questionnaires. The first 10 questions were adopted from Venbles's respiratory questionnaire.⁴⁹ This consists of 9 questions and asks about respiratory symptoms during the last 4 weeks. Two modifications were made to the questionnaire: One question about cough at night was added and the time scale

was extended to cover the last 12 months. Cough was included as a possible unusual presentation of asthma or a separate disease among cleaners. The duration was extended to capture a larger number of subjects, and because this time scale was also used by other studies.^{206, 269} The final set of respiratory symptom questions consisted of questions about cough; chest tightness; difficulty in breathing and wheeze at different times and whilst doing different activities. These included nocturnal or early morning symptoms; symptoms while running and climbing stairs; or while being in dusty or smoky place.

The other 5 questions were extracted from the ECRHS questionnaire.⁷⁶ They assessed the presence or absence of physician-diagnosed asthma; use of asthma medication in the last 12 months; and hay fever as a marker for atopy.

Duration of work and cleaning-related respiratory symptoms

Three items were included under this section. One was to measure total duration of work as a cleaner. The relationship between work and respiratory symptoms was addressed in two items. These investigated whether chemical products used at work caused cough, wheeze or breathlessness. There are no validated questions of work-related respiratory symptoms; however, previous studies^{202, 206} used a similar approach.

Smoking habits and demographic features

Smoking status was assessed by five questions covering smoking habits; duration of smoking; and the average number of cigarettes smoked per day. These allowed subjects to be classified into one of three categories: current smoker; former smoker or never smoker. It was considered important to know smoking status for two reasons: 1) it is strongly related to COPD which might present with symptoms similar to asthma and 2) it causes worsening of asthma symptoms²⁷⁰ and might even cause new cases of asthma in adults.²²⁵ Hence, smoking might be an important confounder causing respiratory symptoms in those exposed to cleaning chemicals.

Subjects were also asked to report their gender and date of birth as both influence asthma development.

Whether subjects would participate in the further steps of the study

Two questions were added to determine whether the subject would like to participate further in another survey or clinical tests or both.

Subjects' personal data

Information about subjects' names and contact address was requested to be used when the researcher wanted to invite those who expressed their willingness to participate further in the study.

5.4.3 Recruitment

Initially, subjects were recruited through their managers or supervisors only. This involved sending managers/supervisors letters enclosing questionnaires together with an information sheet (appendix 3) and prepaid envelope. Managers in turn distributed the letters to supervisors who delivered it by hand to the subjects they were in charge of. The subjects were asked to return the questionnaire either directly to the manager or to post it back to the researcher using the prepaid envelope provided.

It was planned to send a follow-up letter a month later but there were two major issues with that. Firstly, managers were unable to release a list of their staff due to ethical considerations. Accordingly, it was not possible to identify non-responders only, and reminder letters would need to have been sent to all of the study population (n=2299). Secondly, the initial response rate was relatively low and it was uncertain whether the effort and expense of reprinting questionnaires, information sheets, and the cost of pre-paid envelopes would be counterbalanced by a substantial improvement in response rate. Therefore, it was decided to test the effect of sending reminders on a subgroup of 800 subjects. None of the questionnaires were returned, and a decision was made to cancel this step.

Alternative approaches were used to improve recruitment: Firstly, attempts were made to arrange a series of meetings with the cleaners. In the Freeman hospital, some lunchtime meetings were arranged but these proved unpopular and unproductive as cleaners were preoccupied by eating and having friendly conversations, and other people (staff and visitors) used the same areas. The managers of Newcastle University and Northumbria University arranged grand

meetings with their staff and explained the importance of the study in general and the importance of subjects' involvement in particular. The researcher needed to state clearly that participation was optional. The subjects were given an opportunity to ask questions. Most subjects returned the questionnaire directly to the researcher and a few passed it to their supervisor who delivered it to the researcher.

Secondly, the questionnaire was re-distributed via the occupational health nurse manager in Royal Victoria Infirmary who was implementing a respiratory screening programme for all employed cleaners at the time of the study. A consent letter was attached with the distributed questionnaire so that only cleaners, who gave their consent, would have their information be passed to the researcher. Only few additional subjects (n = 10) agreed to take part in the study through this way.

Thirdly, more cleaners were recruited from an additional organisation, Sunderland Royal Hospital. This time, it was decided that a native English speaker would lead the process of encouragement for both managers and cleaners. It was thought that unfamiliarity of the researcher with the UK culture and being a non-native English speaker could have affected the recruitment. The total number of the cleaners' staff was uncertain by the management and were estimated to be 200-250 cleaners. The recruitment process was different. The researchers requested permission to meet the cleaning staff in person in order to explain the study, as this approach was found by the researcher to be more effective in encouraging cleaners to participate than merely distributing the questionnaires via managers. The manager however considered this request unfeasible and suggested instead talking to the cleaners in the supervisors' room when they clocked-in at the start of the work shift, or when they clocked-out at the end of the shift. The researchers attempted this approach of recruitment and found it to be inconvenient for several reasons. First, the cleaners at the suggested time were in a hurry either to start the duty or to leave the work, this left the researcher with little time to explain the study. Second, although it was anticipated to meet at least 200 cleaners, only about 100 cleaners were seen. The exact reason is unknown and the researcher kept the remaining questionnaires with the supervisor to be distributed to other cleaners. Third, the researcher also found it difficult to attend the early morning

shift (7:00 a.m.) as this required leaving Newcastle at an earlier time (6:15 a.m.). This was inconvenient for the researcher due to the commitment to other work. After the first two visits only 36 questionnaires were returned, reflecting a response that was no better than that in other organisations. Because of the aforementioned reasons and the uncertainties about the number of the cleaners and the number of the distributed questionnaires, the participation from Sunderland was withdrawn.

Finally, to facilitate recruitment, all those who returned the questionnaire were entered into a £100 prize draw.

5.4.4 Data entry and analysis of the respiratory questionnaire

A spreadsheet was set up in Minitab, version 16, so that an answer to each question of the respiratory questionnaire occupied one column only. Since almost all questions were dichotomous, the answers were numerically coded as e.g. yes=1; no=0, female=1 and male = 0. Each row of the spread sheet corresponded to one responder. A missing answer was considered a negative answer for the questions about respiratory symptoms, while a missing answer was coded as missing for the rest of the questions.

Data entry accuracy was checked by three methods: 1) checking randomly selected questionnaires for incorrectly entered data; 2) checking frequency distribution which identified incorrect codes; and 3) using cross tabulation especially for filtering questions.

Characterization of the study population

Descriptive statistics were calculated and presented for the following variables: age, gender, smoking status, atopy, and duration of work.

Descriptive analysis for continuous variables such as age and duration of work as a cleaner was performed by measuring central tendency (mean or median) and dispersion (standard deviation; range or quartiles). First, Normality was examined by visual assessment of the distribution of raw data using dot plots or histograms with the help of an expert statistician. If the resulting diagram looked Normally distributed, mean and standard deviation were used to summarize the data but if the resulting diagrams showed skewness, median and range or quartiles were used to describe the data.

A descriptive analysis using frequency and percentages was undertaken for the categorical variables: gender; atopy and smoking status. The latter was categorized into (current; former and never smoker).

Calculating the prevalence of respiratory symptoms

For the purpose of estimating the prevalence of individual respiratory symptoms, the nine respiratory questions were grouped into 4 main themes:

Respiratory symptoms	Related questions
Wheeze	When you have run or climbed stairs fast, have you wheeze? Has your sleep been broken by wheeze? Have you woken up in the morning with wheeze? Have you wheezed in dusty room or smoky room?
Difficulty in breathing	Have you woken up in the morning with difficulty in breathing ? Has your sleep been broken by difficulty in breathing?
Chest tightness	When you have run or climbed stairs fast, have you had tightness in your chest?
Cough	When you have run or climbed stairs fast, have you had cough? Has your sleep been broken by cough?

Calculating the prevalence of work-related symptoms

Prevalences of work-related wheeze/shortness of breath and work-related cough were calculated for the cleaners. A comparison of the frequency of these symptoms was made in cleaners who self-reported physician-diagnosed asthma and those who did not. The significance of the difference between the two groups was tested by chi-square. The test statistic was compared with the chi-square distribution with 1 degree of freedom.

Calculating the prevalence of physician-diagnosed asthma

This was defined as a positive answer to the questions “have you ever had asthma” and “has a doctor ever diagnosed your asthma”. This definition is commonly used in asthma studies; and this would allow comparison of the results.

Calculating the incidence of physician-diagnosed asthma

The incidence of asthma developing while working in cleaning was computed using the equation:

$$\frac{\text{number of newly developed asthma cases}}{\text{person-years at risk of working as cleaner}} \times 1000$$

To identify asthma cases developing while working in cleaning, the answers to the following questions were used:

- “Has a doctor ever diagnosed your asthma?” (to confirm asthma status)
- Date of birth and “How long have you worked as a cleaner?” This information helped in calculating the age when the asthmatic subject started working as a cleaner, this is calculated by subtracting years in cleaning from the age at time of the survey.
- “How old were you when you first had asthma?” (Age of asthma onset is compared with the age when the subject started working as cleaner. This is to distinguish asthma cases that developed while working in cleaning from those which are developed earlier.

When asthma occurred before starting a cleaning job, the subject was considered have had asthma unrelated to cleaning work and was excluded from the incidence analysis. Furthermore, subjects who did not provide an answer to any of these questions were excluded from the incidence calculation.

Person-years at risk for subjects who have asthma was defined as the time a subject was at risk of developing asthma, that is the time from starting working in cleaning to the age when diagnosed with asthma.

Person-years at risk for subjects who did not develop asthma was the total duration of work in cleaning.

Measuring the association of demographics and personal factors with physician-diagnosed asthma

A comparison of the distribution of established and potential risk factors for asthma in individuals with physician-diagnosed-asthma and individuals without asthma was performed. The risk factors investigated included demographic

factors; atopy; smoking status (current and ex-smoking) and duration of work. In the first step, univariate analysis was carried out to investigate the association with individual risk factors. The results were expressed as unadjusted ORs and 95% CIs. Then, the association of asthma with particular risk factors adjusting for the influence of other factors was investigated using multivariate logistic regression analysis. The results were expressed as adjusted ORs with 95% CIs.

5.5 Phase II Clinical study for supporting asthma diagnosis

The laboratory based investigations in this phase were performed in the chest clinic, Royal Victoria Infirmary.

5.5.1 Population

Subjects who were likely to have asthma and who answered positively to the question “would you like to attend for clinical tests?” in the respiratory questionnaire were recruited. Asthma in this phase was defined as reporting *physician-diagnosed asthma, any asthma symptoms OR the use of an inhaler*. Using this definition it was hoped to identify as many subjects as possible with asthma. Although this definition might lead to the inclusion of people without asthma this was not considered to be a major concern since methacholine tests would be performed to support the diagnosis.

Exclusion criteria

Subjects who did not write their name and contact address were excluded (n=6).

Phase II Study participants recruitment

Subjects were recruited either by a phone call or posting a letter, based on the contact information provided in the respiratory questionnaire.

Subjects, who provided only a home/work address or did not answer phone calls were sent an information sheet (appendix 5) which included researcher’s contact details. As initially no-one contacted the researcher after receiving this it was thought that the length of the information sheet (3 sheets) stopped subjects from reading it. Therefore, the information sheet was substituted with an invitation letter printed on a single sheet of paper (appendix 6). A few subjects responded back positively. Most appointments were made by telephone contact. During a phone conversation, the researcher explained to the subject the reasons for them being chosen, the tests that were to be performed, the duration of the tests, and the aims of the study. An appointment was arranged and a query about asthma medication was made. Subjects who used reliever inhaler were asked to withhold it for at least 12 hours before the test.

5.5.2 Procedure of supporting asthma diagnosis

On attending the chest clinic, the subject was given another explanation of the aim of the study and the methods of assessment to be used; and was given an opportunity to ask questions before consent was sought. The researcher also checked that asthma medication had been withheld before the test for at least 6-8 hours for short-acting bronchodilators and 24 hours for long-acting bronchodilators. In addition, the researcher confirmed with the subjects that they had had no acute respiratory tract infection in the past 2-3 weeks as infection might cause transient increase in airway responsiveness.^{271, 272}

Laboratory investigations comprised: height and weight measurements for calculating predicted values of FEV₁ and FVC; spirometric lung function and measurements of airway responsiveness to methacholine.

Height and weight measurements

Height was measured using a wall-mounted stadiometer. The subject was asked to stand straight with heels together in bare or stockinged feet. The subject looked straight ahead and height was recorded to the closest millimeter.

For weight measurement, the participant was asked to stand barefoot on electronic scales and the weight was recorded in Kg. Both height and weight were used to calculate body mass index, calculated by dividing subjects' weight in Kg by the square of his/her height in metres.

Spirometry

Baseline lung function (FEV₁ and FVC) was assessed with a Vitalograph® spirometer (Vitalograph Ltd., Buckingham, UK) which was calibrated daily. The subject was seated comfortably and instructed on how to perform a forced expiratory manoeuvre starting from a deep inhalation. A minimum of three acceptable measurements, of which the highest two were within 100 ml or 5% of each other, were required. The baseline FEV₁ and FVC were the highest of these.²⁷³ Forced expiratory manoeuvres were repeated up to a maximum of 8 times if reproducible measurements were not obtained at the first attempts. A nose clip was used in all subjects.

The values of FEV₁ and FVC were compared with the predicted normal values derived from those published by European Community for Coal and Steel.²⁷⁴

The subject's sex, age and height were needed to calculate the predicted normal values. The value of FEV₁ was considered normal if it was within 80%-120% of the predictive value.

If FEV₁ was < 60% of the predicted value, the subject did not proceed with the methacholine test to avoid the risk of a marked FEV₁ fall during the methacholine test.¹⁸ If FEV₁ was > 60% of the predicted value, the researcher proceeded with the methacholine test.

Airway responsiveness to methacholine

Preparation of methacholine

Stock solutions of 64 mg/ml methacholine with 0.4% phenol as a preservative were prepared using sterile technique by a pharmacist.

10 doubling concentrations of methacholine were prepared by two-fold serial dilution of the stock solution in a solution of 0.275% sodium bicarbonate. The concentrations were: 3.0, 12.5, 25, 50, 100, 200, 400, 800, 1600, 3200 µg/ml. 4 ml of each solution was placed in each of the designated nebulizers.

Dosing protocol

The methacholine test was performed using a five-breath dosimeter protocol and the Newcastle dosimeter.

The subject was evaluated for contraindications (uncontrolled hypertension, heart conditions). He/she was told about the potential side effects of the test and the possible chest symptoms (cough, tightness) that were to be experienced.

The test was performed in a laboratory equipped with resuscitation equipment; oxygen; and a nebulizer. The researcher watched the subject carefully for any signs of distress and repeatedly inquired about any unusual chest sensations.

a. Baseline pulmonary function was assessed again by measuring FEV₁ with a Jaeger Screenmate Pneumotachometer (Erich Jaeger UK Ltd, Market Harborough, UK) with an Apple Macplus PC running software by Collingwood Measurement Ltd (Packington, Leicestershire, UK).

b. Three sets, each consisting of six FEV₁ measurements, were performed at five minutes intervals (0, -5, -10 minutes), and at each time the highest three of six measurements were used to estimate the mean FEV₁. Baseline FEV₁ was measured as the overall mean of the 3 sets that is the mean of the nine best measurements.

c. On completion of the third set of baseline FEV₁ measurements, the subject immediately started the inhalation of methacholine at the lowest concentration (3.0 µg/ml). The subject was instructed to inhale slowly and deeply from the nebulizer for five seconds during which the dosimeter was triggered automatically. The dosimeter was calibrated to generate a standard dose of 10 µl of methacholine aerosol. Completion of 5 seconds inhalation was signalled by an audible bleep. The subject repeated inhalations for a total of 5 times, that is 50 µl.

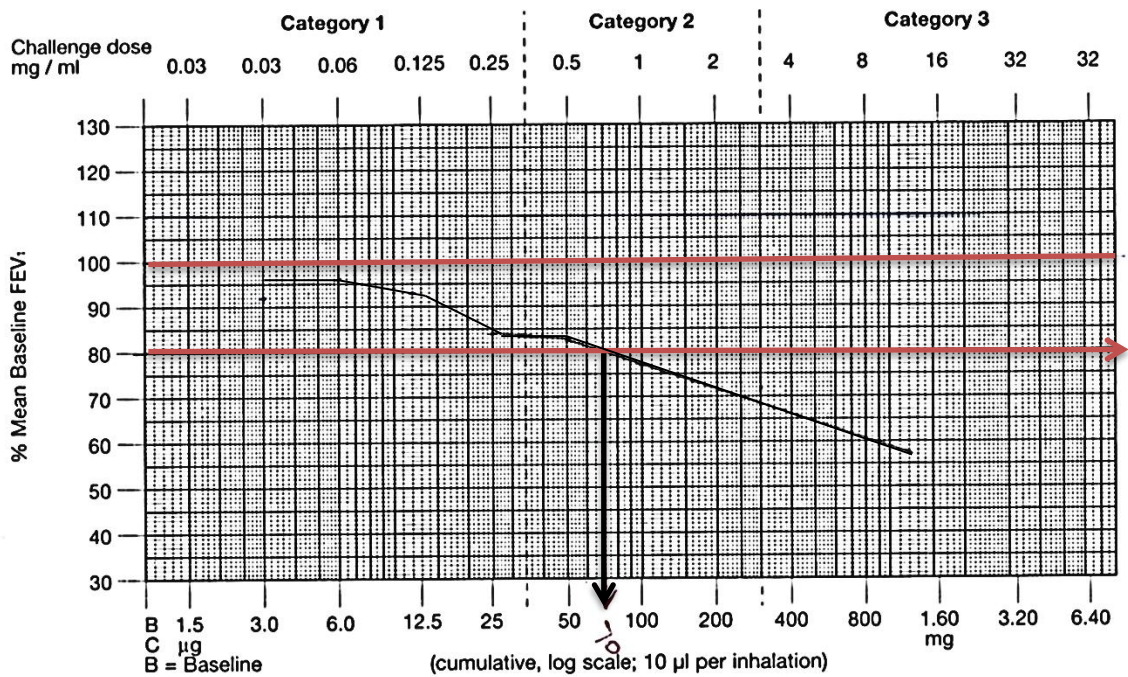
d. Exactly 5 minutes after completion of the previous FEV₁ measurements, subjects performed a further 6 FEV₁ manoeuvres and then proceeded to inhale the second incremental dose.

e. Steps c and d were repeated. The test was terminated if there was a fall of FEV₁ of $\geq 20\%$ from baseline; if there were unpleasant side effects or chest symptoms that compelled the subject to stop; or if the maximum concentration of methacholine, which was 3200 µg/ml, was reached.

At the end of the test, subjects with a fall of FEV₁ of $\geq 10\%$ were given 2 puffs of 400mcg salbutamol and after 10 minutes a minimum of three FEV₁ measurements were made. If the FEV₁ was not within 5% of the baseline, another two puffs were given and FEV₁ measured after another 10 minutes.

A dose-response curve was obtained where the x-axis represented the log of methacholine dose and y-axis was percentage of fall in FEV₁ as illustrated in figure 5-1.

Figure 5-1 Methacholine test chart



Methacholine test was expressed as the dose that provoked a 20% fall in FEV₁, (PD₂₀). This was calculated by linear interpolation of adjacent data points of the dose-response curve according to an international standard.²⁷⁵ Using this method, a PD₂₀ value ≤ 1600 µg was considered suggestive of asthma. This cut off point was chosen based on previous studies in adult populations.^{276, 277} It was found that adults with PD₂₀ values < 200 µg usually have active asthma, and adults with PD₂₀ values between 200-1000 µg possibly have active asthma. The cut-off point was increased for two main reasons: 1) many of the participating subjects were on inhaled corticosteroids which were shown in previous studies to decrease airway responsiveness and, hence, increase PD₂₀ by almost two doubling doses,²⁷⁸ and 2) the methacholine test is usually repeatable within ±1.5 doubling doses.⁶¹ Thus subjects with borderline negative PD₂₀, e.g 1100 µg, would be considered negative if the cut-off point was taken strictly at 1000 µg though a repeated PD₂₀ might be lower than 1000 µg.

5.5.3 Data analysis

Comparisons of characteristics of the responders with the non-responders

The profile of the responders to this phase was compared with those of non-responders.

The categorical variables such as smoking status (current smokers, ex-smokers and never smokers) and gender (female versus male), were summarized for each group, i.e. responders and non-responders, by proportions. The precision of the difference between the proportions was expressed by the 95% CIs.

The Mann-Whitney test was used to compare responders and non-responders on the continuous variables which were age and duration of work since they were non-normally distributed.

Methacholine tests

Results of methacholine tests were presented in a table and were compared with 5 definitions of asthma: 1) physician-diagnosed asthma; 2) use of inhalers in the past 12 months; 3) reporting any respiratory symptoms in the last 12 months without using inhalers ; 4) current asthma, defined as reporting physician-diagnosed asthma and used inhaler or had respiratory symptoms in the last 12 months; and 5) reporting three or more of respiratory symptoms in the last 12 months. This was to measure the sensitivity of each of these definitions.

The association of several risk factors with asthma defined as having positive methacholine tests (i.e. $PD_{20} \leq 1600 \mu\text{g}$) were investigated. The risk factors were: demographic risk factors (age and gender); atopy; current smoking; ex-smoking; body mass index; past history of exposure to fumes/gas; duration of work; and baseline lung function.

The data was presented in a series of 2x2 tables:

	Asthmatic	Non asthmatic
Exposed	A	B
Non exposed	C	D

The association was measured by ORs for the categorical variables.²⁷⁹ For continuous variables, two sample t-tests were used to compare means if the variable was Normally distributed, and Mann-Whitney tests were performed for non-normally distributed data.

5.6 Phase III Establishing the work-relatedness of asthma

5.6.1 Population

Subjects whose methacholine tests suggested asthma (i.e. $PD_{20} \leq 1600 \mu\text{g}$) were chosen.

5.6.2 Tests of work-relatedness

To investigate whether asthma was work related or not, asthmatic subjects were further investigated by serial monitoring of PEF and serial methacholine tests. In addition, these subjects undertook a clinical interview.

Serial PEF

Mini-Wright Digital meters (Clement Clarke, Inc) equipped with computer chip memory that could store up to 240 times and dates stamped PEF measurements were used.

Each subject was asked to perform readings four times per day for four weeks including working weeks and periods off work for a week if possible. Otherwise, the researcher made sure that the subject at least was not working at weekends. The subject was asked to make a minimum of three measurements at each time. The difference between the best two readings was to be within 20 l/min and if not, more measures were to be taken. These criteria should yield a record with adequate data quantity and should identify a work effect in 78% of subjects with occupational asthma.¹²⁰

The researcher demonstrated how to operate the Mini-Wright Digital meters. The subject then was asked to practice the manoeuvre under supervision until their technique was satisfactory. Written instruction (appendix 7) was provided together with a written diary record (appendix 8). The subject was informed that a phone call was to be made after two weeks to check performance and to encourage recording. Another phone call was to be made after four weeks to arrange for collection of the device.

The first 17 subjects were not informed about the ability of the Mini-Wright Digital meters to save the measurements. Seven (41%) of the returned devices had few readings despite the supplementary handwritten diary being largely completed. The discrepancy between the hand-recorded and electronic

measurements was attributed to device error, misuse of the device or subjects inventing readings if they missed many of them. Therefore, for the remaining subjects, the researcher stressed the device's capability to store readings along with the date and time. The researcher provided subjects with a new design of diary where only activities and medications were required to be reported (appendix 9). This was hoped to improve compliance since the participants would realize that what would be stored in the device was the only source of data. In addition, the researcher asked some of the earlier participants to kindly repeat the test.

Method of analyzing serial PEF

The data from the digital mini-Wright device was downloaded automatically to a computer using a USB port and cradle. A record was considered to be eligible for further analysis if:

1. It included at least three readings per day for 75% of the records,
2. There were at least three complexes (work-rest-work) or (rest-work-rest) in the record.

Three readings per day was accepted instead of the recommended four readings because the number of PEF measurements recorded by the digital mini-Wright device was almost always lower than the number on the written records in those with paired readings. As previous acceptability criteria were based on written records,¹²⁰ it is likely that these were based on a lower number of true measurements. Although the lower number of readings is known to affect the test's sensitivity, it is still considered adequate for diagnosing occupational asthma.¹²⁰ Gannon *et al*²⁸⁰ studied the ability of 2 to 10 readings in detecting PEF variability, a feature that is assessed on working and resting days by OASYS to detect work effects. The authors considered the diurnal variation calculated using the all 10 readings as the true diurnal variation, then they compared the diurnal variations calculated using 2-9 of the available readings with that calculated using the full 10 PEF readings. It was found that four readings were optimum to detect PEF changes compared with 10 readings /day with a mean underestimation of the true diurnal variation of 1.3 percentage points. However, when three readings were used to calculate diurnal variation, it

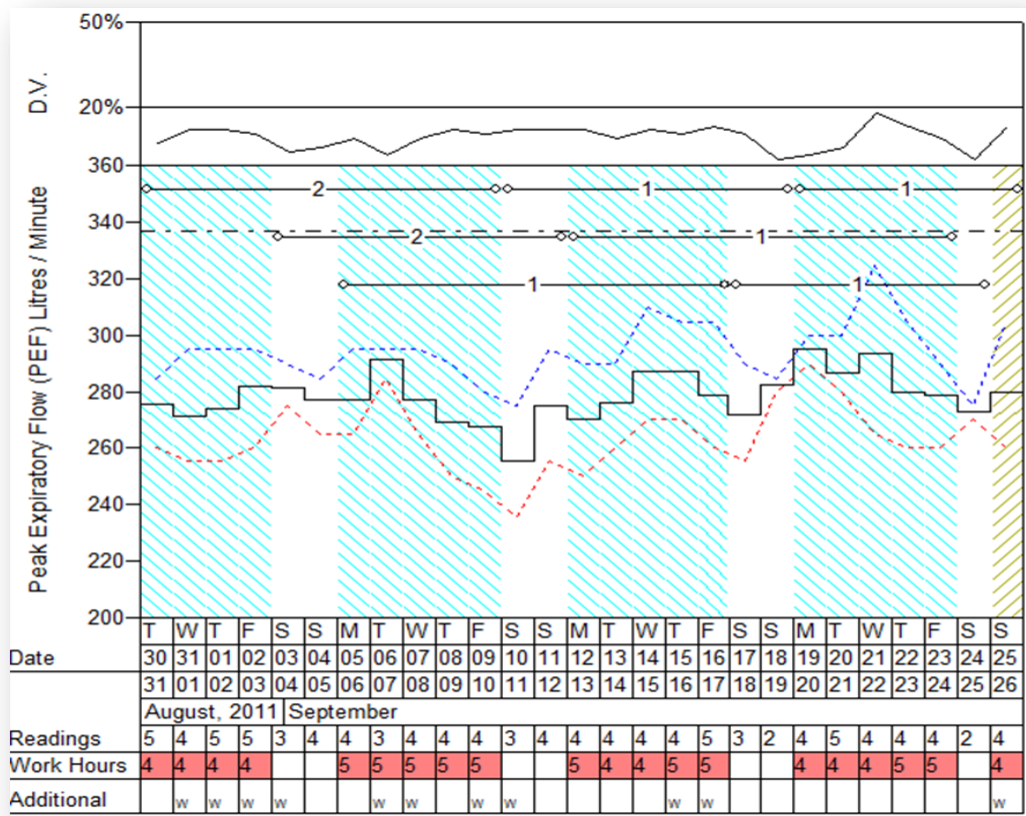
could still detect PEF variability with a small possibility of under-estimation that was found to be 1.7 percentage points.

The requirement to have a minimum of three consecutive workdays in most of the working periods was not strictly adhered to as many subjects worked weekends only or in other patterns that made this impossible.

OASYS-2 was used to plot charts for subjects who returned the device. The chart included daily minimum, mean and maximum PEF, as well as number of readings each day, figure 5-2.

OASYS compares PEF in consecutive work/rest/work periods and rest/work/rest periods and gives an overall score to two decimal places from 1 to 4 to indicate the likelihood of occupational asthma. A total score of > 2.5 was considered to be suggestive of occupational asthma as proposed by Burge and co-workers.¹¹⁸

Figure 5-2 OASYS graphs shows daily minimum - - - - , mean ----- and maximum - - - - PEF for the analysis of working days and leisure days



Serial methacholine tests

Subjects were invited to repeat the methacholine challenge test when they were away from work for a minimum of 7 days. Appointments were arranged at the time of the first visit for most of them. Some could not anticipate when they would be on their next holiday and asked the researcher to contact them later to confirm dates.

Repeated methacholine tests were performed following the same procedures outlined above.

Method of analyzing serial methacholine tests

The results of the methacholine tests at and away from work for each subject were presented in a table to allow comparison.

An increase in PD₂₀ of 1.5 doubling or more when measured away from work was considered suggestive of a work-related adverse effect.¹¹⁰ Previous studies found that smaller changes in PD₂₀ were insignificant and most likely resulted from factors such as normal physiological variation or from variations in the procedure itself.⁶¹ The average change in PD₂₀ was summarised by a geometric mean, and the contrast between the geometric means at and away from work was expressed as the geometric mean ratio.

Clinical interview

An open semi-structured interview was conducted with each participant after the laboratory investigations; the mean duration was 20 minutes.

The questions in the interview were divided into 4 themes: clinical history of asthma/respiratory symptoms, occupational history; cleaning-related symptoms; temporal relationship between work and symptoms.

Theme 1: clinical history of asthma/respiratory symptoms

The subject was asked about asthma/respiratory symptoms in detail, when they started, frequency of asthma attacks or respiratory symptoms, whether medical attention was sought, medications taken, and the effect of the chest symptoms on daily activity. Additional questions were asked about smoking habits, atopic diseases, such as hay fever or eczema, and family history of asthma.

Theme 2: Occupational history

The subject was questioned about previous occupations and whether there was exposure to dust, fumes or vapour. The subject was also asked about the occupation when asthma or the respiratory symptoms started.

Theme 3: work-related symptoms

The subject was asked whether work provoked upper respiratory symptoms (sneezing; rhinorrhoea); lower-respiratory symptoms (wheeze; cough; chest tightness and shortness of breath); or ocular symptoms (lacrimation; itching or redness). If the subject experienced work-related symptoms, he/she was asked about chemicals or activities that elicited these symptoms.

Theme 4: temporal relationship between work and symptoms

In order to explore any temporal association between work and symptoms, the subjects were asked to state whether there was an improvement in their chest symptoms over the weekend or on long holidays. If the subject was on asthma medication, he/she was also questioned about any change in the frequency of using the reliever inhalers on working days compared to days away from work.

5.6.3 Analysis of the combined data from phase III (clinical history, serial PEF, and serial methacholine tests)

The clinical histories and investigations obtained for a number of subjects were summarised and transcribed on to a standard proforma (appendix 10). The summary included the following: gender, age, family history, main history (asthma, work related symptoms and medication), FEV₁, FEV₁/FVC, OASYS score of serial PEF and values of PD₂₀ of serial methacholine tests.

Twenty physicians with an established interest and expertise in occupational lung disease were invited to rate the case summaries. The proformas were sent to participating physicians, who were asked to score the probability of occupational asthma from 0% to 100% for each case twice. The first scoring was based on the clinical history alone, while the second scoring was based on both clinical history and the results of the clinical tests.

Because having access to the results of the investigations might bias the scoring of the clinical history, the researcher provided each clinical history with

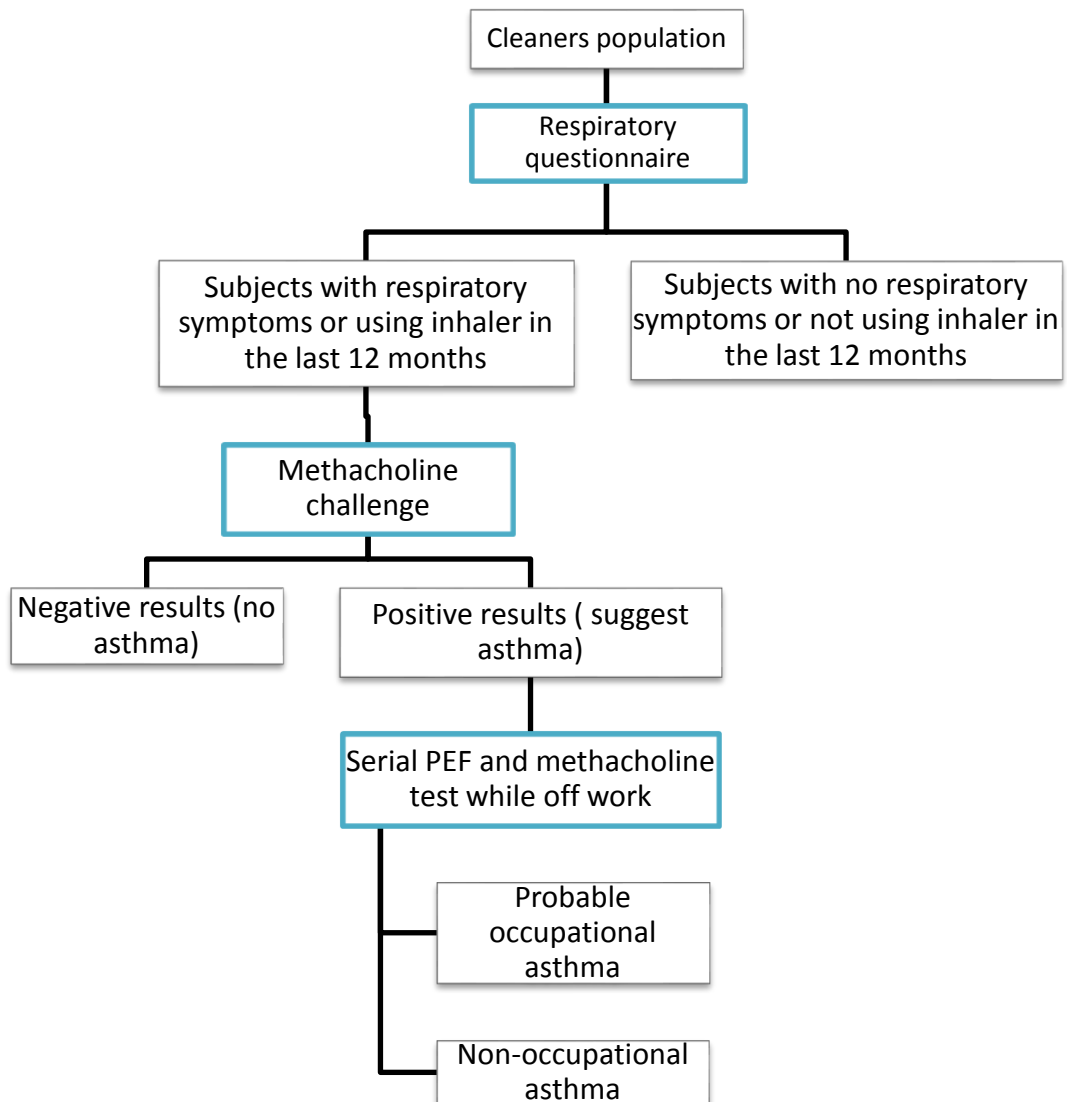
two sets of results one of which was genuine and the other was fabricated. The scores for the fabricated results were not analysed.

A score of 50% meant that the physician was undecided about whether or not the history or the history combined with the investigation results suggested occupational asthma. If the score was greater than 50%, it meant that the diagnosis tended toward occupational asthma and, if less, it meant that in the view of the assessing physician the diagnosis was less likely to be occupational asthma.

The median score of the likelihood of occupational asthma and the range across physicians was calculated for each case. Likewise, the median score and the range of scores were calculated for each physician across the cases.

The flow chart below summarizes the participant's journey through the study from phase-I to phase-III, figure 5-3.

Figure 5-3 Flow chart presenting the participant's journey through the study



5.7 Phase IV Identifying risk factors for asthma in cleaners

5.7.1 Study design

This was a nested case control study which investigated the association of work-related risk factors for asthma, including tasks and products used, with the presence or absence of asthma.

Case/control definitions

Subjects were categorized into cases or controls based on their response to the respiratory questionnaire in phase-I of the study.

A subject was considered a case if she/he had one of the following criteria:

- a) Physician-diagnosed asthma and used inhaler or had any respiratory symptom in the past 12 months, OR
- b) Reported three or more respiratory symptoms without a previous diagnosis of asthma. The assumption that this sub-group was most likely to have asthma was based on the Venbles *et al* study⁴⁹ which found that 78% of subjects with three or more symptoms had reported a history of asthma while 92% of subjects with fewer symptoms did not have asthma.

The definition of asthma used in this phase was more restrictive than the asthma definition in phase two. This is because the aim of this phase was to identify risk factors associated with asthma in cleaners, thus, cases who were truly asthmatic needed to be identified otherwise false positive cases would mask an association and bias the risk estimates (i.e. OR) towards unity. In the earlier phase the clinical definition of asthma was supplemented by the measurements of airway responsiveness.

All subjects who did not meet the case criteria were considered controls.

5.7.2 Population

Subjects were recruited from those who expressed their consent by answering positively to the question “Would you mind answering another survey from us?” in the respiratory questionnaire.

Exclusion criteria

Those who worked as a cleaner for less than 6 months and those who did not provide a name and contact address were excluded.

5.7.3 Questionnaire

A Pre-piloted “work practice” questionnaire was developed based on a review of the literature and early observational visits (appendix 2).

Questions were centred mainly on: cleaning activities; chemical products used at work; and work practices in the previous two years. This time limit was chosen because it should have been long enough to capture tasks and practices that were consistently done, and, at the same time, it should not have been long enough to cause a major recall problem.

The questionnaire also covered areas of training and education; general health; and details of the current job. Table 5-2 presents the items of the questionnaire and their rationale.

Table 5-2 Items in work-practice questionnaire

Item (code of questions)	Rationale
Dusting and vacuuming (1.1 &2.1)	Cleaning in general causes re-suspension of dust especially if done with a dry cloth. Since cleaners perform this task more frequently than the general population, they are expected to be exposed to a higher dust level. This could be a risk factor for asthma as dust contains organic constituents such as mites which are well known to cause asthma, in addition to many non-organic particles that cause respiratory irritation. ²³³
Cleaning windows, mirrors or glass (3.1)	This task is usually carried out using sprayers which are associated with asthma. ^{209, 281}
Cleaning toilets (4.1)	This is considered a task with a high inhalation exposure potential since more than one product is usually used in a confined area which would cause a rapid increment in the concentration of airborne chemicals. ²⁸² The major concern is the inhalation of high concentration of bleach which is used for cleaning toilets in a number of the participating organisations.

Item (code of questions)	Rationale
Products used for dusting, cleaning windows and toilets (1.4, 3.3, 4.3)	The aim of this question was to investigate the association of asthma with the products used for cleaning.
Total Duration and frequency (1.1;1.2;2.1;2.2;3.1;3.2,4.1 &4.2)	The levels of exposure, whether to dust or chemicals, were quantified based on the frequency of performing the cleaning tasks and time spent on each task. The frequency was assessed using a scale (every day; more than once a week; monthly or rarely) that was developed based on feedback from the cleaners who were interviewed in the pilot study. The question on the average time spent on tasks was adopted from a previously used questionnaire by Obadia <i>et al.</i> ²⁰⁶
Bleach, ammonia and sprays (Q 5; 6 & 7)	These products were particularly highlighted as the literature has consistently associated them with asthma. ^{145, 209} The extent of exposure to each was assessed by inquiring about how long the product was used in years, and about how often, i.e. duration and frequency.
Dilution and mixing of chemicals (Qs 8&9)	Improper dilution or mixing of bleach with acids or alkaline agents, e.g, ammonia, can lead to the evaporation of chlorine and chloramines respectively in high concentration. Such inhalation accidents were found to be associated with asthma. ¹⁴⁵ Again, the total number of years expended in doing these and frequency were requested as measures of exposure.
Cleaning-related respiratory symptoms (Q10)	Upper respiratory irritant symptoms (<i>Watery eyes/ redness of the eyes; Runny/itchy nose</i>) and lower respiratory tract symptoms (<i>wheeze; cough</i>) triggered by cleaning agents were inquired about. The aim was to investigate their prevalence since this might support a role of irritation in causing asthma.
Using rubber gloves (Q11)	Use of latex gloves would increase the risk of asthma. ²³⁹
Education and training (Qs12 &13)	These questions aimed to explore how well the cleaners were educated and trained about the chemicals they used. This might help when planning preventive measures.
Cleaning home (Q14)	Cleaners were asked whether they used cleaning products at home. Non-occupational exposure might confound the results.

Item (code of questions)	Rationale
Previous jobs (Q15)	Cleaners could have been involved in other occupations known to be of high risk of asthma.
General health (Qs16 &17)	The aim was to find out whether the cleaners had other conditions that might be misdiagnosed as asthma.
Further details of the current job (Qs 18;19 &20)	The area of work was inquired about because cleaners could be exposed to other chemicals unrelated to cleaning, e.g. in laboratories, or might be involved in intensive cleaning in one place, e.g. theatre, than others, e.g. office.

5.7.4 Data entry and analysis of work practice questionnaire

Microsoft Access 2007 was used to enter data from the work-practice questionnaire because it was relatively long and included open ended questions and questions with multiple options. Therefore, there was a higher chance of typographic and data entry errors in a spreadsheet. Data entry was checked manually for any errors, and these were corrected instantly. The data then was exported to Minitab to run the analysis.

For the open ended questions (questions about listing chemicals used in cleaning tasks and about describing previous jobs), two simple coding schemes were prepared *a priori* as follows:

1. Coding for the chemical agents

Chemicals with respiratory effects: coded (1).

Chemicals without respiratory effects: coded (0).

Information on potential health effects of a cleaning chemical was drawn from the material safety data sheet.²⁸³ Information on the potential health effects of a cleaning chemical was drawn from the material safety data sheet.²⁸³ This is a document that identifies the basic information about the products such as its hazardous ingredients and the adverse health effects. It is considered a valuable reference for both workers and health care providers. However, many studies have found that material safety data sheets may include inaccurate information with regard to the chemical composition²⁸⁴⁻²⁸⁶ or the potential

adverse health effects.^{287, 288} Accordingly, miscoding might occur if the reported health information in the material safety data sheet was incomplete. In addition, ingredients that are less than 1% of the total concentration are often not mentioned in the material safety data sheet. Accordingly, even if the products contained sensitiser agents, e.g. enzymes, these might not be listed if it is in low concentration. Nevertheless, it is the only source that could give information about the products used.

2. Coding system for the previous jobs

Job or industry known to be associated with increased risk of asthma: coded (1).

Job or industry not or less known to have increased risk of asthma: coded (0).

Assigning individual jobs/industries in either of these categories was based on the available information and the assessor's judgement.

The researcher scrutinised the answers so that each answer was coded appropriately.

Comparisons between responders and non-responders

The first step was to compare the characteristics of the responders to the work-practice questionnaire with those of the non-responders using their data from the respiratory questionnaire. This was to investigate if there were any significant differences that may have caused a response bias.

For the categorical variables, such as gender and atopy, the data was summarized as the proportion for each group. The differences between the proportions were then tested for significance by calculating the 95% confidence intervals.

Since the distribution of continuous variables such as age showed skewness, median and interquartile ranges were used to summarize the data. The differences between responders and non-responders were tested using Mann-Whitney test.

Comparison between cases and controls

Responders were coded as either cases (=1) or controls (=0). Cases were defined as subjects who reported current asthma or had 3 or more respiratory symptoms in the past 12 months while controls were anyone else. A comparison of the demographic and other personal characteristics was then carried out between cases and controls.

The categorical variables such as smoking status (current smokers, ex-smokers and never smokers) and gender (female versus male), were summarized for each group by proportions. The significance of the differences in proportions were tested by computing the 95% CIs.

Mann-Whitney tests were used to compare continuous variables which were age and duration of work as the data distribution was skewed.

Graphical presentations (bar charts) were used to present and compare the knowledge and training of cases and controls. The significance of the difference between cases and control was tested using Chi square test. The test statistic was compared with the chi-square distribution with 3 degree of freedom.

Measuring the association of cleaning products and work-tasks with asthma

In order to investigate the association of cleaning related variables (products and tasks) with asthma, a two stage analysis was done. At the first stage, univariate logistic regression analyses were performed to assess the association of each risk factor with the presence or absence of asthma. The results were presented as unadjusted ORs and 95% CIs. In the second stage, multivariate logistic regression analyses were carried out to adjust for the confounding effect of age, gender and smoking status and results were expressed as adjusted ORs and 95% CIs.

The potential risk factors included the following: dusting, hovering, cleaning windows/mirrors, cleaning toilets, mixing, diluting cleaning products, using bleach, ammonia, and spray.

For the regression analysis, the responses to the questions concerned with the frequency of a task were dichotomised because there was a low response to some categories. In these questions, the participants had to choose from a

short ordinal scale that included four categories (every day, more than once a week, monthly or rarely). The cut-off point of dichotomization was selected based on the frequency of responses in each of the category, typically to obtain two distinct categories with similar numbers of subjects. For the questions relating to the frequency of using a product, a fixed cut-off point was used that categorised subjects into a high exposure group (daily and weekly exposure) and a low exposure group (monthly, rarely or no exposure).

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Chapter 6 Results

6.1 Introduction

This chapter presents the findings of the four different phases in the study: the cross sectional survey of asthma and asthma symptoms prevalence in cleaners; the clinical study for the verification of asthma; the investigations for features of occupational asthma; and the identification of risk factors for asthma in cleaners using a case-control design. Each section starts with the description of the response rate and the characteristics of the participating subjects. This is followed by detailed results that are specific for each phase.

6.2 Phase-I: Cross-sectional survey of asthma in cleaners

6.2.1 Response rate

Response rate in this study was defined as the number of returned questionnaires divided by the number of the distributed questionnaires and multiplied by 100. The denominator, however, was uncertain because of methodological issues, i.e. uncertainties about the number of cleaners who actually received the questionnaires.

Methodological issues in the distribution of the questionnaire

There were two main issues that made the final number of the distributed questionnaires questionable. First, in the initial meetings with the managers about the numbers of employees, it was not possible to obtain the accurate number of their cleaning staff as explained in section 5.4.1, thus, the total sample size was uncertain and was estimated to be 2299-2427 cleaners. Second, three organisations reported having many 'spare' questionnaires at the end of the survey despite reportedly having distributed them to all current cleaners, table 6-1.

Table 6-1 Assumed number of the distributed questionnaires in three organisations

Organisation	Number of questionnaires distributed	Number of spare questionnaires	Assumed distributed questionnaires
Newcastle University	208	4	204
Northumbria University	261	23	238
North Tyneside Hospital NHS trust	300	50-100	250

There is a possibility that a number of potential subjects were missed because they were on leave but, this would not have explained the large number of spare questionnaires at North Tyneside Hospital. This suggests inaccuracy of the information on the number of cleaners employed. The possible defects in the method of recruitment could have been at any stage of the process as presented in the following chart:



- ? Provide inaccurate number of cleaning staff
- ? Missed providing questionnaires to cleaners working in sites other than the main hospital e.g. specialized clinics.
- ? Distributed the questionnaires to cleaners in nearby locations only
- ? placed the letters in one place, e.g. near the clock in machine, where cleaners were expected to take one if they noticed it.

Since neither the number of the cleaners nor the number of the distributed questionnaires was certain, the exact response rate could not be determined.

Table 6-2 presents the finalized estimated numbers of distributed questionnaires.

Table 6-2 Number of the distributed questionnaires in the study

Organisation	Estimated number of distributed questionnaires
Royal Victoria Infirmary	350
Freeman hospital	236
Newcastle University	204
Northumbria University	238
Mental Health Trust	122
North Tyneside Hospital	250
Newcastle City Council	800
Total	2200

Estimated response rate assuming that 2200 questionnaires were distributed

A total of 695 completed questionnaires (31.6%) were returned (response rate). Of these, the following subjects were excluded: those who had worked as cleaner for fewer than 6 months (n=25), and those with incomplete data about duration of work (n=17). Another 3 duplicated questionnaires were also excluded, so the final number of completed questionnaires was 650.

The response rate for each participating organisation is shown in table 6-3. Only 110 out of 800 subjects working for Newcastle city council returned the questionnaire. These cleaners often worked in small numbers in locations such as schools, and so the recruitment process faced obstacles that were not present in the larger organisations. There was thus a question of whether the questionnaire was distributed to all of potential participants. This was reinforced when no one returned a questionnaire after reminder letters were distributed.

Because of the uncertainties associated with the very low response rate the data for the city council cleaners was not included in the analysis. For the other centres the response rate was (543/1400= 38.8%).

Table 6-3 Response rate of individual participating organisations

Organisation	Assumed number of delivered questionnaire	Number of returned questionnaire	Response rate (%)
Newcastle University	204	105	51.5
Newcastle City council	800	110	13.8
Mental Health Trust	122	66	54.1
Northumbria University	238	136	57.1
Royal Victoria Infirmary	350	102	29.1
North Tyneside hospital	250	66	26.4
Freeman hospital	236	110	44.6
Total	2200	695	31.6

6.2.2 General characteristics of the participants

The participants' characteristics are presented in table 6-4. Most of the participants were female (88%) with a mean age of 49.9 years, and had worked in cleaning on average 10 years. More than half (56.2%) of the cleaners were either former or current smokers.

Table 6-4 General characteristics of the participants (n= 543)

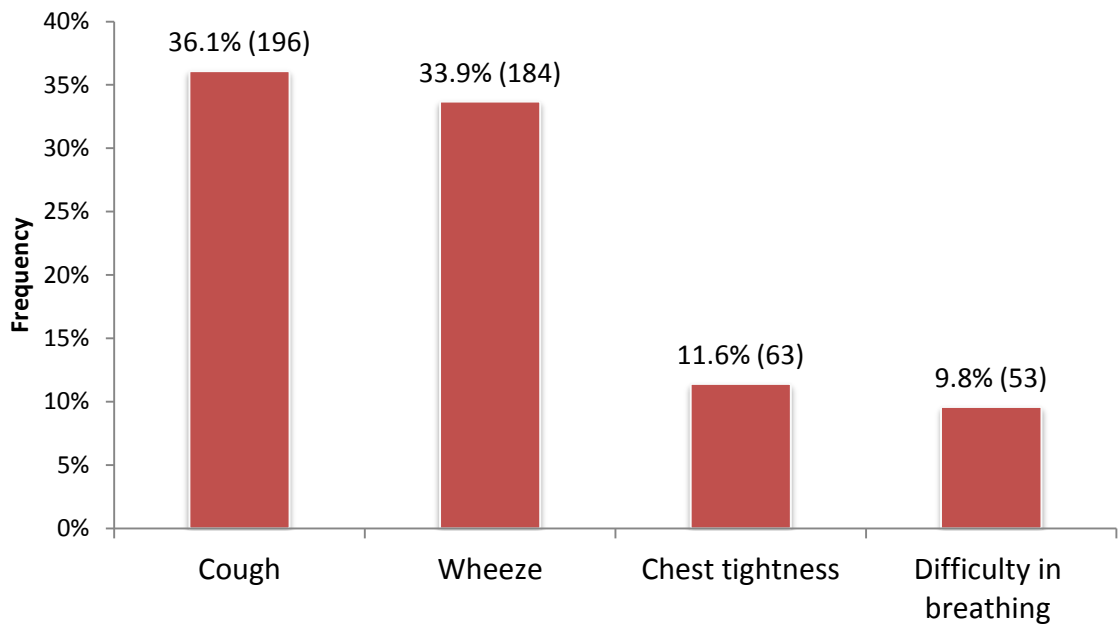
Categorical variables*	Number (%)
Female	472 (87.9)
Never-smoker	234 (43.3)
Former smoker	143 (26.7)
Current smoker	158 (29.5)
Subjects with hay fever	147 (28.0)
Continuous variables*	
Age Mean (standard deviation)	49.9 (10.7)
Years worked Median (interquartile range)	10 (15)

* 6 subjects with missing data on gender, 8 subjects with missing data of smoking status, 18 subjects with missing data on hay fever, 44 missing data on age.

6.2.3 Prevalence of respiratory symptoms

Around half of the subjects (n=265, 48.8%) reported at least one respiratory symptom in the past 12 months and of these, 124 subjects (23%) reported at least three symptoms. Figure 6-1 shows that cough was the most commonly reported symptom (36.1%).

Figure 6-1 Prevalence of respiratory symptoms among cleaners



6.2.4 Prevalence of physician-diagnosed asthma

Of the 543 cleaners, 73 (13.5%) reported ever having had physician-diagnosed asthma, 95% CI (10.7% to 16.7%). Of those who reported the age of asthma onset (n=68), 48 (70.6%) had their first asthma attack after the age of 14 years.

6.2.5 Prevalence of work-related symptoms

About one quarter of the participants reported work-related wheeze, breathlessness or cough. These symptoms were about twice as common in those with a diagnosis of asthma compared with others. This difference in the prevalence of work-related wheeze or breathlessness was statistically significant, $p < 0.001$, table 6-5.

Table 6-5 Prevalence of work-related symptoms

	Work-related wheeze or breathlessness			Work-related cough only		
	Number	%	P-value*	Number	%	P-value*
All cleaners (n=543)	94	17.4	-	46	8.5	
Cleaners with physician-diagnosed asthma (n=73)**	25	34.2	< 0.001	10	13.7	0.09
All other cleaners with no physician-diagnosed asthma (n=468)	69	14.7		36	7.7	

* Chi-square test** 2 missing value about the data of physician-diagnosed asthma.

6.2.6 Incidence of asthma

The incidence of asthma was calculated based on the responses of 449 subjects.

Of the total 543 subjects, 94 subjects were considered ineligible and were excluded:

- 2 subjects missed data on asthma status
- 44 subjects missed data on age
- 43 subjects developed their physician-diagnosed asthma before commencing cleaning.
- 5 had incomplete data about asthma onset

There were 23 cases of physician-diagnosed adult onset asthma amongst the 449 subjects. The total person-years at risk for these 449 subjects was 5007 years. The incidence of asthma was thus:

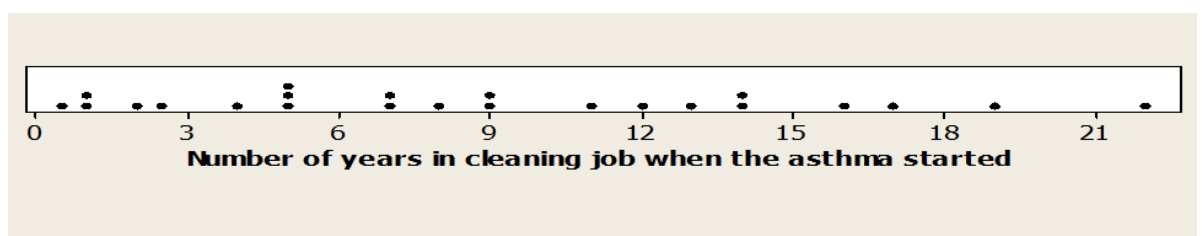
$23/5007 \times 1000 = 4.6$ per 1000 person-years (95% CI 2.9 to 6.9 person-years).

For computing the incidence in women cleaners (n= 394), male cleaners (n= 52) and 3 more subjects who had not provided data on gender were subtracted from the denominator. Hence the incidence for women cleaners was:

$23/4616 \times 1000 = 5.0$ per 1000 person-years (3.2 to 7.5 person-years)

Asthma developed after a variable number of years cleaning ranging from 0.5 to 22 years with a median of 8 years, figure 6-2.

Figure 6-2 Dot plot of the number of years in cleaning work at the asthma onset



6.2.7 Comparison of the characteristics of subjects with physician-diagnosed asthma with those without physician-diagnosed asthma

In order to identify the independent risk factors for the presence of asthma in cleaners, multivariate logistic regression was performed, table 6-6. This table indicates that an increased risk of asthma was associated with former smoking; atopy; and longer duration of work.

Table 6-6 Factors associated with physician-diagnosed asthma in cleaners (results of univariate and multivariate logistic regression)

Risk factors	Subjects with physician-diagnosed asthma 1	Subjects without physician-diagnosed asthma 2	Unadjusted OR 95% CI	Adjusted OR* 95%CI
Gender				
Male n (%)	8 (11.0)	57 (12.3)	1	
Female n (%)	65 (89.0)	405 (86.7)	1.1 (0.5 to 2.5)	0.9 (0.4 to 2.1)
Atopy				
Not reporting hay fever n (%)	43 (59.7)	339 (75.2)	1	
Reporting hay fever n (%)	29 (40.3)	112 (24.8)	2.0 (1.2 to 3.4)	1.8 (1.04 to 3.2)
Smoking status				
Never smoker n (%)	21 (30.0)	212 (45.8)	1	
Current smoker n (%)	19 (27.1)	138 (29.8)	0.9 (0.5 to 1.5)	1.5 (0.8 to 3.1)
Former smoker n (%)	30 (42.9)	113 (24.4)	2.3 (1.4 to 3.9)	2.9 (1.6 to 5.6)
Age				
Median (interquartile range)	51 (44, 57)	51 (44, 57.3)	1.0 (0.97 to 1.02)	0.97 (0.94 to 1.0)
Duration of work in cleaning				
Median (interquartile range)	12.0 (4.6, 21.0)	9.5 (4.0, 17.3)	1.04 (1.01 to 1.07)	1.05 (1.01 to 1.08)

¹ Total of 73 with physician-diagnosed asthma, ² Total of 468 without physician-diagnosed asthma, * From logistic regression analysis adjusted for other variables included in the table.

Key findings of phase-I : Cross-sectional survey of asthma in cleaners

48.8% of cleaners reported at least one respiratory symptom, mostly wheeze or cough. Of these, 23% reported at least three respiratory symptoms.

The prevalence of physician-diagnosed asthma in cleaners was 13.5%.

The incidence of physician-diagnosed asthma among cleaners was 4.6 per 1000 person-years.

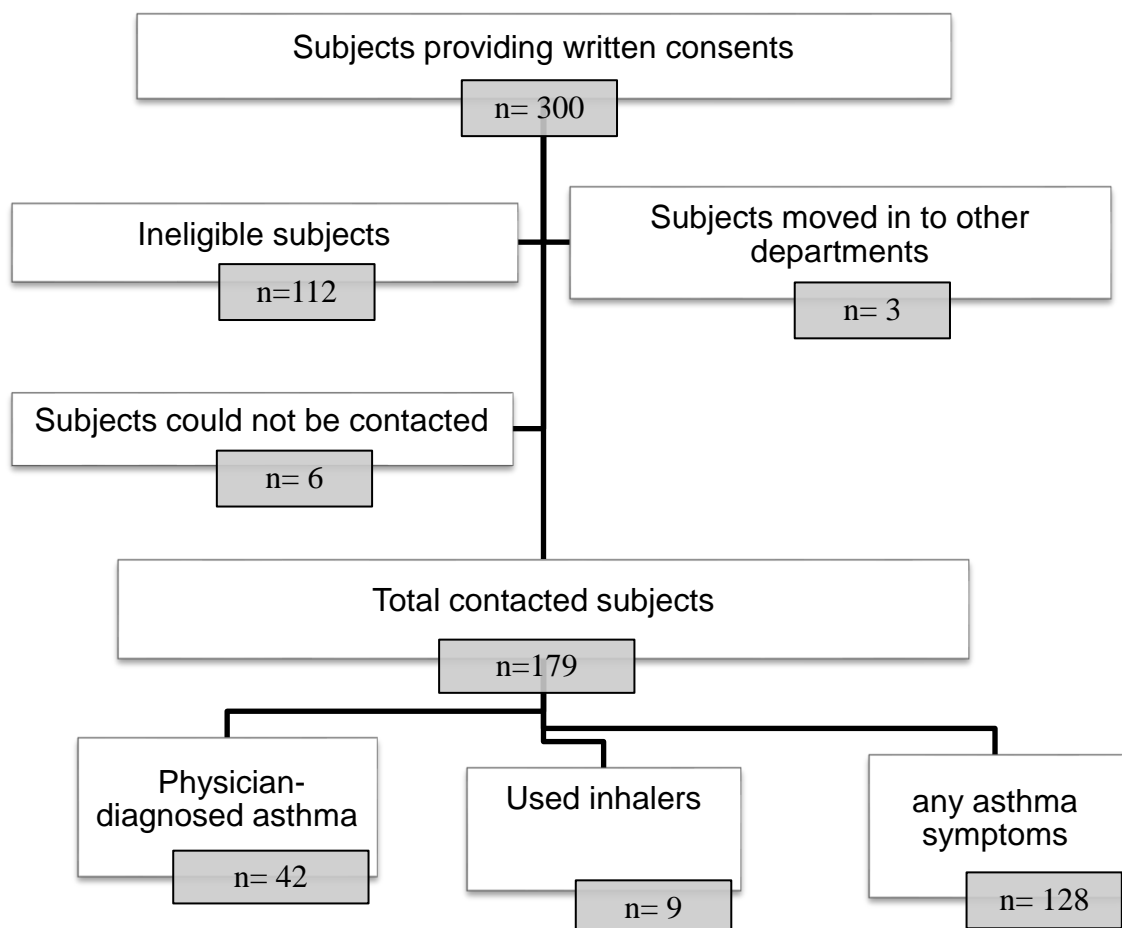
Hay fever, former smoking, and longer duration of work in cleaning were significantly associated with physician-diagnosed asthma.

6.3 Phase-II: Clinical study for supporting asthma diagnosis

6.3.1 Response rate

Of the 543 subjects who responded in phase-I, 300 gave their consent to be contacted for further clinical tests. Of these, 112 subjects did not report asthma or any respiratory symptoms, and three subjects changed their job, and were considered ineligible for this phase. An additional six questionnaires had incomplete contact information, figure 6-3.

Figure 6-3 Selection of the population for the clinical tests study



After inviting 179 subjects to participate in the clinical tests, 60 subjects attended. Five subjects could not proceed to methacholine tests for varying reasons: one subject was recovering from a recent chest infection, another subject used an inhaler just before the test, the third subject was unable to produce repeatable PEF measurements, and two had $FEV_1 < 60\%$ of the

predicted value. Although another appointment was arranged for the first three subjects, none attended. Hence, the final response rate was 31% (55/179).

To investigate whether there was any potential bias in the results from subjects who declined to take part in this phase of the study, the characteristics of those who did and did not give permission to be contacted for further clinical tests were compared. The characteristics of those initially agreed to take part but then did or did not respond to the request to take part in phase-II were also compared.

6.3.2 Comparison of the characteristics of the subjects who agreed to be contacted for clinical tests with those who did not give permission to be contacted

243 subjects did not give written consent for further participation. Almost half of them [n= 114 (47.0%)] fulfilled the criteria that would have made them eligible for phase-II. i.e. had used inhalers or reported at least one respiratory symptom.

The characteristics of these subjects were compared to the characteristics of subjects who agreed to further tests, table 6-7 and table 6-8. They had similar age, gender, and smoking status. The proportion of subjects who reported physician-diagnosed asthma was similar in both groups.

Table 6-7 Comparison of the characteristics of the subjects who agreed to be contacted for clinical tests with those who did not give permission to be contacted (categorical variables)

Characteristics**	Accepted clinical tests¹ n (%)	Declined clinical tests² n (%)	Difference in proportions %	95% CI
Female	162 (90.5)	101 (91.0)	- 0.5	- 7.3 to 6.4
Atopy*	55 (31.8)	42 (37.8)	- 6.0	- 17.4 to 5.3
Current smoker	63 (35.8)	39 (34.5)	1.3	- 10.0 to 12.5
Former smoker	56 (31.8)	29 (25.7)	6.1	- 4.4 to 16.7
Never smoker	57 (32.4)	45 (39.8)	- 7.4	- 18.8 to 3.9
Physician-diagnosed asthma	42 (23.7)	23 (20.2)	3.6	- 6.1 to 13.2
Work-related wheeze, cough or breathlessness	87 (48.9)	50 (43.9)	5.0	- 6.6 to 16.7

¹ Total of 179 subjects who accepted clinical tests, ² Total of 114 subjects who declined clinical tests, * Reporting hay fever, ** The proportions of subjects with presented characteristics was calculated from valid number of subjects in each group which was slightly differed for each characteristic.

Table 6-8 Comparison of the characteristics of the subjects who agreed to be contacted for clinical tests with those who did not give permission to be contacted (continuous variables)

Characteristics	Accepted clinical tests ¹	Declined clinical tests ²	P-value*
Age** Median (interquartile range)	51.0 (44.0, 57.0)	52.0 (44.5, 57.5)	0.4
Duration of work (years) Median (interquartile range)	10.0 (3.2, 20.0)	10.7 (6.2, 20.0)	0.2

¹ Total of 179 subjects who accepted clinical tests, ² Total of 114 subjects who declined clinical tests, *Mann-Whitney test, ** 23 subjects (14 accepted clinical tests, 9 declined clinical tests) missed data on age.

6.3.3 Comparison of the characteristics of subjects who attended the clinical tests with those who did not respond to the invitation to the clinic

Table 6-9 and table 6-10 presents the characteristics of subjects who did participate in the clinical tests (n=55) compared to those who agreed on the questionnaire that they would attend but did not respond positively to the invitation (non-responders n=122). Although not statistically significant, non-responders were younger males, more often atopic, non-smoker, and worked for a shorter duration in cleaning employment with lower percentage of work-related symptoms but the width of the confidence intervals shows that any differences are estimated imprecisely.

Table 6-9 Comparison of the characteristics of subjects who attended the clinical tests with those who did not respond to the invitation to the clinic (categorical variables)

Characteristics**	Responders ¹ n (%)	Non-responders ² n (%)	Difference in proportions %	95% CI
Female	51 (92.7)	109 (89.3)	3.4	- 5.4 to 12.2
Atopy*	14 (25.5)	41 (35.0)	- 9.6	- 24.0 to 4.8
Current smoker	18 (33.3)	44 (36.7)	- 3.4	- 18.6 to 11.9
Former smoker	19 (35.2)	36 (30.0)	5.2	- 10.0 to 20.3
Never smoker	17 (31.5)	40 (33.3)	- 1.8	- 16.8 to 13.1
Physician-diagnosed asthma	16 (29.1)	25 (20.8)	9.0	- 5.8 to 22.3
Work-related wheeze, breathless or cough	32 (58.2)	54 (44.6)	13.6	- 2.2 to 29.3

¹ Total of 55 subjects who respond to the invitation to the clinic and attended methacholine tests, ² total of 122 subjects who did not respond to the invitation to the clinic, * Reporting hay fever, ** The proportions of subjects with presented characteristics was calculated from valid number of subjects in each group which was slightly differed for each characteristic.

Table 6-10 Comparison of the characteristics of subjects who attended the clinical tests with those who did not respond to the invitation to the clinic (continuous variables)

Characteristics	Responders ¹	Non-responders ²	P-value*
Age** Median (interquartile range)	52 (46.0, 58.0)	50 (41.8, 56.3)	0.1
Duration of work (years) Median (interquartile range)	11 (5.0, 20.0)	9 (3.0, 19.5)	0.2

¹ Total of 55 subjects who responded to the invitation to the clinic and attended methacholine tests, ² total of 122 subjects who did not respond to the invitation to the clinic, *Mann-Whitney test, **12 non-responders missed data on age.

6.3.4 Results of methacholine tests

A total of 55 methacholine tests were carried out but one was not completed as the subject withdrew because of the subject's concerns that the inhaled methacholine may have systematic side effects, despite the assurance of the researcher that the test is safe and methacholine would affect mainly the respiratory system.

Twenty five subjects had positive methacholine test results (i.e. $PD_{20} \leq 1600 \mu\text{g}$) and were considered to have asthma, and 29 subjects had negative results (i.e. $PD_{20} > 1600 \mu\text{g}$) and were considered not to have asthma.

Asthma was defined with varying degrees of stringency in each phase of the study. The total number of subjects fulfilling each definition and the proportion with positive methacholine tests are presented in table 6-11. It was found that two thirds of subjects with physician-diagnosed asthma had positive methacholine test. There were smaller proportions of positive methacholine tests among subjects identified using other asthma definitions.

Table 6-11 Proportion of subjects who had positive methacholine tests using different asthma definitions

Definition of asthma (phase of the study where the definition was used)	Total number n = 54	Positive methacholine test Total n= 25	
		n	%
1. Physician-diagnosed asthma (phase-I)	16	11	68.8
2. Using inhaler <u>OR</u> reporting any asthma symptoms (phase-II)			
Using inhaler	17*	10	58.8
Reporting any asthma symptoms	37	15	40.5
3. current asthma (reported physician-diagnosed asthma and used inhaler or reported respiratory symptoms in the last 12 months) <u>OR</u> reported 3 or more asthma symptoms in the last 12 months (phase-IV)			
Physician-diagnosed asthma and asthma symptoms or using inhaler	16	11	68.8
No physician-diagnosed asthma+ ≥ 3 asthma symptoms	16	8	50.0

* Of the 17 subjects using inhalers, 14 have physician-diagnosed asthma

6.3.5 Comparison of the characteristics of subjects who had positive methacholine test with those who had negative test

To identify possible risk factors for asthma, defined as having positive methacholine tests, personal and occupational characteristics of subjects who had positive methacholine tests were compared with those for whom the test was negative, table 6-12 and table 6-13. Low baseline FEV₁ and FEV₁/FVC were significantly associated with a positive methacholine test, P < 0.001 for both. Multivariate logistic regression analysis was not used to adjust for the influence of various risk factors due to the small number of subjects in each group.

Table 6-12 Comparison of the characteristics of subjects who had positive methacholine test with those with negative test (categorical variables)

Characteristics	Positive methacholine test ¹ n (%)	Negative methacholine tests ² n (%)	Unadjusted OR	95% CI
Gender				
Male	2 (8.0)	2 (7.0)	1	
Female	23 (92.0)	27 (93.0)	0.9	0.1 to 6.5
Atopy				
No hay fever	17 (68.0)	23 (79.3)	1	
Hay fever	8 (32.0)	6 (20.7)	1.8	0.5 to 6.2
Body mass index*				
< 30 kg/m ²	14 (58.3)	12 (50.0)	1	
≥ 30 kg/m ²	10 (41.7)	12 (50.0)	0.7	0.2 to 2.2
Smoking status (reference = never smoke)**				
Never smoker	4 (16.7)	13 (44.8)	1	
Current smoker	11 (45.8)	7 (24.1)	2.7	0.8 to 8.6
Ex-smoker	9 (37.5)	9 (31.0)	1.3	0.4 to 4.2
Exposure to dust, vapours or fumes***				
No exposures	18 (70.2)	19 (70.4)	1	
Yes	7 (28.0)	8 (29.6)	0.9	0.3 to 3.0

¹ Total of 25 subjects with positive methacholine tests, ² Total of 29 subjects with negative methacholine tests, * 5 subjects (1 subject with positive methacholine test, 4 subjects with negative methacholine tests) missed data on body mass index, **1 subject with positive methacholine test miss data on smoking status, *** 2 subjects with negative methacholine test missed data on exposure to dust, vapour or fumes.

Table 6-13 Comparison of the characteristics of subjects who had positive methacholine test with those with negative test (continuous variables)

Characteristics	Positive methacholine test ¹	Negative methacholine tests ²	P-value*
Age			
Median (interquartile range)	53 (44.0, 58.0)	52 (46.0, 57.0)	1.0
Duration of work in cleaning (years)			
Median (interquartile range)	11.4 (5.2, 19.6)	10.5 (4.6, 2.0)	0.8
Baseline lung function parameters			
FEV ₁ (% of predicted) Median (interquartile range)	93 (77.5, 102)	106 (96.0, 113.0)	P < 0.001
FEV ₁ /FVC (% of predicted) median (interquartile range)	78.5 (73.0, 80.8)	83 (79.5, 87.0)	P < 0.001

¹ Total of 25 subjects with positive methacholine tests, ² Total of 29 subjects with negative methacholine tests,

*Mann Whitney test.

Key findings of phase-II: Clinical study for supporting asthma diagnosis

25 (45%) subjects selected because of reporting of physician-diagnosed asthma, the use of an inhaler, or asthma symptoms had positive methacholine tests.

Lower lung function than normative baseline was significantly associated with positive methacholine tests.

6.4 Phase-III: Establishing the work relatedness of asthma

Two tests were performed in this phase: serial PEF and serial methacholine tests.

6.4.1 Response rate

a. Serial PEF

Of the twenty-four cleaners who received the Mini-Wright digital PEF device, 18 returned it along with the manual diary. One PEF record was excluded since the subject was working 7 days a week. Two devices had few recordings despite the manual record being completed.

35.3% and 41.2% of the returned records included three and four readings per day respectively. Thirteen records were of adequate quality for OASYS analysis with 3 to 4 readings per day and ≥ 3 work/rest/work complexes. The satisfactory response rate was $(13/24 = 54.2\%)$.

Table 6-14 shows the data quality of the returned PEF records.

Table 6-14 The number and proportion of the returned PEF records of varying quality

Criteria of data quality	Returned PEF records* n (%)
4 readings per day for $\geq 75\%$ of the records	7 (41.2)
3 readings per day for $\geq 75\%$ of the records	6 (35.3)
≥ 3 consecutive workdays in most of the working days	12 (70.6)
≥ 3 complexes (adequate duration)	15 (88.2)
Achieving recommended criteria for OASYS analysis: 4 readings per day for $\geq 75\%$ of the record, ≥ 3 complexes and ≥ 3 consecutive workdays for $\geq 75\%$ of the working period	5 (33.3)
Achieving minimum criteria for OASYS analysis : 3 readings per day for $\geq 75\%$ of the record, and ≥ 3 complexes	8 (53.3)
Poor quality for OASYS analysis: 3 readings per day in most of the record, or < 3 complexes	2 (11.8)
Records with few (5-10) scattered readings	2 (11.8)

* Total number of returned records=17

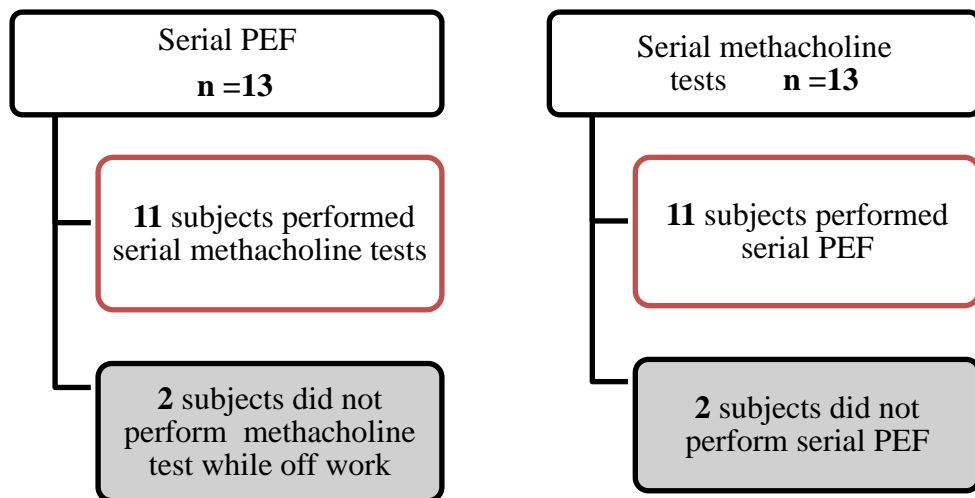
b. Serial methacholine tests

Twenty five subjects (n=25) were invited to perform repeat methacholine tests when they were off work for 7 days on average. Only thirteen subjects attended giving a response rate of 52%.

6.4.2 Comparison of the characteristic of subjects who performed serial PEF and serial methacholine test with those who performed one or none of the tests

Eleven subjects performed both tests as presented in figure 6-4, all were females.

Figure 6-4 The number of the subjects who performed serial PEF and serial methacholine tests



The characteristics of these 11 subjects were compared with those who did not perform both tests or who performed one test (n= 14) to investigate any potential non-response bias. As shown in table 6-15 and table 6-16, responders were older than non-responders (54 years old versus 49.5 years), they tended also to have worked in cleaning for a longer period, and to have more work-related symptoms. However, none of these differences was statistically significant and the width of the confidence intervals shows that any differences are estimated very imprecisely with such a small sample size.

Table 6-15 Comparison of the characteristics of subjects who performed serial PEF and serial methacholine test with those who performed one or none of the tests (categorical variables)

Characteristics	Subjects who performed serial PEF and serial methacholine tests¹ n (%)	Subjects who performed serial PEF or serial methacholine tests or none of them² n (%)	Difference %	95% CI
Atopy*	3 (27.3)	4 (28.6)	- 1.3	- 36.7 to 34.1
Ever smoker	10 (90.9)	11 (78.6)	12.3	-15.1 to 39.7
Physician-diagnosed asthma	5 (45.5)	6 (42.9)	2.6	- 36.6 to 41.8
work-related wheeze, cough or breathlessness	8 (72.7)	7 (50.0)	22.7	- 14.4 to 59.9

¹ Total of 11 subjects who performed both tests, ² Total of 14 subjects who performed one or none of the tests

* Reporting hay fever.

Table 6-16 Comparison of the characteristics of subjects who performed serial PEF and serial methacholine test with those who performed one or none of the tests (continuous variables)

Characteristics	Subjects who performed serial PEF and serial methacholine tests ¹	Subjects who performed serial PEF or serial methacholine tests or none of them ²	P-value*
Age Median (interquartile)	54 (51.0, 60.0)	49.5 (43.0, 56.3)	0.1
Duration of work in cleaning (years) Median (interquartile)	15 (8.0, 26.0)	8.5 (4.5, 16.0)	0.1

¹ Total of 11 subjects who performed both tests, ² Total of 14 subjects who performed one or none of the tests, * Mann-Whitney test.

6.4.3 Results of phase-III

a. OASYS scores and serial methacholine tests

Table 6-17 presents the results of the tests performed in phase-II. The OASYS score of the thirteen cases ranged from 1.15 to 3.29 with a median of 2.2. Three cases had a score ≥ 2.51 (cases 1, 6, & 14) which was suggestive of an occupational effect.

Five cases (cases 1 to 5) showed a clinically relevant change in their airway responsiveness as indicated by an increase in the PD_{20} by ≥ 1.5 doubling doses when measured at the end of a holiday period.

The results of serial PEF and methacholine test were both suggestive of occupational asthma in case 1; i.e. the OASYS score was > 2.5 and the change in the PD_{20} was ≥ 1.5 doubling doses. There was discordance between OASYS score and serial methacholine measurements in four cases (2, 3, 4 & 6). In the first three cases PD_{20} improved substantially when re-measured away from work while OASYS score was not suggestive of an occupational effect. The opposite occurred in case 6 where OASYS score was suggestive of occupational asthma but the results of serial methacholine test were not, table 6-17. Overall differences in the geometric mean of the PD_{20} at and away from work were not significant.

Table 6-17 The results of the methacholine test at work and away from work (expressed as PD₂₀) and the OASYS analysis

Case	Methacholine test PD ₂₀ # <u>on work</u>	Number of days off work	Methacholine test PD ₂₀ # <u>off work</u>	OASYS score
Cases with clinically relevant change in airway responsiveness, i.e. the PD ₂₀ increased by ≥ 1.5 doubling doses off work				
1	180 µg	7	560 µg	3.29
2	50 µg	42	220 µg	2.15
3	100 µg	5	1600 µg	1.67
4	46 µg	21	320 µg	1.17
5	700 µg	7	2400 µg	NA
Cases with a smaller change in airway responsiveness, i.e. the PD ₂₀ changed by ≤1.5 doubling doses off work				
6	260 µg	5	300 µg	2.57
7	100 µg	10	100 µg	2.2
8	110 µg	14	270 µg	1.7
9	320 µg	10	130 µg	1.43
10	73 µg	5	70 µg	1.15
Cases where PD ₂₀ decreased by ≥ 1.5 doubling doses off work				
11	810 µg	16	270 µg	2.5
12	500 µg	14	70 µg	1.88
13	520 µg	8	110 µg	NA
Case carried out methacholine test at work only				
14	160 µg		--	2.58
15	1400 µg		--	2.27
Statistical summary of the tests (OASYS and serial methacholine tests)				
Median of OASYS score (interquartile range)	2.2 (1.5, 2.5)			
Geometric Mean of PD ₂₀ * (95% CI)	On work :		Off work :	
	189.6 µg (103.7 to 346.5)		258.8 µg (133.1 to 502.7)	
Geometric ratio: geometric mean PD ₂₀ at work/geometric mean PD ₂₀ off work	1.4 (95% CI 0.6 to 3.2)			

PD₂₀ is provocation dose causing 20% fall in FEV₁, *Geometric mean for the 13 subjects who had PD₂₀, at and away from work.

b. Score of the case summaries

Summaries of the clinical history and the results were prepared for ten of the eleven cases who performed all the tests, appendix 10. One case was excluded as the patient denied having any respiratory symptoms in the last 12 months. These case notes were evaluated for the likelihood of occupational asthma by nine specialists in occupational lung diseases. Each specialist scored from 0-100% for the likelihood of occupational asthma based on the clinical history alone and then re-scored the case based on the history plus investigative results. A score > 50% was considered suggestive of occupational asthma.

The score for the cases who had positive serial PEF or positive serial airway measurements are presented separately in table 6-18. These cases may be considered to have occupational asthma based on the objective tests.

In Table 6-18, score-1 is the likelihood of occupational asthma based on the history alone and score-2 is the rate based on history plus the investigative tests. It is apparent from this table that median scores-1 across experts based on medical history were < 50%. This indicates that none of the cases were identified as occupational asthma when experts rated the cases based on history alone. However, when experts relied on both history and investigative results to score the same cases, two cases, (case 1 and case 3) had a median score-2 of probability of occupational asthma of > 50%.

Table 6-19 shows the likelihood of occupational asthma for cases that did not have positive results for neither serial PEF nor airway responsiveness measurements. Score-1 and score-2 are the likelihoods of occupational asthma based on history alone and on the history plus investigative results respectively. The results show that all the cases had median probability scores across experts of 47% or lower (whether or not the investigative results were used; i.e. score-1 and score-2) indicating that the opinion of physicians was towards a non-occupational asthma diagnosis. There was close agreement among physicians about cases 7, 9 & 10 which had narrow range of both scores 1 & 2 with a range width of < 30%.

Table 6-18 Physicians' score of likelihood of occupational asthma for cases with positive serial PEF and/or positive serial methacholine tests

	Case 1*		Case 2*		Case 3*		Case 4*		Case 6*		Median for each physician% (range)	
	OASYS score 3.29 PD ₂₀ on work 180 µg PD ₂₀ off work 560 µg		OASYS score 2.15 PD ₂₀ on work 50 µg PD ₂₀ off work 220 µg		OASYS score 1.67 PD ₂₀ on work 100 µg PD ₂₀ off work 1600 µg		OASYS score 1.17 PD ₂₀ on work 46 µg PD ₂₀ off work 320 µg		OASYS score 2.57 PD ₂₀ on work 260 µg PD ₂₀ off work 300 µg			
Physician	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2
1	50	95	20	40	30	80	30	60	20	70	30 (20-50)	70 (40-95)
2	60	80	40	70	20	80	10	80	30	30	30 (10-60)	80 (30-80)
3	50	95	20	40	45	45	20	20	55	75	45 (20-55)	45 (20-95)
4	0	70	10	40	25	50	5	20	30	35	10 (0-30)	40 (20-70)
5	30	70	20	40	10	60	50	70	40	30	30 (10-50)	60 (30-70)
6	60	90	20	60	30	90	0	80	10	50	20 (0-60)	80 (50-90)
7	10	75	10	10	51	60	10	10	0	10	10 (0-51)	10 (10-75)
8	50	80	20	50	10	50	15	30	5	20	15 (5-50)	50 (20-80)
9	40	70	30	51	20	60	10	15	5	10	20 (5-40)	51 (10-70)
Median for each case% (range)	50 (0-60)	80 (70-95)	20 (10-40)	40 (10-70)	25 (10-51)	60 (45-90)	10 (0-50)	30 (10-80)	20 (0-55)	30 (10-75)	-----	

Score-1 is the rate of likelihood (0-100%) of occupational asthma based on the history alone, score-2 is the rate (0-100%) based on history plus the investigative tests.* Numbering of the cases is identical to that in table 6-17.

Table 6-19 Physicians' score of likelihood of occupational asthma for cases with negative results for both serial PEF and serial methacholine tests

	Case 7*		Case 8*		Case 9*		Case 10*		Case 11*		Median score for each physician% (range)	
	OASYS score 2.2 PD ₂₀ on work 100 µg PD ₂₀ off work 100 µg		OASYS score 1.7 PD ₂₀ on work 110 µg PD ₂₀ off work 270 µg		OASYS score 1.43 PD ₂₀ on work 320 µg PD ₂₀ off work 130 µg		OASYS score 1.15 PD ₂₀ on work 73 µg PD ₂₀ off work 70 µg		OASYS score 2.5 PD ₂₀ on work 810 µg PD ₂₀ off work 270 µg			
Physician	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2	Score 1	Score 2
1	30	20	20	60	20	20	10	10	35	65	20 (10-35)	20 (10-65)
2	10	10	10	20	10	10	10	10	60	10	10 (10-60)	10 (10-20)
3	20	10	40	45	20	10	10	5	50	30	20 (10-50)	10 (5-45)
5	0	0	5	5	0	0	5	0	45	45	5 (0-45)	0 (0-45)
5	10	10	20	60	10	0	10	0	80	60	10 (10-80)	10 (0-60)
6	10	10	50	10	0	0	0	0	60	50	10 (0-60)	10 (0-50)
7	0	20	0	0	10	10	0	0	49	49	0 (0-49)	10 (0-49)
8	0	0	20	30	0	0	0	10	50	30	0 (0-50)	10 (0-30)
9	5	5	30	49	3	0	5	30	60	40	5 (3-60)	30 (0-49)
Median for each case% (range)	10 (0-30)	10 (0-20)	20 (0-50)	30 (0-60)	10 (0-20)	0 (0-20)	5 (0-10)	5 (0-30)	50 (35-80)	45 (10-65)	-----	

Score-1 is the rate of likelihood of occupational asthma (0-100%) based on the history alone, score-2 is the rate (0-100%) based on history plus the investigative tests.* Numbering of the cases is identical to that in table 6-17.

Key findings of phase-III: Establishing the work relatedness of asthma

Thirteen subjects carried out serial PEF measurements, three of them had OASYS scores > 2.5 suggestive of an occupational effect.

Thirteen subjects underwent serial PD₂₀ measurements at and away from work. Overall, there were no significant changes in airway responsiveness. Geometric mean PD₂₀ at work was 189.6 µg and away from work was 258.8 µg (95% CI 0.6 to 3.2). Five cleaners showed clinically relevant increase in airway responsiveness away from work, i.e. PD₂₀ off work increased by more than 1.5 double doses.

None of the subjects with positive serial PEF and/or serial airway responsiveness had a median score of probability of occupational asthma across experts of > 50% when scoring based on history alone. However, two cases were rated on average > 50% when the experts relied on investigative results in addition to the history.

6.5 Phase-IV Identifying risk factors for asthma in cleaners (nested case control study)

6.5.1 Response rate

Of the original population (n=543), 432 gave their consent to receive another survey from the research team. The questionnaire was returned by 181 subjects only (response rate 41.9%).

In the first step of analysis, a comparison between responders and non-responders in demographic, health-related factors, and work duration was made to investigate any differences that may have caused bias.

6.5.2 Comparison of the characteristics of the responders and non-responders to work-practice questionnaire

As the table 6-20 and table 6-21 show, there was a significant difference between the responders and non-responders in median age, with responders being older, $P = 0.02$. In addition, responders reported more work-related symptoms than non-responders but this was of borderline significance. Non-responders, on the other hand, were more often smokers and atopic but this was not statistically significant.

Table 6-20 Comparison of the characteristics of responders and non-responders to work-practice questionnaire (categorical variables)

Characteristics*	Responders ¹ n (%)	Non responders ² n (%)	Difference In proportions %	95% CI
Female	162 (90.0)	221 (89.1)	0.9	- 5.0 to 6.7
Atopy	47(27.0)	72 (29.9)	- 2.9	- 12.2 to 5.2
Current smokers	48 (27.1)	81 (32.7)	- 5.6	- 14.3 to 3.2
Former smoker	47 (26.6)	67 (27.0)	- 0. 4	- 9.0 to 8.1
Never smoker	82 (46.3)	100 (40.3)	6.0	- 3.5 to 15.6
Physician-diagnosed asthma	26 (14.4)	39 (15.7)	- 1.3	- 8.1 to 5.6
Subjects with ≥ 3 symptoms	43 (23.8)	54 (21.5)	2.3	- 5.8 to 10.3
Work-related wheeze, cough or breathlessness	59 (32.6)	61 (24.5)	8.1	- 0.6 to 16.8

¹ Total of 181 subjects who responded to the questionnaire, ² Total of 251 subjects who did not responded to the questionnaire, * The proportions of subjects with presented characteristics was calculated from valid number of subjects in each group which was slightly differed for each characteristic.

Table 6-21 Comparison of the characteristics of responders and non-responders to work-practice questionnaire (continuous variables)

Characteristics	Responders ¹	Non responders ²	p-value*
Age** Median (interquartile range)	52 (45.0, 58.0)	50 (42.0, 56.0)	0.02
Duration of work in cleaning (years) Median (interquartile range)	10 (4.0, 20.0)	10 (3.0, 17.8)	0.29

¹ Total of 181 subjects who responded to the questionnaire, ² Total of 251 subjects who did not respond to the questionnaire,* Mann-Whitney test, ** 35 subjects missed data on age (11 responders, 24 non-responders).

6.5.3 Comparison of the characteristics of cases and controls

The characteristics of cases (n=50), defined as subjects with physician-diagnosed asthma who used asthma medications or had symptoms in the last 12 months or those who reported at least three respiratory symptoms without having previous diagnosis of asthma, were compared to those of controls (n=131) who were everyone else. This aim of this comparison is to recognize any significance differences that may bias the results.

Table 6-22 and table 6-23 shows that cases and controls were similar in age and gender. Half of the controls were non-smokers and this proportion was significantly higher than cases. Cases reported having COPD more often than controls, $P < 0.001$.

There were 16 subjects in the case group with other cardio-respiratory conditions that might have caused symptoms similar to those of asthma. Ten of these reported physician-diagnosed asthma at the same time. Four cases, two with heart disease and two with COPD, attended for methacholine tests, and three had results suggestive of asthma. So 13 of 16 subjects with other cardio-respiratory disease were having asthma at the same time based on either self-reporting of physician-diagnosed asthma (n= 10) or on methacholine tests (n=3). The simultaneous occurrence of asthma with COPD or heart disease is not uncommon, thus, it was decided to keep the three remaining subjects in the case group.

Table 6-22 Comparison of the characteristics of cases and controls (categorical variables)

Characteristics	Cases ¹ n (%)	Controls ² n (%)	Difference in proportions %	95% CI
Gender *				
Female	45 (90.0)	117 (90.0)	0	- 9.8 to 9.8
Atopy**				
Hay fever	17 (34.7)	30 (23.3)	11.4	- 3.8 to 26.6
Smoking status***				
Current smokers	14 (29.2)	34 (26.4)	2.8	- 12.1 to 17.7
Former smoker	19 (39.6)	28 (21.7)	17.9	2.3 to 33.4
Never smoker	15 (31.2)	67 (51.9)	- 20.7	- 36.4 to - 5.0
Other physician-diagnosed cardiorespiratory disease #				
COPD	12 (24.0)	3 (2.3)	21.7	9.5 to 33.8
Heart disease	4 (8.0)	2 (1.5)	6.5	- 1.3 to 14.3
Previous exposure to fumes, vapours or dusts				
Yes	16 (32.0)	27 (20.6)	11.4	- 3.3 to 26.1

¹ Total cases of 50, ² Total controls of 131, # Questions about physician-diagnosed chronic bronchitis, COPD and heart disease in the work-practice questionnaire, *1 subject (control) with missing data on gender, **3 subjects (1 case, 2 controls) with missing data on hay fever, ***4 subjects missing data on smoking status (2 cases, 2 controls).

Table 6-23 Comparison of the characteristics of cases and controls (continuous variables)

Characteristics	Cases ¹	Controls ²	P-value*
Age**			
Median (interquartile range)	53 (48.0, 59.0)	52 (44.0, 57.0)	0.18
Duration of work in cleaning (years)			
Median (interquartile range)	10.6 (4.8, 20.1)	9.9 (4.0, 20.0)	0.33

¹ Total cases of 50, ² Total controls of 131, * Mann-Whitney test. **11 subjects miss data on age (1 case, 10 controls) .

6.5.4 Association between asthma and performing cleaning tasks

The association between asthma and performing dusting, vacuum cleaning, cleaning windows and toilets is presented in table 6-24. Almost equal proportions of cases and controls performed the tasks with the same frequency.

Table 6-24 Association between asthma and cleaning tasks

Risk factors**	Cases¹ n (%)	Controls² n (%)	Crude OR 95% CI	Adjusted OR* 95% CI
Dusting				
Daily exposure#	36 (72.0)	91 (69.5)	1.1 0.6 to 2.3	1.0 0.5 to 2.2
Exposure > 1 hour	14 (28.6)	39 (30.5)	0.9 0.4 to 1.9	1.0 0.4-2.2
Dry dusting	24 (50.0)	62 (47.7)	1.1 0.6 to 2.1	1.0 0.5 to 2.1
Hoovering				
Daily exposure#	30 (60.0)	68 (51.9)	1.4 0.7 to 2.7	1.4 0.7 to 2.7
Exposure > 1 hour	12 (24.0)	34 (26.0)	0.9 0.4 to 1.9	1.0 0.5 to 2.4
Window cleaning				
Daily exposure#	14 (29.2)	36 (28.0)	1.1 0.5 to 2.2	1.1 0.5 to 2.4
Exposure > ½ hours	17 (38.6)	48 (38.7)	1.0 0.5 to 2.0	1.2 0.6 to 2.6
Toilet cleaning				
Daily exposure#	40 (80.0)	100 (76.3)	1.2 0.6 to 2.8	1.2 0.5 to 2.7
Exposure > 1 hour	12 (25.0)	30 (23.1)	1.1 0.5 to 2.40	1.2 0.5 to 2.7

¹ Total of 50 cases, ² Total of 131 controls, *From multiple logistic regression adjusted for smoking, age and gender, # daily versus other categories (more than once a week, monthly and rarely), ** The proportions of subjects with presented risk factors was calculated from valid number of subjects in each group which was slightly differed for each risk factor.

6.5.5 Association between asthma and the use of bleach, ammonia and sprays

There was a significant association between asthma and the frequent use of bleach, OR 2.9 (95% CI 1.4 to 6.1). Using sprays frequently was also associated with asthma with OR 1.9 but that was of borderline significance (OR 1.9, 95% CI 0.9 to 4.1), table 6-25.

Table 6-25 Association between asthma and the use of bleach and sprays

Risk factors**	Cases ¹ n (%)	Controls ² n (%)	Crude OR 95% CI	Adjusted OR* 95% CI
Using bleach				
Yes	24 (48.0)	38 (29.0)	2.3 1.2 to 4.4	2.0 0.98 to 4.1
High frequency***	22 (44.0)	25 (19.1)	3.3 1.6 to 6.8	2.9 1.4 to 6.1
Using ammonia				
Yes	2 (4.0)	2 (1.5)	2.7 0.4 to 19.6	#
High frequency***	1 (2.0)	1 (0.8)	2.6 0.2 to 42.9	#
Using spray				
Yes	36 (72.0)	84 (64.1)	1.4 0.7 to 2.9	1.5 0.7 to 3.3
High frequency***	32 (66.7)	69 (53.1)	1.8 0.9 to 3.5	1.9 0.9 to 4.1

¹ Total of 50 cases, ² Total of 131 controls, *From multiple logistic regression adjusted for smoking, age and gender, # Regression analysis was not done due to the small number of subjects, ** The proportions of subjects with presented characteristics was calculated from valid number of subjects in each group which was slightly differed for each characteristic, *** High frequency defined as using the product every day or more than once a week

As can be seen from the table below, there was no statistically significant difference in the average duration of the use of bleach or sprays between cases and controls.

Table 6-26 Association between duration of using bleach and spray (in years) and asthma

Products#	Cases ¹ Median (interquartile range)	Controls ² Median (interquartile range)	Crude OR* 95% CI	Adjusted OR** 95% CI
Bleach•	7 (3.8-13.5)	6.0 (2.0-18.0)	1.0 0.94 to 1.06	1.0 0.95 to 1.09
Spray**	10 (5.5-20.0)	6.0 (3.0-12.0)	1.06 1.0 to 1.12	1.06 0.99 to 1.13

Analysis for ammonia was not done because of small number of subjects, ¹ Total of 50 cases, ² Total of 131 controls, * OR for one unit extra duration, ** From multiple logistic regression adjusted for smoking, age and gender, •128 subjects missed data on duration of using bleach (28 cases, 100 controls), ** 91 subjects (66 cases, 25 controls) missed data on duration of using spray.

6.5.6 Association between asthma and work practices

From the data in table 6-27, it is apparent that diluting products was a common practice among cleaners but mixing chemicals was not. Cleaners involved in mixing chemicals very frequently had almost a three-fold risk of asthma compared with those who mixed less often. This reached statistical significance, OR 2.7, 95% CI 1.2 to 6.1. There was no significant difference between cases and controls with regard to wearing gloves.

Table 6-27 Association between asthma and work practices

Risk factor*	Cases ¹ n (%)	Controls ² n (%)	Crude OR 95% CI	Adjusted OR** 95% CI
Dilution				
Yes	45 (90.0)	107 (81.7)	2.0 0.7 to 5.6	1.7 0.6 to 4.9
Highly frequently*	37 (77.0)	93 (71.5)	1.3 0.6 to 2.9	1.3 0.6 to 2.8
Mixing				
Yes	18 (36.0)	24 (18.3)	2.5 1.2 to 5.2	2.7 1.2 to 6.0
Highly frequently*	16 (32.0)	22 (17.0)	2.3 1.1 to 4.9	2.7 1.2 to 6.1
Wearing gloves				
Yes	48 (96.0)	130 (99.2)	0.2 0.02 to 2.1	0.2 0.01 to 2.0
Always vs other categories (most of the time, sometimes and rarely)	34 (70.8)	85 (64.9)	1.3 0.6 to 2.7	1.2 0.5 to 2.5

¹ Total of 50 cases, ² Total of 131 controls, * Defined as doing the task every day or more than once a week versus low exposure which included monthly, rarely or no use, ** From multiple logistic regression adjusted for smoking, age and gender, * The proportions of subjects with presented risk factors was calculated from valid number of subjects in each group which was slightly differed for each risk factor.

As table 6-28 shows, the average duration of mixing products was longer among controls (5 years) compared to cases (2.5 years), however the difference was not statistically significant.

Table 6-28 Association between duration (in years) of dilution and mixing cleaning products and asthma

Work practice	Cases ¹ Median (interquartile range)	Controls ² Median (interquartile range)	Crude OR* 95% CI	Adjusted OR** 95% CI
Dilution•	5.0 (2.0-11.0)	6.3 (3.0-12.5)	0.99 0.94 to 1.04	1.0 0.95 to 1.06
Mixing••	2.5 (2.0-8.0)	5.0 (2.0-9.5)	0.95 0.8 to 1.06	0.94 0.8 to 1.07

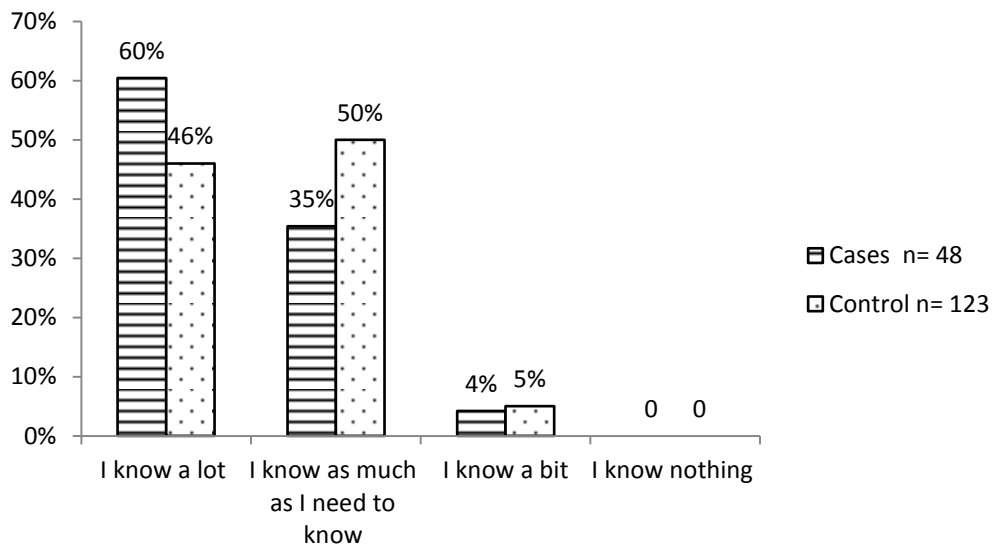
¹ Total of 50 cases, ² Total of 131 controls, * OR for one unit extra duration, ** From multiple logistic regression analysis adjusted for smoking, age and gender, • 52 subjects (11 cases, 41 controls) missed the data on duration of dilution, •• 146 subjects (35 cases, 111 controls) missed data on duration of mixing.

6.5.7 Level of knowledge about cleaning products in cases and controls

The response of 171 subjects to the question about knowledge of cleaning agents showed that 95% of cleaners including both cases and controls, (n= 163) felt they had sufficient knowledge. The level of knowledge of cleaners was not measured or tested by any means meaning that we relied on self-reported answers only.

The bar chart below shows that cleaners with possible asthma were more knowledgeable about cleaning products used, however, the differences did not reach statistical significance, $P < 0.05$ (chi square test, degree of freedom=3).

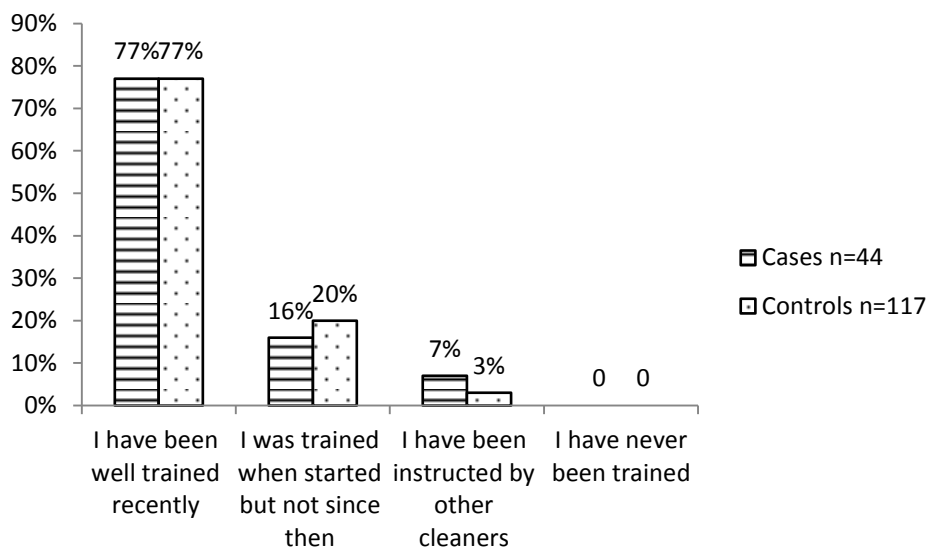
Figure 6-5 Level of knowledge about cleaning in cases and controls products



6.5.8 Level of training received by cases and controls

One hundred sixty one (n=161) subjects answered the question about their training in dealing with chemical products. Of these, 124 (77%) reported that they had received training periodically. Figure 6-6 show that this was equally reported by cases and controls.

Figure 6-6 Level of training received by cases and controls



**Key findings of phase-IV: Identifying risk factors for asthma in cleaners
(nested case control study)**

Cleaning tasks including dusting, vacuum cleaning, cleaning windows and toilets were not significantly associated with asthma in cleaners.

Frequent use of bleach was significantly associated with asthma (OR 2.9, 95% CI 1.4 to 6.1).

Asthma was significantly associated with mixing chemical products (OR 2.7, 95% CI 1.2 to 6.0).

6.5.9 Questions not used for analysis

A number of questions were not analysed for several reasons. Table 6-29 present these questions in themes with the justification for excluding them from further analysis.

Table 6-29 Questions not analysed and the reason for excluding them

Questions theme (code of the questions)	Aim (s)	Justification of excluding
Chemicals or products usually used for dusting? cleaning window? or toilets cleaning? (1.4; 3.3 & 4.3)	To explore any association between asthma and certain products used in these tasks.	1. The researcher noticed that some cleaners reported using cleaning products that would not be used in the work place such as flash glass cleaner and vinegar. This most likely does not represent exposures to all cleaners. 2. General terms were used to describe the products used, such as detergents and descaler, and this did not help in identifying a particular material safety data sheet.
Previous jobs (14)	To investigate previous occupations and exposures as the cleaners might be previously exposed to an agent that is well-known to induce asthma e.g. isocyanates	Most of the cleaners wrote where they worked without describing the nature of the job, e.g. reporting work in a factory without writing in details the nature of their job such as working as a clerical or a manual worker. This made it difficult to anticipate whether the cleaner has been exposed previously to asthma inducer (s).
Using bleach at home (15 & 15.1)	To investigate whether using bleach at home was a confounder agent.	More information was required to assess the difference between cases and controls such as the duration of exposure.
Number of current working hours or working years in current work (22 & 23)	To establish an association between the accumulative work exposure and asthma development.	This might be misleading because cleaners might work less now due to the respiratory conditions. In addition, many cleaners were found to be a cleaner in more than one location, this would not be revealed by this question.

Chapter 7 Discussion

7.1 Introduction

This study is the first study in the UK designed to assess the risk of asthma among cleaners, to identify the proportion of cleaners with occupational asthma based on objective tests, and to identify the work exposures associated with the increased risk of asthma among cleaners. The main findings of the study are summarized below.

In this chapter, the main findings with regard to the research hypotheses are discussed. Following this there is a discussion of the limitations and strengths of the study. Furthermore, the implications of the study are considered.

Table 7-1 Summary of the main findings of the current study

<ul style="list-style-type: none">• Around 50% of cleaners reported at least one respiratory symptom in the last year.
<ul style="list-style-type: none">• The prevalence of physician-diagnosed asthma in cleaners was 14%. In 36% of these asthma developed after subjects started work as a cleaner with a mean interval of 8 years. The incidence of asthma was 4.6 /1000 person-years.
<ul style="list-style-type: none">• Thirteen subjects underwent serial PD₂₀ measurements at and away from work. The geometric mean for methacholine PD₂₀ measured away from work (259 µg) was higher than that measured at work (190 µg) though the difference was not significant (geometric ratio=1.4, 95% CI 0.6 to 3.2). Five cleaners showed 1.5 double doses or more increase in PD₂₀ away from work and three cleaners had an OASYS score of > 2.5. These are suggesting a work related effect.
<ul style="list-style-type: none">• Although a number of work factors were investigated among those who answered the second questionnaire, frequent use of bleach (OR 2.9, 95% CI 1.4 to 6.1) and mixing cleaning products (OR 2.7, 95% CI 1.2 to 6.0) were the only ones significantly associated with asthma.

Hypothesis 1 of this study:

Cleaners have higher risk of asthma compared with the general population.

7.2 Did this study demonstrate a higher than expected prevalence of respiratory symptoms and asthma in cleaners?

7.2.1 Prevalence of respiratory symptoms

This study showed that half of cleaners reported at least one respiratory symptom. Most reported cough (36%) and wheeze (34%) followed by chest tightness (12%) and difficulty in breathing (10%). Whether this prevalence is higher than might be expected in the general population is uncertain as a concurrent control group was not included. However, there are studies of the general population that allow some comparison of the symptoms prevalences.

The ECRHS study⁷⁷ conducted among adults, aged 20-44 years, showed clearly that there is a large variation in the prevalence of asthma symptoms amongst countries. There was seven-fold variation (6%-43%) in the prevalence of cough with a median of 28%. The prevalence of wheeze varied widely ranging from 4% in India to 32% in Ireland with a median of 21%. Differences were also observed for chest tightness (median 14%, range from 6%-21%) and breathlessness (median 7%, range: 2%-11%). Global variation in the prevalence of wheeze was further demonstrated by a study implemented by the World Health Organisation in 2002.²⁸⁹ The prevalence ranged from 3% to 23% in the European countries with an overall estimate of 11%.

Jarvis *et al* (1994)⁴² analysed the data from three UK centres participating in the ECRHS. Of the total sample (n= 9133) recruited from three East Anglian towns, 28% reported being woken by cough in the preceding 12 months, 25% reported wheeze, and 18% and 8% were woken by chest tightness and breathlessness respectively. Similar estimates were observed in another study conducted among adults living in the Greenwich district, UK (1997).²⁹⁰ Subjects aged 18-50 years were posted a questionnaire identical to that used in the ECRHS study. It was found that 29% were woken by cough and 26% reported wheeze. Nineteen percent (19%) reported chest tightness and 9%

had shortness of breath in the preceding 12 months. This respiratory symptom prevalence in the UK thus appears close to the average of those reported worldwide.

There is only one population-based study reported from Newcastle upon Tyne, the area from which the cleaners in this study were selected. Devereux *et al* (1996)²⁷⁷ posted the ECRHS questionnaires to adult men aged 20-44 years. The responders' mean age was 32 years. Of them, 24% reported cough, 29% wheeze, 11% chest tightness, and 7% had shortness of breath in the preceding 12 months. These are slightly lower than the estimated prevalences among cleaners in the current study. Table 7-2 presents a comparison of the prevalence of symptoms from three studies (ECRHS, Devereux *et al* and the current study)

Table 7-2 Prevalences of asthma-like symptoms in the ECRHS study, Devereux *et al* study and the current study

Asthma-like symptoms	Prevalence in the last 12 months		
	ECRHS ⁷⁷	Devereux <i>et al</i> study ²⁷⁷	Current study
Wheeze	21%	29%	34%
Cough	28%	24%	36%
Chest tightness	14%	11%	12%
Breathlessness	7%	7%	10%

Even the Devereux *et al* study²⁷⁷ may not provide a directly comparable population for a number of reasons.

Firstly, Devereux *et al*²⁷⁷ limited their study to men; while this cohort of cleaners was dominated by women. It was observed that women reported more respiratory symptoms than men in the analyses of the German, Canadian and Dutch arms of the ECRHS data.²⁹¹⁻²⁹³ This was also observed in two population based studies investigating respiratory symptoms triggered by various stimuli such as environmental tobacco and dust.^{294 295} This can be explained in part by the higher prevalence and incidence of asthma in females than males after puberty^{265, 292, 296-298} attributed to smaller airway calibre and

consequent greater degree of bronchoconstriction in response to stimuli.²⁹⁸ However, women in the above studies reported more respiratory symptoms than men even when asthmatics were excluded.^{294, 295} This probably reflects the greater ability of women to perceive bronchoconstriction than men.^{33, 35, 50} Women are expected to be more familiar with asthma symptoms and, hence, report them more in respiratory questionnaires.⁵⁰

Second, Devereux *et al* study²⁷⁷ included subjects with a range of socioeconomic status but cleaners in the current study are generally likely to have been of lower socioeconomic status. Studies of the association of socioeconomic status with asthma have produced inconsistent findings. While some reported no associations,^{214, 299} other found higher prevalences of asthma in association with low socioeconomic status.³⁰⁰ The discrepancy was partly attributed to the variety of definitions used to measure socioeconomic status and asthma in these studies.³⁰¹ However, analysis of the ECRHS-I data²¹² showed increased asthma prevalence in participants with lower socioeconomic status whether defined by the educational level (OR 1.3, 95%: 1.0 to 1.6) or occupational class (manual versus non manual) with an OR of 1.5, 95% CI 1.2 to 1.9. Another ECRHS-II data analysis²¹¹ revealed the same association with low educational level (1.2 95% CI 1.0 to 1.5) but not with occupational class. More consistent results were found when studies investigated the association of socioeconomic status with individual respiratory symptoms. A case control study in the UK³⁰² found that low socioeconomic status doubles the risk for adult-onset wheeze. Similarly, other studies in the UK³⁰³ and Nordic countries³⁰⁴ showed a significant association between low socioeconomic status (manual workers) and respiratory symptoms, particularly among female manual workers independently of smoking habits. Several reasons have been proposed to explain this association including exposures to environmental tobacco smoke,³⁰⁵ indoor allergens,³⁰⁶ and occupational exposures.³⁰⁷ Smoking is common among people with lower socioeconomic status³⁰⁸ and several studies reported that smoking is related to the development of individual respiratory symptoms,³⁰³ such as wheeze.³⁰⁹

Third, Devereux *et al*²⁷⁷ focused on young men aged 20-44 but our cohort included older subjects with a mean age of around 50 years. Previous studies^{42, 310} observed that asthma symptoms, excepting breathlessness, were

more frequent among young adults aged < 35 years than among older people. The prevalence of asthma symptoms among subjects with a mean age of 57 years was studied in Australia.³¹¹ The prevalence of wheeze was found to be (21%) which was less than this study's estimate among cleaners (34%). However, the prevalences of chest tightness (14%) and breathlessness (9%) among the Australian general population were comparable to the estimates in the current study (12% and 10% respectively). Note that Australia is among the countries with the highest prevalence of asthma (12%).⁷⁷

Another important point is that the Devereux *et al* study²⁷⁷ was conducted in 1991, and the prevalence of asthma may have changed over the past 20 years. However, the International Study of Asthma and Allergies in Childhood found that the prevalence of asthma symptoms in the UK among children aged 12-14 years decreased between 1997 and 2002, yet the proportion of the children who reported ever having had asthma had increased. These paradoxical findings most likely reflect increase in diagnosing asthma in mild cases.³¹² Likewise, Barraclough and colleagues³³ investigated the changes in asthma symptoms prevalence over 6 years, from 1992/1993 to 1998/1999, in adults of Newcastle upon Tyne. It was reported that prevalence of asthma symptoms and diagnosed asthma increased by an average of 4% but there was a decrease in the prevalence of positive methacholine tests. This mismatch was thought to reflect increased professional and public awareness of asthma rather than any real increase in asthma prevalence. In a recent study (2010) by Simpson and Sheikh,³¹³ the data of 333,294 individuals registered in the database of 422 primary care practice was analysed. The aim was to study the national trend in the epidemiology of asthma from 2001 to 2005. It was found that the lifetime prevalence of asthma decreased significantly by 4.4% among children aged 5-14 years. However, an increase in the lifetime prevalence was observed in the adult groups, i.e. > 14 years in the same period. However, the number of newly diagnosed cases of asthma among adults, i.e. incidence rate, was reduced in the same period. This could also reflect a growing concern that asthma may now be over-diagnosed in primary care. So based on the reviewed literature, asthma prevalence in the UK most likely has not increased since 1990s and any observed changes are

likely due to the impact of the asthma guidelines on the physicians' practice in diagnosing asthma.

In summary, this study shows slightly higher prevalences of asthma symptoms than those obtained in some previous surveys of its type in the general population. This could suggest a higher prevalence of asthma among cleaners. However, the lack of a directly comparable population makes it not possible to conclude that this group of cleaners did have a higher than expected prevalence of asthma.

7.2.2 Prevalence of physician-diagnosed asthma

Symptoms are a sensitive guide to asthma diagnosis in epidemiological studies but they are not specific and are not particularly reliable. Reports of a previous diagnosis are much more specific. The prevalence of previously-diagnosed asthma among cleaners in this study was 14%. This is higher than most estimates of physician-diagnosed asthma prevalence worldwide, for example the 5% (range: 1%-13%) estimated by the ECRHS.⁷⁷ An estimate of doctor diagnosed asthma among European countries was obtained in the World Health Organisation Survey in 2003, and was also found to be 5%.²⁸⁹

There is little literature about the current prevalence/trends of asthma in the UK. Janson *et al*¹⁴ reported that the prevalence of physician-diagnosed asthma in all centres of the UK that participated in the ECRHS was high with an average of 8% (range: 7-10%). The study by Devereux *et al* among 876 adults aged 20-44 years in North England found a prevalence of 12% of lifetime diagnosed asthma.⁵⁰

The cross-sectional design of the current study makes it prone to a number of biases that could have led to under-estimation of asthma prevalence. These include the healthy worker survivor effect and healthy hire effect.³¹⁵ The healthy worker effect is the potential bias which could occur if asthmatic cleaners have already left employment to other jobs as a result of developing asthma, and hence are not available for study. This can be illustrated by the 1958 British birth cohort study in which subjects were followed for up to 42 years.¹⁹⁷ Information on onset of asthma along with occupational history was collected at the age of 33 and 42 years. It was found that cleaners who

developed adult onset asthma spent less time working in this occupation compared to non-asthmatic cleaners (1 year versus 3 years, $P=0.02$) and this was attributed to a healthy worker effect. Asthmatic cleaners may also avoid working in occupations with inhalational exposures such as cleaning jobs, i.e. a healthy hire effect.¹⁷² A study by Butland *et al*³¹⁶ found that subjects who developed hay fever/rhinitis in adolescence were less likely to work in high risk jobs such as cleaning work.

Thus although the prevalence of asthma among cleaners in this study was slightly higher than would have been expected, no firm conclusion can be drawn about the significance of that. It is consistent with but does not add substantial support to the existing epidemiological evidence indicating an increased prevalence of asthma in cleaners.

7.2.3 Incidence of asthma

This study identified 23 subjects who reported that their asthma developed after starting working as a cleaner giving an incidence of 4.6 cases /1000 person-years. This incidence is relatively high compared to that reported in most previous studies of asthma in the general population. In the ECRHS-II,³ 6837 adults who did not report respiratory symptoms or a history of asthma at the baseline were followed prospectively for 9 years. At the end of the follow-up interval 134 adults reported new asthma symptoms giving an estimate of asthma incidence of 2.2 cases per 1000 person-years. In a Swedish study,³¹⁷ adults aged 16-75 were mailed a respiratory questionnaire in which physician-diagnosed asthma and the year of diagnosis were inquired about. Those who developed asthma after the age of 15 were considered to have adult-onset asthma and were included in incidence calculations. This was estimated at 1.8/1000 person-years. Using a similar retrospective approach, de Marco and co-workers³¹⁸ conducted a survey among adults aged 20-45 years. Estimated asthma incidence (1.6/1000 person-years) was based on the answers to the questions about having had asthma and the age at onset of the first attack.

In the UK, Simpson and Sheikh³¹³ used a general practice health database to estimate the incidence of asthma in 2005. This database provides health data of patients registered in 422 general practices throughout England. The incidence among adults aged 15-44 years was estimated to be 4.5/1000

patient-years. Incidence of asthma in the UK general population was also estimated in a case-control study that investigated the relationship between asthma and gastroesophageal reflux disease.³¹⁹ Controls were 8105 subjects aged from 2-70 years that were randomly selected from the General Practice Research Database in 1996. After a follow-up period of three years, 99 cases of asthma were identified giving an incidence of 3.8/1000 person-years. However, there are reasons to believe that these figures derived from general practice registries might be over-estimates. The incidence in 1996 (3.8/1000 person-years) was lower than the incidence in 2005 (4.5/1000 person-years) though another study based on data derived from variety of resources including the general practice database showed a fall in the annual incidence of asthma in all age groups over the same period.³²⁰ Over the same period, many validation studies have examined the accuracy of the diagnosis reported in the general practice database. A recent systematic review (2010)³²¹ identified 212 publications from 1987 to 2008 in which the accuracy of 183 different diagnoses was validated. In most of these papers validation was achieved by comparing data in the electronic patient record with the GPs' responses to questionnaires requesting verification of the diagnosis. The study overall indicated that most of the diagnoses in the UK general practice database were well recorded. However, studies have shown that timing of diagnosis is less accurate.³²² In a study about the quality of data obtained from the database for irritable bowel diseases, it was found that the date of first diagnosis was inaccurate for 25% of incident cases.³²³ This error is likely to lead to misclassification of prevalent cases as incident cases. Since children who are known to be more often diagnosed with asthma than adults³²⁴ were included in one study, the true incidence might be lower than that estimated for adult age group.

The estimate of the current study is comparable to a previously reported incidence of 3.35 cases/1000 person-years in a prospective cohort study among Finnish female cleaners.⁴ In this Finnish study, a large cohort of women cleaners (n= 53,708) and administrative workers (n= 202,751) was followed for asthma incidence through a record linkage study in 1986-1998. It was shown that incidence of asthma among cleaners was approximately 50%

higher than that of administrative workers giving a relative risk of 1.5 (95% CI 1.4 to 1.6).

Although comparable to those of other epidemiological studies, the estimate in the current study is uncertain because of methodological limitations. It was based on a relatively small sample size and on analysis of retrospective information about age when asthma started, and duration of work. Thus, recall errors in self-reported data could lead to misclassification. However, Toren *et al*⁴⁰ found that the self-reported year when asthma started was highly reliable. In his study, 225 subjects had a detailed interview about their asthma at baseline and ten years later. Almost all subjects with asthma reported accurately the year of onset with a recall error of ± 2 years. This is supported by the Pattaro *et al*²⁵ study in which data of 1154 subjects who answered both surveys of ECRHS at the baseline (phase-I) and 10 years later (phase-II) were compared. They found that two thirds of the participants wrote the age at the first asthma attack in both surveys with a difference ≤ 1 year.

With regard to reporting duration of work, there is a concern that cleaners who worked intermittently in cleaning jobs may have poor recall of the total duration and might under- or overestimate that affecting the denominator for the incidence calculation. There is no information about the accuracy of cleaners' occupational histories but studies of other workers which relied on self-reported work histories to estimate exposures reported that information provided by workers was generally reliable.³²⁶ In a study by Bourbonnais *et al*,³²⁷ 100 workers in the shipbuilding industry were asked to provide detailed information about their occupational histories including all jobs held for at least six months and the starting and finishing date of each job. The information obtained was compared with the company records. The study found 90% agreement for the job title and 76% for the starting date.

The use of physician-diagnosed asthma to define cases in relation to asthma incidence could have potentially influenced our estimate. It was shown that this definition most likely leads to under-detection of asthma either because of under-diagnosis by physicians or under-reporting by the subjects themselves.³²⁸ Hence, the estimate of incidence in the current study may be an under-estimate of the true incidence of asthma among cleaners.

As mentioned previously, there is also the possibility that cleaners with respiratory symptoms have already left their jobs and the study was influenced by a survivor bias, and that individuals who developed asthma symptoms before entering the workforce would choose to work in jobs without potentially irritant exposures.

Irrespective of these limitations, our estimate of the incidence of asthma (4.6/1000 cleaner-years) was higher than was estimated in previous epidemiological studies (1.6-2.2/1000 person-years)^{3, 317, 318} among the general population. It was comparable to some UK estimates (3.8-4.5/1000 person-years)^{313, 319} based on GP registration data though these are suspected to be over-estimates. Our estimate (4.6/1000 cleaners-years) was also comparable to an estimate of a robust prospective (1985-1995) Finnish study among cleaners (3.4/1000 cleaners-years)⁴ which showed that cleaners are at higher risk of asthma compared to a reference group of administrative workers. It is at least consistent with the view that cleaners have a higher incidence of asthma than the rest of the population.

7.2.4 Findings with regard to research hypothesis 1 “Cleaners have higher risk of asthma compared with the general population.”

The prevalence of asthma and respiratory symptoms among cleaners in the current study was higher compared with those previously reported in the general population. Furthermore, our asthma incidence is comparable to other studies which showed that cleaners were at higher risk of asthma. All this supports hypothesis 1 of the study.

Hypothesis 2: Cleaning-induced asthma is an example of low-dose irritant-induced asthma that presents with a history that is atypical of occupational asthma and so is not recognized by the physicians

7.3 Do the clinical features and/or the results of the investigations allow a diagnosis of occupational asthma to be established in any of the individual cleaners ? If so, is that the number of cleaners that would be expected to have occupational asthma in this cohort?

Epidemiological studies have shown RRs for asthma in cleaners between 1.5 and 1.7, and this suggested that some of the excess may be linked with their work. However, the data from occupational disease reporting schemes indicates that a much smaller proportion of cleaners are identified by physicians as having occupational asthma.

The hypothesis under investigation here is that this discrepancy is best explained by cleaners suffering from low-dose irritant-induced asthma. If asthma develops gradually, there may be few symptoms on a day to day or week to week basis that allow the typical work-related features to be recognised and the diagnosis of occupational asthma established. Alternatively, cleaners may have typical features of occupational asthma but for a variety of reasons clinicians have to date generally failed to recognise them.

7.3.1 How did we investigate for this hypothesis?

Two tests were used to investigate this hypothesis: serial PEF and serial airway responsiveness measurements. Asthmatic cleaners were asked to carry out these tests to identify the proportion of cleaners with features of occupational asthma and a group of physicians with a specialist interest in occupational lung disease was asked to evaluate the clinical histories for features of occupational asthma. Serial PEF and serial airway responsiveness measurements each identified a small number of subjects with features that

met conventional criteria for the diagnosis of occupational asthma though there was little consistency in the findings of the two tests. The clinical histories alone were not thought by any of the physicians to show features that allowed a diagnosis of occupational asthma to be established on the balance of probabilities.

7.3.2 Serial airway responsiveness

Although serial PEF is often considered the first-line approach to diagnose sensitiser-induced occupational asthma, it was anticipated here that if cleaners' asthma is a form of low-dose irritant-induced asthma serial airway responsiveness might be the more sensitive test. If the relative risk of asthma in cleaners is 1.5-1.7 as suggested by epidemiological studies then 30% to 40% of cleaners with asthma have work-related disease and might be expected to have serial airway responsiveness changes suggestive of occupational asthma. That, however, depends on two key factors. The first is the speed with which changes in airway responsiveness might occur. It is generally accepted that airway responsiveness in cases of sensitiser-induced asthma can rapidly return to normal, even within a few days of sensitiser avoidance, though there is little direct published evidence to support this.⁶⁹ Several studies among workers exposed to different sensitizing agents have shown that recovery of airway responsiveness could occur over months or even years but much less is known about recovery over days or weeks.³²⁹⁻³³² In a study by Perfetti et al,³³³ for example, 91 subjects with occupational asthma were assessed and separated into two groups based on the duration of cessation from exposures: 1) group removed for more than 5 years (n=48), and 2) group removed for less than 5 years (n=51). The assessment included airway responsiveness measurements. It was found that one third of subjects had a normal level of airway responsiveness at the follow-up visit. Recovery of airway responsiveness to normal level was significantly higher among subjects removed from exposures for > 5 years than in the group removed for < 5 years. It is potentially relevant that these studies were mainly among workers with sensitiser-induced asthma.

If cleaners' asthma developed through a mechanism involving low-dose irritant exposures, the underlying effects on airway responsiveness might be different

from those associated with sensitiser-induced asthma and the time course of the changes in airway responsiveness might be different. It is known that sensitized-induced asthma often develops in the first two years after exposure starts.¹⁵⁶ However, it is speculated that cleaner's asthma is a form of low-dose irritant asthma that develop gradually with slow incremental increase in airway responsiveness and, reflecting that, might need a longer time off work to allow a significant improvement to be demonstrable. In the current study, 75% of the cases had developed asthma after a minimum exposure of 4 years with a median of 8 years. Accordingly, one to two weeks away from exposures may not be sufficient to demonstrate a significant improvement in airway responsiveness. The absence of changes over a week or two would not disprove the hypothesis that cleaner's asthma was caused by their work but it is impractical to study changes over longer periods. In the current study, the median duration of the period off work was 7 days (range: 5-42 days).

The second key factor that could influence the results of serial airway responsiveness testing is the extent of reversibility of airway responsiveness after exposure cessation with this type of asthma. Again, it is reported that early recognition of sensitiser-induced asthma and early removal from exposure leads to full recovery of the asthma.³³⁴ However, a longer duration of exposure after the onset of asthma symptoms is associated with persistence of airway responsiveness even after stopping exposure. This is at least partly attributable to permanent pathological changes in the airways due to chronic inflammation.³³⁵ Cleaners' asthma, if caused by a low-dose irritant mechanism, could also be irreversible even at an early stage in its natural history. Data from one study among pulp mill workers found that intermittent exposures to modest level of irritants caused transient increase in airway responsiveness with subsequent improvements.¹⁴⁷ Increased airway responsiveness due to lower level of irritants, thus, could also be reversible after stopping exposure allowing a work-related effect to be demonstrated. However, it is observed in two studies^{145, 205} that asthma prevalence was higher among former cleaners than current cleaners. Medina-Ramon *et al*¹⁶⁰ study, for example, found that former domestic cleaners had a higher asthma risk (OR 1.8, 95% CI 1.3 to 2.3) than current cleaners (OR 1.2, 95% CI 0.8 to 1.8). Another study²⁰⁵ among non-domestic cleaners had also found higher prevalences of respiratory

symptoms and physician-diagnosed asthma among former cleaners compared with current cleaners. This implies that the asthma persisted despite quitting cleaning jobs. The persistence of asthma in former cleaners may be because cleaning-induced asthma is irreversible, or possibly because of continuing exposures to cleaning agents in non-occupational setting, for example, while house cleaning. There are other possible explanations for persisting asthma after stopping exposure such as development of cross-reactivity between antigens but these are proposed in relation to sensitiser-induced asthma and may not be applicable to cleaners' asthma.

This study showed an improvement, although not statistically significant, in the PD_{20} during periods away from work (geometric mean for the 13 subjects who had airway responsiveness measurements off and at work = 259 μ g) compared with periods at work (geometric mean = 190 μ g) giving a change of about 1.4-fold, i.e. 0.7 double doses. Although it was not significant, it may still indicate the presence of an occupational effect. Perhaps, more marked changes in airway responsiveness could have been demonstrated if re-assessment of airway responsiveness was done after a longer period off work. Equally, it is unlikely that all the cleaners in this cohort had occupational asthma so the effect of any changes in airway responsiveness in those who did have occupational asthma would have been diluted by the absence of change in those who did not.

It was anticipated that 30%-40% of the cleaners would have occupational asthma and, hence, would show a significant improvement in airway responsiveness of ≥ 1.5 double doses. In the current study, five subjects of 13, i.e. 38%, showed substantial changes in airway responsiveness which fits with the theory. There was one case with a slightly lower change in airway responsiveness of > 1.2 double doses. Although the change in this case did not reach the pre-determined magnitude of 1.5 double doses, it should not be overlooked as a potential case of occupational asthma.

Demonstrating an increase of ≥ 1.5 double doses in the provocation dose causing a 20% fall in the FEV_1 when off work supports a diagnosis of occupational asthma. The reason for selecting cut-off point of 1.5 double doses is the observation of previous clinical and epidemiological studies which

had used the same technique of the current study, i.e. five breath Newcastle dosimeter, that a repeated methacholine test for the same subjects usually lay within ± 1.5 double doses.^{61, 277} Accordingly, PD₂₀ increases of 1.5 double doses indicate a significant change. However, although a change in airway responsiveness of 1.5 double doses is considered significant at an individual level, smaller changes could also be significant if most of the subjects show a similar magnitude of change. In other words, if it was observed that most of the cleaners with possible occupational asthma had changes in their airway responsiveness of, e.g., 1.2 double doses, such a magnitude of changes would be significant for this particular type of asthma. Even if a smaller magnitude of change is not significant, it could still be considered important as it may indicate the presence of physiological effects. As mentioned above, an improvement in airway responsiveness may sometimes take months before it is clinically significant. Accordingly, a small improvement may indicate that a recovery process has started but it needs a longer period away from exposure before demonstrating a significant change in airway responsiveness.

Airway responsiveness measurements might be influenced by factors unrelated to work that may lead to false negative or positive results, including technical factors, such as nebulizer output, and taking bronchodilator medications before the test.

Serial airway responsiveness measurements have been shown to have sensitivities of 50% to 68% and specificities of 50% to 78% for detecting occupational asthma.^{121, 134} The relatively low sensitivity compared to serial PEF (up to 87%) may be partly explained by the fact that airway hyper-responsiveness may need a longer time away from exposure before hyper-responsiveness improves.¹²⁸

The issues arise whether the observed changes in airway responsiveness are genuine indicators of occupational asthma in this cohort of cleaners or might have been falsely positive or negative.

Could the serial airway responsiveness changes be falsely positive or falsely negative?

It was observed in the current work that some cleaners had dramatic improvements (4-16 folds) in airway hyper-responsiveness away from work.

This magnitude of improvement is higher than is reported (2-3 fold) in other studies among workers with occupational asthma.^{121, 130, 134} There have been isolated cases reports of occupational asthma in which changes of this magnitude in airway hyper-responsiveness were reported.³³⁶⁻³³⁸ However, it would be surprising with such great changes in airway responsiveness, if they were genuinely work-related, that the work relatedness of asthma is not more obvious clinically.

Some cleaners, on the other hand, were found to have significant improvements in their airway responsiveness when they were at work. This observation raises the possibility that there are factors that may have occasionally reduced the repeatability of the test leading to false positive or negative results. Another possibility is that subjects were exposed to non-occupational allergens while off work, for example cats or pollens that could have triggered asthma.

Technical factors

A number of technical factors related to aerosol output, method of inhalation or solution preparation⁵⁸ are known to influence the measurement of airway responsiveness and the repeatability of the measurements. In the current study, a dosimeter was used (Newcastle dosimeter) rather than nebulizer with tidal breathing since a dosimeter ensures delivering a precise amount of aerosol during each inspiration manoeuvre. Cleaners were instructed about the proper manoeuvre of inhalation and were observed closely during the test. The methacholine solution was prepared each time adhering to the same protocol. Furthermore, great care was taken while measuring FEV₁, which is the main outcome of the methacholine test. The subjects were carefully instructed to perform high quality manoeuvres. They were observed to ensure having complete inhalation as incomplete inhalation may cause false reduction in FEV₁.¹⁸ In addition, the method used to estimate FEV₁ after each methacholine dose, that is mean of the highest three of six measurements, was shown to contribute to the precision of the measurements of airway responsiveness compared to having three FEV₁ measurements only.⁶¹ For these reasons, technical factors most likely were well controlled and would have not affected the results.

Effect of medication

Medication is another issue that should be considered when interpreting serial airway responsiveness measurements. Previous studies found that administration of short acting bronchodilators increased the PD₂₀ to methacholine by up to 8-fold.^{339, 340} If cleaners took asthma medications shortly before they undertook the test when they were away from work, this could cause a dramatic improvement in airway hyper-responsiveness, i.e. false-positive results. However, this possibility can be ruled out as three cleaners with significant improvement in airway responsiveness measurements were not on any asthma medications and the researcher ensured that those on asthma medication withheld bronchodilator for at least 6-8 hours before the tests.

Conversely, failure to stop medication shortly before undertaking the test while at work could mask any deterioration of airway responsiveness, resulting in either a false negative result or even a false impression that airway hyper-responsiveness improved when the cleaner was at work. Nevertheless, cleaners were asked about taking any asthma medications before proceeding with the methacholine tests which would have been postponed if they answered positively. Hence, negative results among cleaners on asthma medication were unlikely to have been confounded by asthma medication.

Since none of the cases who showed an improvement in their airway responsiveness at work were on asthma medication, a third possible explanation for the difference in the airway responsiveness measurements is exposure to non-occupational allergens to which the cleaner is sensitized while off-work.

Exposures away from work

Airway responsiveness to methacholine can be increased by exposures to common allergens.^{341, 342} Hence, if cleaners were exposed to non-specific allergens, e.g. pollens, dust mite, during their holiday, the airway hyper-responsiveness would get worse, resulting in the apparent improvement in airway hyper-responsiveness at work. Indeed, one cleaner reported being outdoor most of the time while another spent the holiday cleaning her house.

However, these confounding exposures were impossible to control as there are a large number of exposures/conditions that may alter airway responsiveness. In addition, it would not be convenient for the cleaners if attempts were made to minimize exposure by restricting their activities during their resting days.

Duration of time away from work

There are factors that predict the likelihood of recovery of airway responsiveness away from work in those with occupational asthma including the airway calibre and airway responsiveness assessed by the FEV₁ and PD₂₀ values at the time of diagnosis, the length of time after removal from exposure, and duration of exposure.^{329, 332, 333}

Guidelines for the diagnosis of occupational asthma suggest that serial airway responsiveness testing be performed when the worker is away from work for at least 10 days.^{81, 343} As mentioned previously, it has been accepted that removing patients with occupational asthma from exposure would lead sometimes to the full recovery of airway responsiveness within days. However, there is no evidence that support this notion except for one study by Mapp *et al.*⁶⁹ In this study, 6 subjects with isocyanates-induced asthma were exposed to isocyanates and then underwent methacholine testing at 8 hours, 1 day, 1 week and 1 month after exposure. The study showed that full recovery occurred with 1-4 weeks.

In the current study, full recovery of airway hyper-responsiveness was demonstrated in two cases after being away from work for on average two weeks (21 & 7 days). Three more cleaners had a significant improvement in their airway hyper-responsiveness after on average 17 days (range 5-42 days) yet it remained in the asthma range. These indicate that cleaners' asthma could be reversible over short periods of time. However, this does not necessarily mean that cleaners who did not show significant changes within such short periods are not having occupational asthma. As discussed in the section 7.3.2, little is known about the natural history of low dose irritant asthma in relation to its time to develop; triggering factors; or individual predisposition. Recovery of cleaners' asthma might need longer periods away

from exposures. Further studies are needed to better understand the time course of asthma in the case of low-dose irritant asthma.

Conclusion

The serial airway responsiveness measurements were carried out with careful control of technical factors that might have influenced the results and any confounding effect of medication was excluded. There is therefore no reason to believe that the inherent repeatability of the tests was less than that reported previously. Accordingly, the observed changes in airway responsiveness most likely represent genuine change in asthma activity. Overall changes in airway responsiveness were modest but that was to be expected as it is unlikely that more than half of the cleaners had occupational asthma. There were five subjects with substantial changes in airway responsiveness that were suggestive of occupational asthma. This supports the hypothesis that some of the cleaners have occupational asthma and that serial airway-responsiveness measurement could be a reliable tool to detect that.

7.3.3 Serial PEF

Serial PEF is the most commonly used technique for investigating possible cases of occupational asthma. In the current study, cleaners were provided with digital peak expiratory flow meters and asked to record a minimum of four PEF measurements, on days at work and away from work, over a four weeks period. Data obtained were analysed using OASYS-2 software which produced a score from 1-4 indicating the likelihood of a PEF record showing an occupational effect. A record was considered positive, i.e. showed a significant work-related effect, if the OASYS score was > 2.5 . Burge and colleagues¹¹⁸ found that analysing PEF record by computer-based OASYS-2 would identify correctly 75% of cases with occupational asthma (sensitivity) and 90% of cases with no-occupational asthma (specificity). A positive PEF record, however, does not necessarily mean that the worker has occupational asthma because even workers with work-exacerbated asthma, defined as pre-existing asthma worsened by work exposure, could also produce positive PEF records.¹³⁰ Exacerbation of asthma at work is likely to be accompanied by

bronchoconstriction which cause reduced PEF measurements at work compared with periods away from work.

Three subjects of thirteen studied (20%) had a positive OASYS score of > 2.5. Two of these underwent serial airway testing and a marked change in airway responsiveness was shown in one. One subject thus had consistent results suggesting occupational asthma. The positive OASYS scores in the subject who did not show an increase in airway responsiveness at work and in the subject who did not undergo paired airway responsiveness measurements could have been due to either occupational asthma or work-exacerbated asthma.

Positive serial PEF measurements may indicate occupational asthma or work-exacerbated asthma

Work-exacerbated asthma is a common condition.¹⁴⁰ In cleaning work, asthma can be aggravated by exertion and exposure to irritants such as chemicals and dust. Cleaning is a very physically demanding job that requires bending and lifting, and this could worsen asthma symptoms in a number of cleaners. A recent study (2012)³⁴⁴ found that exposure to physical exertion was significantly more common among identified cases of work-exacerbated asthma compared with non-work related asthma. Cleaning products and dust are other exposures that could trigger asthma attack. These have been identified as causes of work-exacerbated asthma among female cleaners in the surveillance system (SENSOR) in the United States (1993-1997).^{193, 240}

If the positive PEF records were due to cleaners' exposures to non-specific irritants at levels sufficient to cause bronchoconstriction, this is important in two respects. First, it further confirms the irritant properties of cleaners' exposure, and second, it implies that inducing asthma by low levels of irritants might be possible if the irritant exposure was sufficient to cause bronchoconstriction; it is likely to be also sufficient to induce airway inflammation and asthma through a low-dose irritant mechanism if that entity exists.

To conclude, the positive serial PEF records were probably indicative of work-exacerbated asthma. These cleaners could either have developed asthma due

to low-dose irritant exposures or have coincidental asthma but their symptoms and bronchoconstriction were triggered by irritant exposures.

Negative serial PEF measurements

Of the 13 cleaners who performed serial PEF records, ten cleaners had negative records, i.e. OASYS \leq 2.5. These records either were truly negative indicating the absence of occupational asthma or they could have been falsely negative.

Negative serial PEF measurements may indicate absence of occupational asthma

The ten cleaners with negative serial PEF records might not have occupational asthma. Of these, five cleaners did not show a significant improvement in their airway responsiveness when they were off work which further supports the absence of occupational asthma.

However, four cleaners did show significant changes in their airway responsiveness in the absence of a substantial daily variability in the PEF measurements. This may reflect the nature of cleaners' asthma which possibly lacks some work-related features. However, it is also possible that these cleaners had false negative results bearing in mind that serial PEF has a sensitivity of only 75%.¹¹⁸

Could negative serial PEF measurements be falsely negative?

The ability of serial PEF to identify an occupational affect may have been reduced by many factors as discussed below.

Number of measurements

Cleaners in the current study were provided with digital PEF devices and were asked to record four readings a day for four weeks.

There is only one study that has looked at the effect of taking different number of PEF readings on the ability of serial PEF to detect occupational effect using OASYS-2. Anees *et al*¹²⁰ found that taking three readings instead of four readings reduced sensitivity only slightly from 82% to 77%, while specificity remained unchanged at 87%. This is supported by the Gannon *et al*²⁸⁰ study which investigated the number of PEF readings required per day to assess diurnal variation accurately. It showed that three readings per day can cause

underestimation of the true PEF diurnal variation by 6% compared to 4% with four readings a day. This implies that three readings and four readings a day have a comparable performance in detecting PEF changes.

Quality criteria have been established for serial PEF measurements for diagnosing occupational asthma and include having ≥ 4 readings per day, a minimum of 2.5 weeks, ≥ 3 consecutive work days, and ≥ 3 complexes (work-rest-work, rest-work-rest). Records fulfilling these data quality are found to have 78% sensitivity and 92% specificity.¹²⁰ Less data leads to reduced sensitivity (64%) and specificity (83%).

The quality standard above was assessed based on hand-written records. However, unsupervised PEF measurements are often inaccurate or fabricated. In previous studies 20%-30% of hand-recorded readings were most likely invented, and 10% to 30% of the remaining readings were either mistimed or had inaccurate values.^{124, 125} This suggests that the sensitivity assessment was based on records that included fewer true readings that were analysed.

In the current study, around 40% of the returned records had four readings on most of the days while the rest of the records (60%) had mostly three readings a day. Therefore, sensitivity is likely to have been affected by a number of daily records but it is not possible to estimate to what extent.

[Absence of sufficient work-rest periods](#)

It is not just the number of measurements that is important for accurate diagnosis using serial PEF measurements. There also have to be sufficient work/rest periods for analysis. In the current work, most cleaners met this criterion though there was one cleaner who worked only two consecutive days a week. This could have reduced sensitivity of her serial PEF measurements.¹²⁰ Workers generally do not have control on their pattern of work and the requirement to have 3 consecutive work days has been found to be the commonest reason for reducing quality standards.^{123, 345}

[Measurement technique](#)

Good measurement technique is also important for obtaining accurate serial PEF measurements. It was shown in a study that lack of effort would lead to progressive deterioration in PEF over both working and resting days.¹²⁷

This would lead to a false negative record. Alternatively, inconsistent efforts would lead to alternative periods of deterioration and recovery that can falsely be attributed to an occupational effect.

Cleaners in this study were carefully instructed about the correct technique. They were contacted several times in an attempt to ensure adequate data quality. It is therefore unlikely that suboptimal respiratory efforts while taking the measurements would have influenced the results.

Method of analysis

There are several methods of analysing PEF including OASYS-2; visual analysis, area between the two curves (ABC) score; and the time point differences analysis. The most commonly used tests are OASYS-2 and visual analysis by experts. OASYS-2 was chosen to analyse serial PEF measurements in the current study for two reasons. First, OASYS-2 was found to have higher specificity than visual analysis which reduces the chance of incorrectly diagnosing occupational asthma for workers with non-occupational asthma. In a recent systematic review (2009)¹²⁹ of 16 papers that investigated sensitivity and specificity of serial PEF, the authors observed that visual analysis was slightly more sensitive (78%) than computer-based analysis (71%) but had lower specificity (69% versus 91% of computer-based analysis). However, visual analysis in these studies was often based on agreement by 2-3 physicians unlike what usually happens in clinical practice where physicians make interpretations independently. Second, since physicians have different experiences, the same serial PEF could be interpreted differently. This is illustrated by Baldwin *et al*¹¹⁷, who asked various respiratory physicians to rate serial PEF for the probability of occupational asthma. It was found that there was a low level of agreement within physicians particularly, if the serial PEF was indeterminate. This implies that if visual analysis was used in the current study, the repeatability of results would be doubtful and the reliability would depend on how efficient the physician was in interpreting the records. So OASYS-2 seems to have advantages over the visual analysis in providing consistent interpretation of the same record.

The ABC scoring system was devised by Moore and co-workers to improve the diagnostic value of computer-based PEF analysis.³⁴⁶ This system uses

OASYS analysis to create two separate curves for work and resting days using plots of PEF measurements. The score is then calculated from the area between the two curves, hence called the ABC score. Its sensitivity (69%) was found to be a slightly lower compared with OASYS-2 (75%) but the ABC score has the advantage of requiring shorter PEF records with ≤ 3 consecutive resting days but a minimum of six readings per day. Using ABC score may improve compliance in future studies and, hence, increase the return rate of good quality records but this requires further study.

In the time point difference analysis, Stenton *et al*³⁴⁷ calculated the mean and standard deviation of hourly measurements of FEV₁ at rests days. The FEV₁ measurements on the working days were meaned into 2-hourly time segments and then a series of statistical operations was performed to identify whether the mean work day FEV₁ at any particular time was statistically lower than the mean FEV₁ for rest days. The limitation of the this method is that it requires the waking times to be closely similar (less than 2 hours) on work and rest days, a requirement which may not be convenient for workers in general. A difference of > 2 hours in the waking time between working and resting days was observed in the current study.

Effect of medication

A major complication in the clinical investigation of occupational asthma is that many workers who are referred for further investigation have already been prescribed asthma treatment. Weaning subjects off corticosteroids or bronchodilators would ensure the most reliable PEF records, however, that may cause asthma deterioration. Therefore, it is considered sufficient to ensure that asthma medications are taken regularly during working and resting days.¹¹¹

Long term use of corticosteroids reduces airway responsiveness to allergens^{278, 348} and therefore could minimize the changes detected in serial PEF between periods at work and away from work. In the current study four cleaners were on corticosteroids. In early studies of Burge *et al* (1979), false negative serial PEF tests were more prevalent among workers taking inhaled steroids^{349, 350} but later studies showed conflicting results. Cote *et al* (1990)¹³⁴ and Malo *et al* (1993)¹¹² for example, showed that taking corticosteroids did

not affect the sensitivity of serial PEF when analysed visually. Likewise, computer-based analysis was not influenced by taking corticosteroids. A recent study (2009) of workers in a detergent formulating and packing company observed that the mean PEF OASYS score of workers with suspected OA and taking corticosteroids (3.2 ± 0.7) did not differ significantly from that (2.8 ± 1.0) of workers who were not taking it.³⁴⁵ Since the bulk of evidence supports the absence of an effect of corticosteroid treatment on the reliability of serial PEF records, it can be concluded that corticosteroids most likely did not reduce the sensitivity of the tests of cleaners in this study. Cleaners in the current study on corticosteroids had a median OASYS score of 1.8 (range: 1.2-3.3) which was not significantly different from that of the cleaners who were not on corticosteroids (2.0, range: 1.2-2.6, $P=0.9$).

Using reliever inhalers irregularly can cause errors in the interpretation of serial PEF. Misinterpretation is most likely to occur if reliever inhalers are taken more often on work days compared with rest days as this would diminish PEF variability. Five cleaners in the current study reported using medications as required when their asthma was triggered by non-specific exposures, e.g. dust. To minimize the potential error from this, cleaners were requested to record PEF measurements before taking reliever inhalers.

Conclusion

Three of thirteen subjects had positive serial PEF records, most probably caused by work-exacerbated asthma. Several of the PEF records of subjects whose serial airway responsiveness measurements suggested occupational asthma were negative suggesting that continuous exposure to low-dose irritants as experienced by cleaners may not produce work-related airway changes. Therefore, serial PEF may not be a sensitive tool to identify potential cases with this type of asthma.

7.3.4 Physician's opinion about cleaners' asthma

Ten anonymous case summaries were circulated to physicians who specialized in occupational lung disease. They were asked to assign a likelihood score (0-100%) for occupational asthma. A score > 50% was taken to indicate probable occupational asthma.

Diagnostic agreement for occupational asthma between physicians

There are few studies that have investigated the level of agreement between physicians when making a diagnosis of occupational asthma and these have reported that diagnostic agreement is highly variable.^{153, 154, 351} In Fishwick *et al* study,³⁵¹ 19 cases with suspected occupational asthma were selected randomly from a large series of patients referred to secondary care respiratory centres. The hospital case notes were reviewed and clinical information (history, investigations) for each case was converted into an anonymous summary document. Twelve physicians, of whom 75% were respiratory consultants with a clinical interest in occupational lung disease, were sent these summaries and asked to rate the probability of occupational asthma. A wide variation was found in the scores provided and in all cases except one, the range of probability crossed 50%. In another study, Turner *et al*¹⁵³ used the same 19 case summaries to investigate the diagnostic agreement among 104 physicians with different clinical disciplines (occupational and respiratory medicine). Physicians were provided first with the clinical histories only. In the second phase, physicians were provided with the clinical histories plus investigative results. Again, there was a considerable variation in the scores given in all of the cases.

In the current work, there was a close agreement between physicians in scoring probability of occupational asthma based on history and objective tests in four of the 10 cases. The range of scores in each case was ≤ 30 . The scores of the individual physicians in these cases were all either above 50% indicating high probability of occupational asthma or were below 50% reflecting higher probability of non-occupational asthma. This is considerably better agreement than observed in previous studies.

The provision of information from clinical tests was expected to improve agreement between physicians since serial PEF and airway responsiveness

measurements helps in establishing the diagnosis in most cases of occupational asthma. In the current study, better agreement was obtained when OASYS score and serial airway responsiveness measurements were either both suggestive of occupational asthma, i.e. OASYS score > 2.5 and the change in PD₂₀ was > 1.5 double doses while off work, or both were suggestive of non-occupational asthma. However, disagreements occurred when one of the objective tests was positive while the other was negative. This probably reflects the differences in the diagnostic practice and of the physicians, as some may rely more on OASYS score while other on airway responsiveness measurements.

It is inevitable that there is some variation in diagnostic agreement between physicians in relation to occupational asthma. However, in this study agreement was relatively good in comparison with that reported previously. That is probably because the scores were all very low and most subjects showed very little clinical evidence of occupational asthma.

Diagnosing occupational asthma among cleaners based on the history

Reporting improvement of symptoms at weekends and on holidays is a sensitive indicator for detecting occupational asthma. Previous studies^{101, 102, 352} found that improvement of symptoms at weekends and on vacations in workers with occupational asthma confirmed by objective assessments had sensitivities of 70%-77% and 74%-88% respectively. Therefore, physicians often diagnose non-occupational asthma in the absence of work-relatedness. However, these studies on the features of the clinical history were performed mainly among workers with sensitiser-induced occupational asthma.

In the current study, no cases of occupational asthma were identified based on the history alone using 50% probability score as a cut-off point. Assuming that some of the cleaners did have occupational asthma as suggested by the epidemiological context and the serial airway responsiveness measurements, this suggests that occupational asthma among cleaners is under-recognizable or poorly recognizable if clinicians rely only on the clinical history alone. The absence of work-related symptoms may reflect the nature of cleaning-related asthma in which low-dose irritant exposures would not trigger symptoms on a

day to day or week basis but gradually and cumulatively increase airway responsiveness.

Alternatively, cleaners might have suffered work-related respiratory symptoms but have denied them because of fear of losing their job or promotion.¹⁸² This is possible since cleaners generally have a low educational level and have few employment options. This is illustrated by a study among female hotel cleaners (n=941),²³² where 94% experienced work-related illness but only one third reported it to their management. Fear of getting fired, losing work-time, and eliciting a punitive reaction from management was among the reasons cited for not reporting. However, denying work-related symptoms is unlikely to have happened in this study since some cleaners informed the management about worsening of their asthma symptoms particularly after using bleach (case 1 &10).

One other possible explanation for not reporting worsening of asthma symptoms is if subjects are not able to perceive narrowing in their airway. Previous studies^{25, 35} found that some individuals do not perceive respiratory symptoms during challenge tests despite having measurable airway obstruction. However, such poor perception was found mainly among males and our population included only females who, on the contrary, were found in previous studies to be good perceivers of respiratory symptoms.^{35, 50}

There is thus no fully satisfactory explanation for the physicians' failure to identify occupational asthma from the history other than (a) there were no cases of occupational asthma in this cohort which is unlikely, given the epidemiological evidence and the results of the airway responsiveness measurements, or (b) those with occupational asthma truly did not have typical symptoms of the disease.

Diagnosing occupational asthma among cleaners based on the history and investigative results (OASYS score and serial airway responsiveness measurements)

Of the four cleaners who showed significant changes in airway responsiveness, none was identified by the assessing physicians as having probable occupational asthma based on the history alone but two were identified as such (median score > 50%) after provision of the results. Cleaners who did not show an improvement in airway responsiveness were

identified by physicians as having non-occupational asthma (median score < 50%) whether they relied on the clinical history alone or on the investigations.

So, after the results of the investigation were made available to the assessing physicians, the diagnosis was shifted from non-occupational asthma to occupational in two cases (20%). This implies that the tests showed marked work-related changes that were suggestive of occupational asthma although the history lacked typical work-related symptoms. It is unlikely that these subjects denied work-related symptoms as some subjects have already reported to the management about having respiratory symptoms after using cleaning agents. Hence, this finding most likely indicates that cleaners with occupational asthma would not present to the physicians with work-related symptoms and thus, would generally fail to be diagnosed by physicians.

7.3.5 Findings with regard to the hypothesis “Cleaning-induced asthma is an example of low-dose irritant-induced asthma that presents with a history that is atypical of occupational asthma and so is not recognized by the physicians”

In this study, some cleaners showed changes in airway responsiveness measurements suggestive of occupational asthma. However, most of them had negative serial PEF suggesting the absence of day to day changes in airway calibre. The participating physicians could not identify occupational asthma in these cleaners when they relied on the clinical history alone. These findings support the above hypothesis, however, further studies with alternate trial designs, e.g. cohort studies, that include a sufficient sample size to obtain precise results are needed to further prove the hypothesis.

Hypothesis 3: Bleach is the principal cause of asthma in cleaners.

7.4 Do the results indicate a specific cause of occupational asthma in cleaners?

Cleaners are exposed to a wide range of cleaning agents and perform variable tasks. In this study a case-control design was used in an attempt to identify occupational exposures (chemicals and tasks) that could be associated with asthma.

7.4.1 Bleach

Bleach, a chlorine-liberating agent,³⁵³ is arguably the most likely cause of asthma in cleaners. This is because chlorine is well known to cause RADS after a single high-level exposure.^{354, 355} Repeated exposure to moderate levels of chlorine has also been shown to induce asthma among workers in paper and pulp mills.³⁵⁶ In a large scale study, 39,122 non-asthmatic workers employed in paper or pulp plants were followed up for 12 years.⁹⁰ The relative risk of new onset asthma was doubled among workers exposed to recurrent gassing incidents compared to unexposed workers. None of the identified asthma cases met RADS criteria. The level of chlorine exposure was not measured and it is not known at what exposure level RADS would occur.

In recent years, chronic exposure to lower levels of chlorine has also been suggested to induce asthma. Several studies have found an association between attending chlorinated swimming pools and the development of asthma.³⁵⁷⁻³⁵⁹ Poolside workers were found to have a two-fold risk of developing asthma compared to a reference population¹⁴² and the risk of developing new-onset asthma was found to be associated with the number of hours spent in the swimming-pool environment.³⁶⁰ It was hypothesized that the increased asthma risk among swimmers was due to the use of chlorine-based compounds to disinfect water.³⁶¹ This process causes release of free chlorine which reacts with nitrogenated substances found in water, for example urine, leading to by-product formation such as chloramines.³⁶² There have been no

epidemiological studies that have examined the dose-response relationship between chlorine air levels and asthma and only few epidemiological studies among pool workers that have examined the dose-response relationship between asthma and measured chloramines levels in pool areas.^{142, 148, 249} These did not find any association. Thickettes *et al*⁹¹ identified three cases of what appeared to be typical occupational asthma among lifeguards exposed to chloramines. The workers had symptoms suggestive of occupational asthma and showed decreased pulmonary function after provocation challenge tests with trichloramines. These cases not only supported the possibility that chloramines might cause asthma but also suggested that it may induce asthma through sensitization. However, none of the cases showed any increase in airway responsiveness after the challenge and that is atypical of sensitiser-induced occupational asthma. The observed bronchoconstriction during the provocation test could have been due to a nonspecific irritant response rather than true positive test. Along the same lines, a recent experimental study (2012) found that exposure to low level of trichloramines could decrease pulmonary function.³⁶⁰ In this study, 37 healthy subjects who were irregular attenders to swimming pools and 14 workers at swimming pools were exposed to filtered air in a chamber in one occasion and on another occasion to trichloramines at levels of 0.15 to 0.23 mg/m³ which were within the recommended exposure guidelines (0.2-0.3 mg/m³).³⁶³ A reduction in FEV₁ and FEV₁/FVC was reported after trichloramines exposure and not after filtered air exposure, FEV₁ reached < 70% in few three subjects. The possibility that these reactions were caused by sensitization was not tested as airway responsiveness measurements were not performed in this study. The bulk of the evidence relating to exposure to low level chloramines exposure is derived from cross-sectional studies which are prone to under-estimate of risks because of healthy worker effect. Fornander *et al*,³⁶⁴ for example, found a high prevalence (30%) of airway irritation symptoms among those who worked less than three years in swimming pools and a lower prevalence (6%) in the group with 4-7 years of employment. It seems that affected workers had already left the job leading to a decrease in the measured prevalence.

In summary, chloramines seem to have potential harmful respiratory effects but the existing evidence is not conclusive either about their having a causal

association with asthma or its potential mechanism. It may be that the observed increased asthma with low level exposures was partly caused by exposure to free chlorine. Many studies have reported that levels of chlorine or its by-products that are associated with asthma in the swimming atmosphere remain within the national recommended limits.^{148, 358, 360} Therefore, the observed increased risk of asthma among swimming pool attenders seems to be caused by chronic exposures to low levels of irritants.³⁶⁵

In cleaning work, bleach is usually diluted with water before use. Cleaners use this solution in many tasks, such as cleaning floors and sanitary fittings. Bleach disinfects by releasing chlorine slowly at a low concentration. Chloramines may also be liberated if the chlorine reacts with organic compounds in water. Accordingly, cleaners are likely to inhale chlorine/chloramines at low levels as long as they are working with bleach solutions. Chlorine levels were found to range from 0.0-0.4 ppm with peaks up to 1.3 ppm during cleaning¹⁴⁵ which is higher than the short-term limit exposure (0.5 ppm). Bello *et al* also found that inhalational exposures to airborne compounds of cleaning products, such as volatile organic compounds, generated during toilet cleaning were high and may have exceeded the occupational limits particularly if the toilet was small and unventilated.³⁶⁶ This scenario is similar to that of the swimming pool workers who continuously inhale chlorine while standing near the pool at exposure levels (0.5-1.5 ppm).³⁵⁸ Hence, an increased risk of developing asthma among cleaners from exposures to low level of chlorine is plausible. Since chlorine is not known to cause asthma through sensitization, cleaners' asthma would be a type of low-dose irritant-induced asthma.

The current study showed that cleaners who frequently used bleach had three-fold odds (adjusted OR 2.9, 95% CI 1.4 to 6.1) of having asthma compared to cleaners who were infrequently exposed to bleach. These findings give support to the hypothesis that exposures to chlorine/chloramine at low levels contribute to the development of asthma. The results are in agreement with previous findings from case-control studies,^{145, 205, 208} though not all of these show statistical significance.

Another finding was that mixing cleaning products was more prevalent amongst asthmatic cleaners (36%) compared with non-asthmatic cleaners (18%), this difference reached statistical significance (adjusted OR 2.7, 95% CI 1.2 to 6.0). Commonly reported mixtures involved bleaches together with acids or alkaline products such as hydrochloric acid and ammonia.^{145, 367} These mixtures cause the release of a large amount of chlorine and chloramine fumes.^{261, 368} Development of RADS after inhalation of fumes from mixing incompatible products is documented in the medical literature,^{254, 369} some were among cleaners.²³⁰ Epidemiological studies among cleaners have also suggested an association between developing asthma and the inhalation of a noticeable amount of fumes.^{145, 208} In a case-control study of domestic cleaners, Medina-Ramon *et al*¹⁴⁵ showed that accidental inhalation of high levels of irritants increased the risk of asthma by almost four-fold, OR 3.8 (95% CI 1.0 to 14). Similarly, Macaira *et al*²⁰⁸ compared asthmatic non-domestic cleaners (n=39) with non-asthmatic cleaners and found that ever involvement with inhalation accidents in the past was associated with asthma with borderline statistical significance, OR 2.7 (95% 0.96 to 7.1). The failure to demonstrate a significant association was probably because the inhalational accidents in Macaira's study were not limited to exposures to fumes/gases, but also included other conditions such as spills and exposure to dust. The relationship between the latter and cleaners' asthma is not established yet and their inclusion might have led to under-estimation of the risk estimates. The current study did not systematically evaluate cleaners for the possibility of RADS after inhalation accidents but no anecdotes of this were reported.

The results of this study identified an association between self-reported use of bleach and asthma and this finding supports the hypothesis that asthma among cleaners is a type of low-dose irritant-induced asthma. The exact underlying mechanism is not known and further studies of the potential mechanism of low-dose irritant asthma are needed.

7.4.2 Sprays

Chemical products in spray form are commonly used in the UK to accomplish tasks such as glass and furniture cleaning.²⁸¹ Sprays may be a risk factor for developing asthma among cleaners for two reasons: first, application through spraying generates aerosols which are released close to cleaners' breathing zones. Hence, cleaners are more likely to inhale high levels of cleaning chemicals than they would be if they used liquid cleaning agents. Second, sprays in general contain chemical ingredients that enhance the effect of the cleaning agents and facilitate removal of surface contaminant (fat, dust) for example glycol ethers and sodium hydroxide.³⁷⁰ These components were found to cause mainly irritant respiratory symptoms,³⁷¹⁻³⁷³ However, other chemicals such as terpenes are added sometimes for example to produce a pleasant odour. Some of these have been found to have sensitizing properties³⁷⁰ and cleaners may develop typical sensitiser-induced asthma caused by a chemical component in the sprays.

In the current study, using sprays more than once a week was associated with asthma with borderline statistical significance (adjusted OR 1.9, 95% CI 0.9 to 6.1). This result is consistent with those from other studies.^{209, 281} In a prospective cohort among 1011 female cleaners, Nielsen and Bach found a three-fold increase in risk of asthma among cleaners who used sprays during the follow up period compared with those who had never used sprays, OR 3.0 (95% CI 0.9 to 10.0) but this was also of borderline significance. In a study among Spanish domestic cleaners, using products in spray form was found to be significantly associated with asthma, OR 3.5, 95% CI 2.0 to 6.0.²⁰⁷ None of these studies are particularly robust because they were based on small numbers of subjects; they might have been subjected to recall bias; or they might have been influenced by healthy worker effect.

A number of cleaners in this study reported using "flash glass cleaning sprays". Material safety data sheet for this product included ethanolamines which have been related to sensitiser-induced occupational asthma.^{374, 375} Ethanolamines are widely used in industry and may be present in many agents in trace concentrations. Given that material safety data sheets are required to report only ingredients at concentrations > 1% of the products,

many cleaning agents could contain ethanolamines that are not listed in the material safety data sheet. Although ethanolamines were found to induce asthma at very low concentrations,³⁷⁵ a few cases of ethanolamine-induced asthma have been identified among workers across various industries.^{237, 374} This suggests that it is unlikely that ethanolamines play a key role in inducing asthma among cleaners.

Other potential sensitizers in cleaning products include enzymes which are bacterially or fungal derived proteins. Four main types of enzymes (proteases, amylases, lipases and cellulases) were introduced into detergent products to facilitate removal of deposits and stains.³⁷⁶ These enzymes were reported to cause sensitizer-induced occupational asthma mainly among detergent-manufacturing workers^{377, 378} but a few cases were reported among consumers in the early years (1960s) when enzymes first introduced. However, by using different formulations of enzymes, e.g. encapsulation, occupational exposures has been reduced markedly with a subsequent reduction in enzyme-induced asthma among detergent manufacture workers.³⁷⁹ Testing for sensitization for detergent enzymes was carried out among 67 cleaners in a study investigating products associated with asthma among cleaners.²⁰⁷ None of the cleaners showed sensitization. Since there are no other studies examining this aspect, the possibility of enzyme-induced asthma in cleaners cannot be excluded.

Using products in spray form is probably a risk factor for asthma because spraying facilitates inhalation exposures to irritant aerosols. Some sprays contain ingredients that have ability to induce sensitizer-induced asthma. The contribution of this mechanism to the development of cleaner's asthma is uncertain but the evidence suggests that it is not likely to be a common occurrence.

7.4.3 Cleaning tasks

Cleaning comprises a wide range of activities. Some of these activities may put cleaners at increased risk of developing asthma, either because they expose cleaners to hazardous agents (e.g dust), or because they impose higher risks of inhalational exposures compared to other tasks. For example, in cleaning toilets, several products are used that would increase the level of airborne chemicals.

This study was not able to demonstrate an association between vacuum cleaning/dusting, window cleaning, or toilet cleaning and the development of asthma. Zock *et al* (2001)²⁰⁷ did find that these tasks were risk factors for asthma among domestic Spanish cleaners. However, in Medina-Ramon *et al*¹⁴⁵ case-control study among domestic cleaners, there was no association between asthma and different cleaning tasks. Another study among non-domestic cleaners found that the frequency of different cleaning tasks was the same in cases and controls.²⁰⁸ The Zock study was relatively small (n=23) and the cleaners were requested in a telephone interview to recall information about their cleaning tasks that occurred 6 years ago, and these might have affected the reliability of the results. Zock *et al* recruited those who worked in cleaning in 1992, while Medina-Ramon *et al* studied women who were employed in domestic cleaning in 2002. There could have been changes in work practice (amount and the number of products used) over the years that caused a reduction in the exposure levels among these workers. Cleaners who participated in the Zock study were domestic cleaners who most likely were not trained properly or merely received informal training. They could thus have been less knowledgeable about the hazards of chemicals,²⁴³ and unsafe work practices, such as mixing or over-use of chemicals would make them more prone to high levels of exposure. Cleaners in the current study were recruited from educational institutions and hospitals where 93% reported receiving training on the proper use of the cleaning products (amount and methods of application). They were provided with cleaning products which were selected by the management because of their low potential health hazards.

Overall, the current and the previous literature suggests no relation between having asthma and a wide range of cleaning tasks. That suggests that the risk of asthma is a feature of some aspect of cleaning that is common for all types of cleaning activities. Since studies yielded more consistent results for the relationship between asthma and some products such as bleach and sprays, the increased asthma risk is likely to be more related to the products used rather than to task performed.

7.4.4 Other potential risk factors

Latex gloves

Natural rubber latex is widely used in manufacturing medical devices such as powdered latex gloves, and other articles such as household gloves. In 1980, it was identified to cause IgE-mediated allergic reactions, mainly skin rashes.²³⁹ In 1990, latex emerged as a major cause of occupational asthma, particularly among health care workers.²³⁹ This was caused by the inhalation of latex contaminated powder which was aerosolized when the powdered latex gloves were removed. In recent years, however, latex-induced asthma has been reported to be largely reduced after substitution of powdered latex gloves with low-protein, powder-free latex gloves or latex-free gloves.^{380, 381} However, this might not be applied to every health facility. In the UK, for instance, a study conducted by Bell *et al* (2001)³⁸² in a large (5,000 staff) UK acute hospital, found that 20% of the wards still had powdered latex gloves. No other UK-based studies have been reported investigating the compliance with and effectiveness of the latex policy in reducing latex-induced asthma. Therefore, latex allergy might be considered as a possible cause of asthma in cleaners.

There is only one study that investigated the relationship between wearing gloves and work-related asthma symptoms in school and racetrack cleaners.²⁰⁶ The authors found that male cleaners who usually wore gloves were at significantly increased risk of asthma symptoms, however, this association was statistically non-significant among female cleaners. In the current study, there was no association between wearing gloves and asthma, adjusted OR 0.2 (95% CI 0.01 to 2.0). The reason for not finding association in the current work is that the participating organisations have substituted non-latex gloves for latex gloves. Using gloves, instead, may help in reducing the

risk of developing asthma as under use of gloves can place cleaners at risk of developing dermatitis, and there is some evidence of a possible link between occupational skin disease and developing asthma.³⁸³ The broken skin in these conditions may facilitate the passage of allergens with subsequent sensitization. Skin exposures to isocyanates, for example, were found to increase the risk of developing occupational asthma.³⁸⁴ Contact dermatitis are found to be common among cleaners^{385, 386} which might be a consequence of the wet work and using cleaning products that contain potential irritants and allergens.³⁸⁷ There is only one study³⁸⁸ among non-domestic cleaners (n= 549) that investigated the association between asthma and skin rash. It was found that cleaners with dermatitis were more likely to have physician-diagnosed asthma but that was statistically significant only amongst male cleaners. A significant association was also found in the same study³⁸⁸ between skin rashes and reporting respiratory work-related symptoms. No other studies have investigated this association in the workforce. Thus, there is little evidence suggesting that cleaners might develop asthma through skin sensitization.

Chemical products dilution

Diluting cleaning products was also investigated in the current work as a possible risk factor for developing asthma. During this procedure, fumes are generated often in low concentration but higher exposure levels may also occur with accidental over-concentration or when using hot water rather than cold water as recommended by manufacturer. Analysis of the data suggested that diluting products was not associated with a risk of having asthma (adjusted OR 1.7, 95% 0.6 to 4.9). None of the other case-control studies reported in the literature investigated the association of this work practice with asthma. It is possible that the absence of an association with diluting in this study was due to healthy worker effect. During the study, a number of asthmatic cleaners mentioned that they often asked their co-workers to dilute the cleaning product as the resulting irritating fumes would trigger respiratory symptoms. It was observed that dilution was often done in a room without windows or another type of ventilation.

7.4.5 Finding with regard to the hypothesis “*Bleach is the principal cause of asthma in cleaners*”

The finding of a significant association between asthma and the use of bleach supports the hypothesis that bleach is a likely cause of asthma in cleaners. However, since the study could not investigate the association of asthma with other cleaning products, it is not confirmed yet that bleach is the principal cause.

7.5 Generalisability of the study findings

The study has included cleaners in only two settings, i.e. hospital and educational institutions. Cleaners work in many other settings, such as shops and factories, where the cleaning products used and cleaning practice are most likely different. The study, thus, could be generalisable to cleaners who are working in hospitals and educational institutions in the UK as they most likely will have similar practices and would use cleaning products with similar properties, i.e. products with good hygienic properties. The possibility that the low response rate (40%), the drop out of the cleaners during the different phases of the study have made the cleaners sample in the current study not representative of all cleaners is unlikely. The available evidence from a number of studies in asthma prevalence^{217, 218} suggests that a low response rate is highly unlikely to introduce a large non-response effect. Indeed, the characteristics of the cleaners who responded to the different phases of the current study were not different from those who did not respond. Therefore, it is unlikely that the low response rate has largely affected the representation of the sample.

7.6 Strengths and limitations of the study

7.6.1 Strengths

This is the first study in the UK

This is the first workforce-based study of professional cleaners conducted in the UK with the aim of identifying and quantifying the risk of developing occupational asthma.

Cleaners were found to have an excess risk of asthma in previous work-force based studies carried out in Spain (Zock *et al* 2001,²⁰⁷ Medina-Ramon *et al* 2005¹⁴⁵ and Vizcaya *et al* 2011²⁰⁵), Canada (Obadia *et al* 2009),²⁰⁶ Brazil (Maciara *et al* 2007)²⁰⁸ and Finland (Karjalainen *et al* 2002).⁴ However, cleaners in these countries may have different work practices and use different cleaning products from those used in the UK. This was illustrated by Zock *et al*²⁸¹ who evaluated the use of household products across ten European countries. It was found that the frequency of using sprays and the type of sprays used were different across the countries. For example, the use of glass sprays was common in Spain and not in the UK, whereas, for air refreshers, this was the other way round. Therefore, it was important to carry out a study in the UK to demonstrate that what has been shown consistently by previous studies also applies to UK cleaners.

Occupational asthma among cleaners was of particular interest for two reasons: 1) it has considerable consequences in terms of employment and economic status. A diagnosis of occupational asthma may force a worker to transfer into a less well paid job or to be unemployed⁹⁶ with a subsequent significant income loss.³⁸⁹ It also has negative implications at the level of the community. A recent (2011) UK study found that the costs of using healthcare resources to diagnose, treat and rehabilitate workers with occupational asthma is high, ranging from £70 to £100 million annually.³⁹⁰ Given that occupational asthma is a preventable disease, efforts should be directed to identify workers at a higher risk. 2) The cleaning sector is one of the ten largest occupational groups in the UK with a total number of about 700,000 workers (Labour force survey, 2011).¹⁹⁸

All this indicates the need for an investigation into whether cleaners in the UK have an excess risk of occupational asthma, its extent, its causes, and should there be an excess risk the optimum methods of establishing a diagnosis. The goal is to provide justification for any future recommendations about applying preventive or regulatory measures in this workforce.

Occupational asthma diagnosis was established using objective tests

The current study attempted to establish the diagnosis of occupational asthma based on both history and objective tests including serial PEF and serial measurements of airway responsiveness. This step allowed further characterization of the clinical features of asthma among cleaners.

In serial airway responsiveness testing, the test is performed when the subjects are at work and then repeated when they are away from work. The magnitude of change in airway responsiveness is assessed and considered positive, i.e. there is a work-related effect, if airway responsiveness increases by ≥ 1.5 double doses when the subjects are away from work. In order to make sure that the observed change in airway responsiveness measurements is a true change and not due to measurements error, the technique used for measuring airway responsiveness should be precise and repeatable. In the current study, airway responsiveness was measured using the Newcastle dosimeter method which is characterized by: 1) using a nebulizer that is connected to a dosimeter which would ensure delivering a precise methacholine dose, 2) measuring the FEV₁, which is used to reflect the airway calibre, by taking the mean of the best three reading out of six measurements instead of three measurement as in other protocols. These two features together have been shown to provide precise and repeatable airway responsiveness measurements with a 95% confidence interval for a repeated measure of 1.5 double doses.⁶¹

Standard Mini-Wright meters are the most commonly used to monitor PEF in clinical and research settings. Subjects using these devices are required to record PEF measurements on a diary card. Previous studies, however, found that about 60% of handwritten recorded measurements were either inaccurate or falsified.^{124, 125} Therefore, digital devices which can save the measurements along with the time and date were used in this study. The stored PEF data was

then analysed by the OASYS-2 programme for possible occupational asthma. To the best of our knowledge, this is the first study that relied on electronically stored PEF data instead of hand written PEF measurements to evaluate possible occupational asthma. By using digital devices, the problem of falsification was abolished.

7.6.2 Limitations

Small size of the population study and the low response rate

In the current study, 1200 questionnaires were distributed. However, this was an approximate estimate as most managers did not give an accurate number of their cleaning staff. Although attempts were made to ensure accuracy of the information, managers did not respond to the request as was hoped because of time constraints or having a high staff turnover. Of the 1200 distributed questionnaires, 543 questionnaires were returned giving a response rate of about 40%. It was uncertain whether all potential subjects received the questionnaire as some cleaners reported not receiving it and some organisations reported that some questionnaires remained undelivered. Therefore, the estimated response rate of 40% is uncertain.

The overall response rate was lower than anticipated when the study was planned. However, participation rates in postal health surveys in general have been found to be decreasing in recent years.²¹⁶ Two main reasons were found to contribute to this negative trend: participants have been increasingly refusing to participate, and researchers find it harder to contact eligible participants.²¹⁶ Refusing to participate to postal respiratory surveys was found to be attributed mainly to lack of time and lack of interest in the matter.^{391, 392} Difficulty in contacting participants, in case of postal surveys, was mainly due to incorrect contact addresses.³⁹² However, in the current study, the difficulty in approaching cleaners directly was due to ethical considerations which necessitated distributing the questionnaires through the managers. This may have partly contributed to the low response rate as the questionnaires might not have been delivered to all potential participants.

The median response rate in population-based studies that investigated the relationship between asthma and occupational exposures^{2, 78, 144, 160} was fairly low (62%, range: 37% to 90%) but the response rate was even lower in

studies of asthma that recruited cleaners only (39% and 18%).^{205, 206} Cleaners thus seem to be less likely than others to participate in health related surveys. This can be attributed to several factors. First, cleaners often have low level of education and this has been found to be associated with lower participation in studies compared to more educated people.²¹⁰ This most likely reflects the increased awareness among well-educated people of the importance of scientific studies in improving everyday lives. Second, since cleaners have low socioeconomic status, they may need to hold more than one job or work more than one shift. Longer working hours reduce the free time that may be dedicated to participating in a study. Therefore, while the response rate obtained in the current study (40%) is lower than we hoped for, it is not unreasonable given the features of the population under investigation.

The potential problem with a low response rate lies in non-response bias, i.e. errors introduced in to the study when responders differ substantially from non-responders in the survey variables of interest such as asthma status and work practice. This may cause over²¹⁸ or under estimation³⁹³ of the association/estimate under investigation. Due to ethical considerations, it was not possible in this study to collect information about the non-responders to compare their features with those of the responders. However, low response rate might not have had any substantial effect on the prevalence estimates. This is illustrated by Verlato *et al*²¹⁷ who found less than 1% difference in the ever asthma estimates (3.5% for responders compared to 2.6% for non-responders) despite their low response rate (30.5%). In line with these studies, De Marco *et al*²¹⁸ found that prevalence estimates for asthma symptoms of the responders were similar to those of non-responders to the Italian arm of the ECRHS. The authors reported that the highest difference was in the prevalence of chest tightness but this was only 0.6% (8% versus 7.4%).

To summarize, the response rate in the study is low but it is within the range of response rates observed in previous similar studies. It is uncertain whether results were biased by the low response rate, though, previous studies suggest any effect would have been small.

The results could be influenced by healthy worker effect

The healthy worker effect is the selection bias that results either from selecting healthier individuals for employment (healthy hire effect) or when sicker workers are transferred to a less exposed job or leave the job (healthy worker survivor effect).³¹⁵

It is possible that the findings of the current study were influenced by a healthy worker survivor effect. Medina-Ramon *et al.*,¹⁶⁰ for example, observed that the magnitude of the asthma risk was higher for former domestic cleaners than current cleaners. Vizcaya *et al.*²⁰⁵ also reported in their study of non-domestic cleaners that the highest risk for adult-onset asthma was seen among former workers. The likely explanation is that cleaners who developed asthma had already left the job before the survey leading to a higher prevalence of asthma in former workers and reduction of prevalence in the current cleaners. Indeed, the recent study of the 1958 birth cohort in the UK (2013)¹⁹⁷ reported that asthmatic ever cleaners had spent significantly less time (1 year) in cleaning jobs than non-asthmatics (3 years). A healthy hire effect may also have influenced the results. It was found in the 1958 British cohort³¹⁶ that the development of allergic rhinitis/ hay fever was significantly associated with avoiding high risk jobs. The same study also suggested that adolescents who developed asthma were less likely to join high-risk occupations. Therefore, it is possible that subjects with asthma may not apply for cleaning jobs as they are recognized to be associated with physical exertion and exposures to chemicals and fumes which may make their asthma even worse. Given that asthmatics of lower social level would have few alternative jobs, the healthy hire effect may have only slightly decreased the estimates.

To sum up, the prevalence estimates of asthma and respiratory symptoms among cleaners found in the current study could be lower than the true prevalences due to healthy worker hire or survivor effect.

The use of self-reported data

The data obtained in phase-1 (respiratory questionnaire survey) and phase-IV (nested case-control study), is self-reported. Self-reported data might be inaccurate as it depends on subject's comprehension and recall which might introduce recall bias. In addition, self-reported data might also be subject to social desirability bias.

Recall bias might occur if there was a potential differential recall of past exposures between cases and controls.³¹⁵ Cases might be more motivated to remember exposures particularly if they were aware of the pre-existing association between asthma and cleaning products. This might have led to inflation of the estimated association between certain cleaning products, such as bleach, and asthma. However, during the clinical interviews with the cleaners, the researcher found that most of them were not aware about the possibility of developing asthma associated with their cleaning work.

Social desirability bias refers to the tendency of subjects to give socially desirable responses instead of choosing responses that are reflective of their true behaviour or thoughts. In the current study, the majority of the cleaners self-reported having good knowledge about cleaning products (95%) and having trained periodically (77%). Whether these represent the true level of knowledge and work practice is unknown as no alternative measures were used to assess these two aspects. However, cleaners' poor knowledge of cleaning products' composition was suggested by the answers to the open-ended questions about products used in cleaning tasks. A number of cleaners (n=25) reported using actichlor in cleaning tasks but they answered "no" to the question "have you ever used bleach?" Actichlor and bleach are disinfectants which act through the same mechanism but differ in their physical formulation: bleach is a liquid while actichlor is in a tablet form. The observed discrepancy in the information provided most likely reflects unfamiliarity of the cleaners with the components of the chemical products they used. A similar observation was reported by Donney *et al*²⁴⁵ who investigated the accuracy of self-reported exposures to cleaning agents in hospital workers by comparing it to expert assessment. They found that cleaners and nurses in particular underestimated their exposures to a number of products including bleach. A possible

consequence of this is that some cleaners were misclassified as unexposed to bleach. It was not possible to assess whether this misclassification was equal or not among cases and controls because many cleaners did not answer the question about the chemical products they had used. Accordingly, the responses of the cleaners to the questions about knowledge were possibly subjected to social desirability bias.

Despite the limitations of self-reported surveys, these are widely used tools as they are practical and collect information from a large number of subjects.

Results could have been confounded by smoking

The analysis of the characteristics of the asthmatic cleaners revealed that more than two thirds had smoked and one quarter were still smokers. Smoking is the primary risk factor for COPD and this disease shares many symptoms with asthma. Misdiagnosis of COPD as asthma could therefore have confounded the findings of this study. Several previous studies have shown high rates of misdiagnosis of asthma. In a Swedish study (1999),³⁹⁴ 86 adult patients (> 18 years of age) who were diagnosed with asthma were invited for a comprehensive review. Pulmonary function tests including bronchodilator reversibility testing were found to be highly suggestive of COPD rather than asthma in 15 subjects (17%). In another study, patients older than 40 years of age were recruited from GPs in the UK and United States and underwent reversibility testing. A quarter of subjects with a prior diagnosis of asthma were found to have COPD.³⁹⁵

In the current study, 73 cleaners self-reported physician-diagnosed asthma and of these, 16 underwent methacholine tests. The results were suggestive of asthma, i.e. $PD_{20} \leq 1600 \mu\text{g}$, in 11 cleaners (70%). The negative methacholine tests in the remaining five cleaners suggest misdiagnosed asthma. Two of these subjects had physician-diagnosed COPD. Therefore, it would have been useful if other tests, such as gas transfer factor, could have been done to confirm the correct diagnosis.

In this study, COPD is unlikely to have been misdiagnosed as asthma. The median age of the cleaners when they were first diagnosed with asthma was 29 years. Since COPD commonly occurs in older age groups (> 45 years)³⁹⁶ the probability of confusing COPD with asthma was low. This is supported by

the finding that the lung function results of the five cleaners with a diagnosis of asthma that was not supported by methacholine challenge testing were within normal values: mean FEV₁ was 99% of the predicted (range: 80%-124% of predicted), and mean FEV₁/FVC was 81% of the predicted value (range: 74%-92% of the predicted), despite the long duration of smoking (on average 18 years, range: 12-22 years). Of the 181 cleaners who responded to the second questionnaire, 15 (8%) self-reported physician-diagnosed COPD. A study conducted by Melville *et al*³⁹⁷ in the North East of England has identified a similar prevalence of COPD (10%) in subjects aged 52-64 years. This implies that COPD was not over-represented in our cohort.

In addition to causing COPD, smoking is also suggested to be a risk factor for asthma in adults. However, the available evidence about the association appears to be contradictory. Many cross-sectional studies found no association between asthma and smoking, while others found an increased risk of asthma among smokers.²²⁶ A few longitudinal studies have been carried out to investigate the temporal relationship between smoking and the onset of asthma but the results of these have also been inconsistent.²²⁶ In the current study, a significant association between former smoking and having asthma was demonstrated when asthma was defined based on self-reported physician-diagnosed asthma but not when asthma was defined based on the methacholine test though the number of subjects was small. So if there was a high level of smoking in the past, this might have caused the current increased prevalence of asthma. Of the studies that showed an increased risk of asthma among smokers, Piipari *et al*²²⁵ is the most robust since the asthma status of the recruited subjects was based on objective tests rather than self-reported diagnosis as in other studies. In addition, many confounders were considered and adjusted for such as sex, age, occupational and environmental exposures. The authors found that smokers were at a 30% increased risk of developing asthma compared with non-smokers with a borderline significance (95% CI 1.0 to 1.8). This indicates that, if smoking was more prevalent among cleaners than general population, up to approximately 30% of the observed excess risk of asthma might be attributed to smoking. However, most of the epidemiological studies which reported increased risk of asthma among

cleaners have adjusted for the confounding effect of smoking and so smoking is unlikely to be the cause.

It is also noteworthy that in the current nested case-control study, a significant association was found between asthma and occupational exposures to bleach and sprays after adjustment for smoking.

Lack of quantitative assessment of airborne cleaning exposure

Quantitative measurements of exposures in general are important to identify the chemicals responsible for health hazards and to demonstrate dose-response relationships.^{248, 366} Exposure monitoring can be done of the worker's personal breathing area (personal monitoring) or of the work environment (area monitoring). Since cleaners in different settings are assigned different tasks and use different products, personal exposure monitoring would provide more informative and relevant data than area monitoring. It would show whether cleaners' exposure levels, particularly to chlorine, are within or greater than permissible limits. It would also help in minimizing exposure misclassification if exposure level was known for each individual study participant. There is only one small study where personal exposure for chlorine and ammonia was monitored. This was on one occasion only and for a small number of domestic cleaners (n=10).¹⁴⁵ The study detected an exposure peak of 1.3 ppm of chlorine and 50 ppm for ammonia, and both were greater than the short-term exposure limits (Cl=1.0, ammonia=35 ppm) set out in the Health and Safety Commission document EH40.²⁴⁷ It is not clear how representative these values are as the exposure are likely to vary between cleaners and the exposure for any cleaner may vary over the time. Because of the expected high cost of obtaining representative assessment of exposures in a relatively large study population, and because of the poor co-operation of a number of managers, exposure assessment was not carried out in this study.

7.7 Implications

The findings of the current study have significant implications for the public health.

Cleaners constitute one of the largest sections of the UK workforce (about 700,000) accounting for 2.4% of the working population.¹⁹⁸ Given that asthma prevalence among adult population in the UK is estimated in the ECRHS study to be 8% on average, 56,000 cleaners would be expected to have asthma unrelated to their work. However, since epidemiological studies suggested that the RR of asthma in cleaners is 1.5 to 1.7, there is further increased risk of asthma among cleaners due to their work. Thus about 28,000-39,000 cleaners could further develop asthma because of their work. Cleaners' asthma thus vastly outnumbers any other occupational cause of occupational asthma. Considering the adverse socioeconomic outcomes of occupational asthma, and knowing that it is largely a preventable disease, every effort should be made to control occupational asthma amongst cleaners.

Preventive measures in general are aimed at reducing exposure levels and detecting occupational asthma at an earlier stage. However, these have been designed mainly to reduce the burden of sensitiser-induced asthma of which the mechanism and the time course of the disease is well investigated. Cleaners' asthma, on contrary, has been recognized only recently and the underlying mechanism is still debatable. Due to insufficient knowledge about the nature of cleaners' asthma, its implications are uncertain. It might be similar to those of sensitiser-induced asthma with frequent progressive worsening of disease with continued exposure or it may not be if the underlying mechanism is substantially different. For instance, it is uncertain whether exposure cessation, which often leads to disease resolution in sensitiser-induced asthma, has the same effect in cleaners' asthma. Further studies would be needed to elucidate that. Until then, the implications and the preventative measures of cleaners' asthma will be discussed based on the available literature.

Reducing work-exposure

There is clear evidence with some causes of occupational asthma, such as isocyanates, that the higher the exposure levels, the greater the proportion of workers who are affected.³⁹⁸ Therefore, reducing cleaners' exposures might be effective. This can be accomplished by several methods. First, irritating chemicals such as bleach could be substituted with safer cleaning products such as peroxide sanitizers which often break into water and oxygen and are not known to produce health harmful effects.³⁹⁹ However this approach might not be practical in some settings, e.g. hospitals, where bleach is essential due to its strong disinfection properties. Also, the nature of all of the potentially harmful cleaning chemicals is not known yet. Thus, substitution of one agent for another may not solve the problem if the new agent has the potential for respiratory adverse effects too. In the current study, for example, some of the participating hospitals have replaced actichlor tablets (bleach) with another chemical agent called difficil-s (chlorine dioxide) in attempts to reduce the harmful respiratory effects of bleach. However, many cleaners from this organisation complained of having respiratory symptoms from this new product. This product is newly introduced into the market (around 2009) and thus, its potential health effects are not yet well known. Reviewing its material safety data sheet (reviewed 2010)⁴⁰⁰ does not identify details of many potential health effects.

Some cleaning products may contain enzymes (e.g. proteases) which have been introduced into detergents to improve their performance in removing debris from fabrics. Enzymes are well recognized to be an important cause of sensitiser-induced occupational asthma among workers in detergent factories and to a lesser extent among consumers.³⁷⁶ It is possible that enzymes are the cause of the reported respiratory symptoms among cleaners who have used difficil-s even if it is not mentioned in the material safety data sheet, knowing that material safety data sheet lists only ingredients that have a concentration of > 1% of the product.

Exposure can be reduced by ensuring adequate ventilation. In the current study, for example, it was noted that ventilation is absent in rooms where

cleaners dilute cleaning chemicals and actichlor tablets. In addition, cleaning sometimes is done in poorly ventilated spaces such as toilets.

Since the study lacked measurements of exposure levels, it is not known at what exposure level asthma occurs and whether cleaners are exposed intermittently to levels higher than occupational exposure limits. Therefore, it is not known whether even strict adherence to occupational limits would reduce exposures to a level at which asthma is unlikely to occur.

Alternatively, cleaners might need to be provided with appropriate respiratory protective devices e.g. masks and respirators. However, respirators are often perceived to be uncomfortable especially if they need to be worn for long periods as would be the case in cleaning jobs. Furthermore, they are only effective if the correct type of respirator is provided and if it is worn by the workers. Unfortunately, previous studies among other workforces have reported poor adherence with respiratory protection equipment.^{401, 402} For instance, in an audit of bronchoscopy procedures that was carried out in 159 units (e.g. endoscopy units) across the UK,⁴⁰² it was found that masks were worn by only 27% of the staff in endoscopy units and 50% in operation theatres.

Taken together, the effectiveness of the above means in reducing exposures in cleaning is questionable; and, it might be wiser if efforts focused on early detection of occupational asthma. Early removal from further exposures increase the chance of disease resolution in typical sensitiser-induced occupational asthma though whether that is the case with cleaners' asthma if it develops through a mechanism of low-dose irritancy is unknown. Early detection of occupational asthma is best achieved by medical surveillance.

Medical surveillance programmes

Implementation of a work site medical surveillance programme might help in identifying occupational asthma at an early stage.⁴⁰³

Respiratory questionnaires and assessment of airway responsiveness could be considered for detecting occupational asthma among cleaners since the current study suggests that airway responsiveness measurements may be the best means of detection.

Questionnaires in general which inquire about asthma symptoms, respiratory symptoms at work and smoking habits have been shown to be sensitive¹⁰¹ but they are not specific in detecting occupational asthma. However, some previous studies^{276,404, 405} among workers in other sectors showed poor performance of the questionnaire as a screening tool. That could be due to potential problems of deliberately misleading responses that may occur because of fears about job security. In the current study, the questionnaire used to screen workers included questions about both general respiratory symptoms and work-related respiratory symptoms. Of the 54 subjects who reported any asthma symptoms and who were thought to have asthma, 25 (46%) had positive methacholine challenge test results suggestive of asthma. Of these 25, 13 underwent further assessment for occupational asthma, 5 subjects had serial airway responsiveness measurements suggestive of occupational asthma which account for approximately 40%. The proportion of cleaners who were identified with asthma (46%) is relatively low. This could be explained by over-reporting by the subjects who were concerned about their occupational exposures.

On the contrary, some cleaners might deny respiratory symptoms in the screening questionnaire, perhaps because of fear of the consequences of the positive tests.

Airway responsiveness could be assessed before employment and then at regular intervals. Re-measuring airway responsiveness when workers are away from work should be considered if the methacholine tests show that PD_{20} declines to the asthmatic range ($PD_{20} \leq 1600 \mu\text{g}$) from a normal baseline value ($PD_{20} > 1600 \mu\text{g}$) or, if the PD_{20} worsens in case of workers who already have abnormal PD_{20} at the baseline ($PD_{20} \leq 1600 \mu\text{g}$).

It should be emphasized that the effectiveness of such a programme among cleaners or other workforces with similar exposures to low levels of irritants, has not been assessed previously. Even with sensitizing agents there is scant evidence of the effectiveness of surveillance programmes. In a study by Malo and Cartier,⁴⁰⁶ the effectiveness of several surveillance tests including questionnaire; spirometry; serial PEF and airway responsiveness measurements in identifying occupational asthma was investigated among 51

workers who were exposed intermittently to the low molecular weight agent, spiramycin. The workers were assessed initially before processing of spiramycin, i.e. when workers were away from exposures, and then during the spiramycin production period. In addition, workers who had symptoms suggestive of occupational asthma (n=14) underwent specific inhalation tests with spiramycin. The study found that the combination of a positive response to the questionnaire and a change in airway responsiveness identified correctly workers with occupational asthma, as verified by inhalation challenge.

However, there are a number of practical considerations that make implementation of surveillance programmes that include methacholine tests difficult. These include the requirement for competent technicians to carry out the test and the need for medical supervision; and the need for expensive equipment to obtain more accurate results. Also, methacholine challenge testing is time consuming compared to other tests such as spirometry taking up to 90 minutes. This may be inconvenient to the domestic service management which should redistribute work to cover the absence of the cleaner during the test. Therefore, more evidence is needed to provide solid justification for using methacholine tests in a surveillance programme.

Meanwhile, workers should be educated on the potential health effects of cleaning products; and on their safe handling. They should be taught about the early symptoms of asthma; and the importance of informing management or GPs about their symptoms. Cleaners with asthma symptoms should be assessed for the development of airway responsiveness. Subjects with positive results could then be assessed when they are away from exposure to detect for probable occupational asthma. However, there are major logistic issues that need to be considered. Methacholine tests in general are not available in the primary care clinics and are used in limited hospitals in the UK. With current resources, this would be impractical for cleaners as they may not be able to access the hospitals and to perform the tests. Again, the effectiveness of this approach in reducing occupational asthma is unknown but it is much cheaper than performing serial methacholine tests on all cleaners.

Physicians should also be educated about the possible link between asthma and cleaning. The current study suggests that occupational asthma in cleaners is likely to be missed by physicians if they rely only on medical history.

Therefore, efforts are needed to educate physicians, in particular GPs, and increase their awareness that cleaners' asthma could be work related even in the absence of work-related symptoms.

Serial PEF measurement is often useful to diagnose occupational asthma. However, it is time consuming and relies on the co-operation of the workers. Most importantly, it might not be effective in detecting asthma among cleaners as suggested by the results of the current study.

If a surveillance programme identifies occupational asthma in a cleaner, the question of whether they should be removed from further exposure would need to be considered. In sensitiser-induced asthma, this can lead to full recovery of occupational asthma, however, this might not be true in case of cleaners' asthma if it is induced through a different low-dose irritant mechanism. Cleaners' asthma may or may not be reversible after its onset. Accordingly, stopping cleaners from working in cleaning would not necessarily lead to marked health improvement though it definitely would affect cleaners' socioeconomic status.

In summary, the study was consistent with the previously-reported increased prevalence and incidence of asthma in cleaners supporting the notion that this workforce are at a high risk of developing asthma. This is a major issue considering that the large number of cleaners in the UK (about 28,000 to 39,000 from the total 700,000 cleaners) could be at risk of developing asthma associated with their cleaning job. Therefore, policy makers should consider this as a major public health issue.

The study, however, suggested that cleaners' asthma might be difficult to identify since it appears to have a different clinical presentation than that of sensitiser-induced asthma. It might develop through a different mechanism by exposures to low-dose of irritants and thus might have different time course. Therefore, the efficacy of preventive measures, i.e. reducing work-related exposures and medical surveillance programme, which are mainly described for controlling sensitiser-induced asthma, would be questionable if cleaners'

asthma develops via a different mechanism. In addition, several practical issues arise if an implemented surveillance programme requires airway responsiveness measurements, the test that is found in the current study to be the best method of detecting features of occupational asthma amongst cleaners.

If cleaners' asthma is induced by low-dose irritant exposures, the underlying pathology in airway responsiveness and the likelihood of its reversibility after stopping the exposures is unknown. Hence, even if the surveillance programme could identify cleaners with possible occupational asthma, it is unknown whether stopping exposures would lead to improvement in the airway responsiveness and asthma symptoms.

Based on the above, the best intervention at this stage is to educate the cleaners and managers about the possible adverse health effects of the chemical products; and the methods of safe handling (e.g. how to store, mix, use, and avoid incompatible mixing). There should be also increase in cleaners' and managers' awareness about asthma symptoms and the importance of informing occupational health department and the GP. GPs should also be considered in the educational programmes since they are the first contact point with the patient. These programmes should increase the awareness of the GPs of the possibility of developing asthma due to a cleaning job and the importance of considering occupational asthma in this workforce.

Chapter 8 **Conclusions and recommendations**

8.1 Conclusion

Altogether, this study is consistent with the view that around half of asthma in cleaners is related to cleaning occupation and adds to other published studies demonstrating increased prevalence of asthma in cleaners.^{3, 4} It demonstrates a high incidence and prevalence of asthma though it was not possible to conclude that that was higher than might be expected because of the absence of a reference population for comparison. The study demonstrated features of occupational asthma in about half the cleaners which fell within the anticipated proportion (30%-40%) of occupational disease. It showed that cleaners with possible occupational asthma could not be identified by specialists from cleaner's clinical histories alone. It showed an association between the use of chlorine-containing bleaches and asthma.

The results of the study suggest that serial airway responsiveness measurements may be the best test to identify occupational asthma among cleaners rather than serial PEF as often recommended for investigating occupational asthma. The latter identified features of occupational asthma in a smaller number of cleaners and there was little relationship between the results of the two tests. However, there would be considerable practical problems applying airway responsiveness measurements on the scale.

These observations support the hypothesis that cleaner's occupational asthma has unusual clinical features. It lacks work-related symptoms and symptoms of bronchoconstriction which is typical of sensitiser-induced asthma. Cleaner's asthma therefore possibly develops through low-dose irritant mechanisms. This unusual presentation could explain the under-diagnosis of the condition. Until now, no other study has investigated the functional features of low-dose irritant-induced asthma using both serial PEF and serial airway responsiveness measurements.

The significant association between asthma and the frequent use of bleach suggests that exposure to chlorine is one of the most likely causes of asthma among cleaners. This finding adds to a growing body of evidence suggesting that exposure to low levels of chlorine can induce occupational asthma. It

introduces a possible line of further investigation of the biologic mechanisms and hence possible means of preventing asthma in cleaners. There may also be important implications for asthma in other settings. Asthma is recognised as an environmental disease but as yet little is known about the causes of the disease in the majority of patients.

No data exist on the effect of exposure cessation in patients with low-dose irritant-induced asthma. While it is well known that this is the best way to manage sensitiser-induced asthma, this might not be applicable to low-dose irritant asthma. Considerable further investigation is needed to explore the natural history of the condition and determine the optimum management strategy for affected individuals.

8.2 Recommendations for further research

- Further research on the underlying biologic mechanism of cleaners' asthma is strongly recommended. This may be an example of low-dose irritant-induced asthma, a condition whose existence is still in doubt and about which little is known in relation to its natural history or appropriate management.
- A prospective cohort study of cleaners who are not asthmatic at baseline would help in understanding the natural history of occupational asthma among cleaners. Many issues would be uncovered including: 1) identifying the host factors that would increase susceptibility of a worker to low-dose irritants such as quiescent childhood asthma or asymptomatic bronchial hyper-responsiveness, and 2) exploring the clinical outcomes after cessation of exposure comparing with those with ongoing exposures.
- Studies with detailed exposure assessment are required to identify specific causes and to help evaluate how much of cleaners' asthma is related to specific sensitization to certain chemical exposures and how much is induced by exposures to irritants.
- Chlorine exposure was to be found to be associated with asthma. This should be explored further with laboratory exposure studies where tasks are simulated under controlled work environment conditions such as the ventilation rate, temperature and the number of products used.

- Further studies are required to study the effectiveness and cost effectiveness of medical surveillance system in cleaners.

8.3 Recommendation for health policy makers

In the UK, there are 700,000 employees in cleaning sector and a large number of these are at risk of developing asthma because of their work. If the relative risks demonstrated in some studies are correct then asthma in cleaners by far out numbers all other identified cases of occupational asthma. Therefore it is a public health priority to prevent this disease. Unfortunately, there is limited knowledge about the characteristics of exposures in cleaning jobs, e.g. exposure levels and specific causes, and therefore the effectiveness of preventive measures is questionable until sufficient new evidence becomes available. Policy makers should make every effort to facilitate investigating occupational asthma as it has devastating socioeconomic impacts on both individuals and community.

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Appendices

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Appendix 1 respiratory questionnaire

	Code No. <input type="text"/>
Version No.6	
<h1>Respiratory Questionnaire</h1>	
<p>Thank you for helping us by filling out this form.</p> <p>We are studying how common asthma is and what might need to be done at work to help those with asthma.</p> <p>We would like to hear from everyone so please fill out the form even if you do not have any chest problems or your problems are mild.</p> <p>To make it more fun we are entering everyone who returns the form into a draw for £100 cash.</p> <p>Please answer all the questions the best you can. There are no right or wrong answers. If you need help please contact me at:</p> <p>Institute of Health and Society, Baddiley-Clark Building Richardson Road, Newcastle upon Tyne NE2 4AX E-mail: shalkhah.altallam@ncl.ac.uk Telephone: 0191 222 3544/ 0740 739 0640</p> <p>When you are finished, please put the form in the envelope provided and return it to us. You can give it to your manager or post it if you prefer.</p> <p>All your information will be absolutely confidential. Information about you will not be passed on to your employer or anyone else under any circumstances.</p> <p><u>Now please read the instructions before you start at question 1.</u></p> <p>1. For most of the questions, there are lists of answers with a box printed beside each one. Please choose your answer and put a tick in the box beside it, for example:</p> <p style="text-align: center;">Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>2. There are boxes for some questions to write your answer, for example:</p> <p>How old are you? <input type="text" value="45"/> Years</p> <p style="text-align: center;"><u>Now please turn over to question number 1.</u></p>	

FIRST, THINKING ABOUT YOUR HEALTH

1. In the past 12 months, when you have run or climbed stairs fast, have you

1.1 Coughed..... Yes No

1.2 Wheezed Yes No

1.3 Had tightness in the chest..... Yes No

2. In the past 12 months has your sleep been broken by...

2.1 Wheezing Yes No

2.2 Difficulty in breathing Yes No

2.3 Coughing Yes No

3. In the past 12 months, have you woken up in the morning (or from your sleep if you are a shift worker) with....

3.1 Wheeze? Yes No

3.2 Difficulty in breathing? Yes No

4. In the past 12 months, have you wheezed...

4.1 When you were in smoky room? Yes No

4.2 When you were in a dusty place? Yes No

5. In the past 12 months, have you used any Inhalers? Yes No

6. Have you ever had asthma? Yes No

6.1 IF YES, has a doctor ever diagnosed your asthma? Yes No

6.2 IF YES, how old were you when you first had asthma? Years

7. Have you ever had hay fever? Yes No

NOW, SOME QUESTIONS ABOUT YOUR WORK

8. How long have you worked as a cleaner? Years Months

9. Does any cleaning product you use at work make you breathless or wheezy? Yes No

10. Does any cleaning product you use at work make you cough? Yes No

SOME INFORMATION ABOUT SMOKING

11. Have you ever smoked? Yes No

11.1 If YES, how old were you when you started? Years

11.2 Do you smoke now? Yes No

11.3 If you stopped smoking, how old were you then? Years

11.4 How many cigarettes do or did you smoke per day on average? Cigarettes per day

FINALLY, INFORMATION ABOUT YOUR SELF

12. Surname: _____

Initial Name: _____

13. Are you Male Female

14. Date of Birth (dd/mm/yr): ____/____/____

15. Would you like to enter the prize draw? Yes No

16. Would you mind answering another survey from us? Yes No

17. Would you mind doing simple breathing tests? Yes No

If you agree to participate in another survey or breathing tests, would you please write down the address or phone number you would prefer us to contact you on

A. Home address:

First line:.....

.....Post Code:.....

Telephone Number.....

OR

B. Work address:

First line:.....

.....

Contact number:.....

Appendix 2 Work practice questionnaire



Code No.

Work practice Questionnaire

You may remember filling out a questionnaire about chest problems a few months ago. We would now like to know more details about your work. Thank you for helping us by filling out this form.

We are studying what work activities or products might affect people's chests.

Getting this questionnaire does not mean we think you have a problem. You may have been selected by chance or you may have said you had some chest symptoms before.

We would like to hear from everyone so please fill out the form even if you do not have any chest problems or your problems are mild.

Please answer all the questions the best you can, there are no right or wrong answers. If you need help please contact us at:

Institute of Health and Society, Baddiley-Clark Building

Richardson Road, Newcastle upon Tyne

NE2 4AX

E-mail: shaikhah.alfajjam@ncl.ac.uk

Telephone: 0191 222 3814

When you are finished, please put the form in the envelope provided and return it to us.

All your information will be absolutely confidential. Information about you will not be passed on to your employer or anyone else under any circumstances.

Now please read the instructions before you start at question 1.

1. For most of the questions, there are lists of answers with a box printed beside each one. Please choose your answer and put a tick in the box beside it, for example:

Yes No

2. There are boxes for some questions to write your answer, for example:

How old are you? Years

Now please go to question number 1

WE WOULD LIKE TO ASK YOU SOME QUESTIONS ABOUT YOUR JOB

- Please indicate how often you do these tasks as **PART OF YOUR JOB**.
- We are interesting not just in your current job but your work on average over the **LAST TWO YEARS**
- Please answer the questions the best you can even if it is difficult.

1. DUSTING

1.1 On average, how often over the last 2 years have you dusted?

- Every day ₁
- More than once per week ₂
- Rarely or never..... ₃

If rarely or never, please go to question 2.1

1.2 Thinking of a typical working day, how much time did you spend dusting?

- Less than ½ hr ₁ ½ to 1 hr ₂
- 1 hr- 4 hrs ₃ > 4 hrs ₄

1.3 How do you do dusting?

- Wet dusting..... ₁
- Dry dusting..... ₂
- Both..... ₃

1.4 What chemicals or products did you usually use for dusting?

- 1.....2.....
- 3.....4.....

2. Vacuuming

2.1 On average, how often over the last 2 years have you vacuumed?

- Every day ₁
- More than once per week ₂
- Rarely or never..... ₃

If rarely or never, please go to question 3.

2.2 Thinking of a typical working day, how much time did you spend vacuuming?

- Less than ½ hr ₁ ½ to 1 hr ₂
- 1 hr- 4 hrs ₃ > 4 hrs ₄

3. CLEANING WINDOWS/MIRRORS OR GLASS

3.1 On average, how often over the last 2 years have you cleaned windows?

- Every day ₁ More than once ₂
per week
- Monthly ₃ Rarely or never ₄

If rarely or never, please go to question 4.1

3.2 Thinking of a typical working day, how much time did you spend cleaning windows?

- Less than ½ hr ₁ ½ to 1 hr ₂
- 1 hr- 4 hrs ₃ > 4 hrs ₄

3.3 What chemicals or products did you usually use for cleaning?

- 1.....
- 2.....
- 3.....
- 4.....

4. CLEANING TOILETS

4.1 On average, how often over the last 2 years have you cleaned toilets?

Every day 1

More than once per week 2

Rarely or never..... 3
(If rarely or never, please go to question 5a)

4.2 Thinking of typical working day, how much time did you spend cleaning toilets?

Less than ½ hr 1 ½ to 1 hr 2

1 hr- 4 hrs 3 > 4 hrs 4

4.3 What chemicals or products did you usually use for cleaning toilets?

1.....

2.....

3.....

4.....

NOW SOME QUESTIONS ABOUT CLEANING PRODUCTS YOU USE

5. Have you **EVER** used **BLEACH** as part of your job? Yes 1 No 2

If 'NO' please go to question 6
If 'YES'

5.1 For how many years? Years

5.2 If YES, how often do or did you use bleach?

Every day 1 More than once per week 2

Monthly 3 Rarely 4

6. Have you **EVER** used **AMMONIA** as part of your job? Yes 1 No 2

If 'NO' please go to question 7
If 'YES'

6.1 For how many years? Years

6.2 How often do or did you use ammonia?

Every day 1 More than once per week 2

Monthly 3 Rarely 4

7. Have you **EVER** used **ANY SPRAY** as part of your job? Yes 1 No 2

If 'No' please go to question 8
If 'YES'

7.1 For how many years? Years

7.2 How often do or did you use a spray?

Every day 1 More than once per week 2

Monthly 3 Rarely 4

8. have you **EVER** needed to dilute (water down) any cleaning products as part of your job? Yes 1 No 2

If No, please go to question No. 9
If 'YES'

8.1 For how many years? Years

8.1 If YES, how often do or did you dilute (water down) cleaning products (on average)?

Every day 1 More than once per week 2

Monthly 3 Rarely 4

9. Have you EVER needed to mix cleaning products as part of your job? Yes 1, No 0

If No, please go to question No. 10
If 'YES'

9.1 For how many years? Years

9.2 How often do or did you mix cleaning products?

Every day 1, More than once 2
 per week

Monthly 3, Rarely 4

10. Do any cleaning products cause the following:

10.1 A strong or unpleasant smell..... Yes 1, No 0

10.2 Watery eyes/redness of the eyes Yes 1, No 0

10.3 Runny/itchy nose..... Yes 1, No 0

10.4 Cough..... Yes 1, No 0

10.5 Wheezing..... Yes 1, No 0

11. Have you EVER used rubber gloves at work? Yes 1, No 0

11.1 If YES, how often do or did you use gloves?

Always 1, Most of the time 2

Sometime 3, Rarely 4

□

12. Which of the following sentences best describes your knowledge about cleaning products?

I know a lot Yes 1, No 0

I know as much as I need to know Yes 1, No 0

I know a bit..... Yes 1, No 0

I know nothing Yes 1, No 0

13. Which of the following sentences best describe your training about cleaning products?

I have been well trained recently..... Yes 1, No 0

I was trained when I started work but not since then..... Yes 1, No 0

I have been just instructed by other cleaners on how to clean..... Yes 1, No 0

I have never been trained Yes 1, No 0

THINKING ABOUT YOUR PREVIOUS JOBS

14. Have you ever worked in places where you were exposed to dusts, vapours or fumes? Yes 1, No 0

If YES, please describe them:

Type of work	Number of years

Type of work	number of years

NOW, WE WILL ASK YOU FEW QUESTIONS ABOUT CLEANING YOUR HOUSE

15. Do you currently clean your home? Yes 1, No 2

If 'NO' please go to question 16
If YES,

15.1 Do you use bleach? Yes 1, No 2

If YES, how often do you use bleach?

Always 1, Most of the time 2

Sometime 3, Rarely 4

FINALLY, I WILL ASK YOU FEW QUESTIONS ABOUT YOUR HEALTH

16. Has a doctor ever diagnosed you with any of the following:

16.1 Chronic bronchitis Yes 1, No 2

16.2 Chronic Obstructive Pulmonary Disease (COPD) Yes 1, No 2

16.3 Heart disease Yes 1, No 2

17. Please write down any other health problems you have?

1.....

2.....

3.....

4.....

□

THERE ARE JUST FEW QUESTIONS LEFT

22. How many years have you worked in your current job? Years Month

23. How many hours per week do you work as a cleaner? Hours

24. Which department are you working at?

ICU/Wards 1, Outpatient clinic 2

Laboratory 3, Office 4

Other 5 (specify please.....)

.....



This is end of the questionnaire.

Please put the questionnaire in the envelope provided and return it back.

Appendix 3 Participant information (for all potential participant cleaners)

Participant information sheet

Study about how common asthma is and what causes it among cleaners in the
UK

Principal investigator: Dr. Chris Stenton

Co-investigator: Dr. Shaikhah Alfajjam

Introduction

I am inviting you to take part in a research study. Before you decide whether or not to take part it is important for you to understand why the research is being done. Please take time to read this information sheet carefully and discuss it with others if you wish.

Please contact me if you need any further information or if there still anything that is not clear. Thank you for reading this.

What is the purpose of the study?

This study is being undertaken as part of a PhD research study. Previous studies have shown that people who work as cleaners are more likely to have asthma than others. We do not know whether that is true in the UK, what the cause might be, or what we should do about it.

This is a study to find out how many of our cleaners have asthma and whether it is affected by their work.

Why have I been invited?

You have been invited because you work as a cleaner at the hospital, the university, or one of the other places that are taking part. I am asking all the cleaners in these places to take part.

What does the study involve?

For most people all what I want from you is to fill out the enclosed questionnaire about chest problems. Depending on the answers you may be contacted again and invited to attend for breathing tests. These will be the breathing tests we use all the time to test people for asthma.

Only very few people (about one in twenty) will be asked to do the breathing tests.

For the breathing tests I will check your height and ask you to blow into a machine to find out how much air is in your lung and how fast you can blow it out. I will then ask you to inhale a mist and I will check your breathing again. Depending on the response I might ask you to do this again up to 10 times. If your breathing tests are below normal I might give you 2 puffs of an inhaler we use to treat asthma. These tests will take about two hours. You will be given further information before starting the tests and I will only do them if you agree.

If the results of these tests show asthma then I will invite you to come back once more and to do some breathing tests at home.

Another detailed questionnaire will be sent to some people to ask about their jobs in detail. They will be chosen depending on their initial response to the first questionnaire.

I will be sending everyone a reminder letter about the study via their manager in two weeks and then again in four weeks time. I apologise in advance if you have already replied when you receive either of the reminder letters. Because I do not want your manager to know who has and who has not replied I am sending the reminder letters to everyone.

Do I have to take part?

It is up to you to decide whether to take part. Even if you would not like to do the breathing tests I would still like you to fill out the questionnaire.

You should understand that you are not obliged in any way to participate in the study. Your decision whether or not to participate is entirely private and free.

You will be free to stop taking part immediately at any time without giving a reason if you want.

How will you contact me for the breathing tests?

I will ask you in the questionnaire whether you prefer to be contacted at work through your manager, by phone, or at your home address. I will contact you whichever way you prefer. If you prefer to be contacted at home or by phone I will ask you for your address or phone number. There is no other way I will be able to find these out

Will taking part cost me anything?

If I invite you to come to our department I will pay your travelling costs. I will also pay you for your time or for any time you have to take off work.

Some organisations will allow people to do the tests during their work. If that applies to you, and if you agree, I will arrange time off work with your manager.

What do I have to do now?

If you decide to take part, please fill in the questionnaire and return it in the enclosed envelope. No stamp is required.

By returning a completed questionnaire I am giving my informed consent to take part in this part of the study. I understand that this does not mean that I have signed up for the whole of the study and that separate consent will be taken for the second part of the study.

What are the possible disadvantage and risks of taking part?

I am asking for a little of your time to help with the study. There are no risks of harm from filling out the questionnaire or doing the breathing tests

What are the possible benefits of taking part?

There are no direct benefits to you in filling out the questionnaire but it will help me understand the effects of asthma in cleaners better. If you do the breathing tests you will find out how well your lungs are working, whether you have asthma, and how bad it is.

What will happen if I don't want to carry on with the study?

If you fill out the questionnaire but do not want to take part in the rest of the study I will only use the information you provide on the questionnaire.

What happens to the information?

All your personal information will be kept in a locked cabinet at Newcastle University. The information will be coded using a secret code and then stored and analysed on our computer.

All personal information will be destroyed as soon as the study is finished.

No-one will be able to identify you and no information about you will be passed on to anyone without your consent.

What will happen to the results at the end of the research study?

The results of the study will be reported in scientific publications and at scientific meetings. They should help taking decisions about controlling asthma.

Will my taking part in this study be kept confidential?

Yes. No-one will be able to identify you once your personal information has been locked away and nothing about you will be passed on to anyone without your consent. Your employer will not be informed about your results.

Who is organizing and funding the research?

This study organised by Newcastle University and doctors from the Royal Victoria Infirmary in Newcastle. Dr Alfajam who is doing most of the work is funded by the Ministry of Health, Kuwait. Newcastle RVI Special Trustees are also helping with the funding. The principal investigator is Dr, Cris Stenton, a respiratory consultant in Royal Victoria Infirmary.

Who has reviewed the study?

The study has been reviewed by County Durham & Tees Valley Research Ethics Committee and the Research and Development department of Newcastle Upon Tyne Hospitals NHS Trust.

Thank you for taking time to read this information and to consider taking part in our research study. If you need any more information, please contact me. I will be happy to answer any questions you may have, my contact details are shown below:

Co-investigator

Dr. Shaikha Alfajjam

Institute of Health and Society, Baddiley-Clark Building

Richardson Road, Newcastle upon Tyne

NE2 4AX

Telephone: 0191 222 3544

E-mail: shaikhah.alfajjam@ncl.ac.uk

Appendix 4 Ethical approval

The Newcastle upon Tyne Hospitals 
NHS Foundation Trust

Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Tel: 0191 233 6161

Fax: 0191 201 0155

www.newcastle-hospitals.nhs.uk

AT/NG

17 February 2011

Dr C Stenton
Consultant Chest Physician
RVI Medicine/Respiratory
Royal Victoria Infirmary

Dear Dr Stenton

Trust R&D Project: 5368
Title of Project: Asthma among cleaners in UK
Principal Investigator: Dr Christopher Stenton
Number of patients: 60
Funder (proposed): The Government of Kuwait
Sponsor (proposed): The Newcastle upon Tyne Hospitals NHS Foundation Trust
REC number: 10/H0903/64

Having carried out the necessary risk and site assessment for the above research project, Newcastle upon Tyne Hospitals NHS Foundation Trust grants NHS R&D approval for this research to take place at this Trust dependent upon:

- (i) you, as Principal Investigator, agreeing to comply with the Department of Health's Research Governance Framework for Health and Social Care, and understanding their responsibilities and duties (a copy of responsibilities prepared by the Trust R&D Office is enclosed)
- (ii) you, as Principal Investigator, ensuring compliance of the project with all other legislation and guidelines including Caldicott Guardian approvals and compliance with the Data Protection Act 1998, Health and Safety at Work Act 1974, any requirements of the MHRA (eg CTA, EudraCT registration), and any other relevant UK/European guidelines or legislation (eg reporting of suspected adverse incidents).
- (iii) where applicable, you, as Principal Investigator, should also adhere to the GMC supplementary guidance *Good practice in research* and *Consent to research* which sets out the good practice principles that doctors are expected to understand and follow if they are involved in research – see http://www.gmc-uk.org/guidance/ethical_guidance/5991.asp

Sponsorship

The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as Sponsor for this project, under the Department of Health's guidelines for research in health and social care.

In addition, the Trust has a Research Governance Implementation Plan, agreed with the Department of Health, in order to fully comply with Research Governance and fulfil the responsibility of a Sponsor.

As the Trust is acting as Sponsor for the research and where some of the research is taking place outside of Newcastle upon Tyne, then all costs must be met for research governance audit visits to those sites. It is the responsibility of the PI to provide confirmation to the Trust of who will pay these costs. Audit is required under the Research Governance Framework for Health and Social Care. (Please note that the Trust randomly audits 10% of approved research projects annually.)

Any changes to the study protocol, other study documents (eg, Patient Information Sheets and Consent forms), or any other amendments to the study must be submitted to the Ethics Committee and MHRA (if relevant) for review – see <http://www.nres.npsa.nhs.uk/applications/after-ethical-review/amendments/> for guidance). The R&D office must also review these notices of amendments in parallel with ethical and regulatory review so that implications of the amendment can be assessed. Therefore, you must send a copy of all amendment documents to the R&D office at the same time you are submitting these to the Ethics Committee/MHRA. If changes or amendments to the study have implications for costs or use of resources, you must also submit details of these changes to the R&D office.

It is also the Principal Investigator's responsibility to ensure that all staff involved in the research have Honorary Research Contracts or the necessary letters of access. These need to be issued prior to commencing the research.

In addition, unless otherwise agreed with the Trust, the research will be covered for negligence under the CNST (Clinical Negligence Scheme for Trusts), however cover for no-fault harm is the responsibility of the Principal Investigator to arrange if required.

Please also note that for any NHS employee who generates Intellectual Property *in the normal course of their duties*, it is recognised that the Intellectual Property Rights remain with the employer and not the employee.

Yours sincerely



Amanda Tortice
Research Operations Manager

Enc: Principal Investigator Responsibilities Document

CC: Mr G Regan, Finance Department, Room 203, Cheviot Court, Freeman Hospital
Dr I Purcell, Clinical Director, Freeman Hospital

Appendix 5 Participant information sheet (for cleaners eligible for phase-II)

Participant information sheet

Study about how common asthma is and what causes it among cleaners in the UK

Introduction

Thank you for answering the short questionnaire I sent to you recently about your chest and breathing. This has been very helpful as I am trying to find out how common asthma is amongst cleaners.

You have been chosen for the next part of the study as some of your answers suggest you may have had some breathing or chest problems.

Before you decide whether or not to take part it is important for you to understand why the research is being done. Please take time to read this information sheet carefully and discuss it with others if you wish.

Please contact me if you need any further information or if there still anything that is not clear. Thank you for reading this.

What is the purpose of the study?

This study is being undertaken as part of PhD research study. Previous studies have shown that people who work as cleaners are more likely to have asthma than others. We do not know whether that is true in the UK, what the cause might be, or what we should do about it.

This is a study to find out how many of our cleaners have asthma and whether it is affected by their work.

Why have I been invited?

Your answers to the initial questionnaire suggest that you may have some chest problems. This part of the study will let you know whether you have definite asthma or not.

What does the study involve?

In this part of the study, you will undertake breathing tests. These will be the breathing tests we use all the time to test people for asthma.

For the breathing tests I will check your height and ask you to blow into a machine to find out how much air is in your lung and how fast you can blow it out. I will then ask you to inhale a mist and I will check your breathing again. Depending on the response I might ask you to do this again up to 10 times. If your breathing tests are below normal I might give you two puffs of an inhaler we use to treat asthma. These tests will take about two hours. You will be given further information before starting the tests and I will only do them if you agree.

If the results of these tests show asthma then I will invite you to come back once more and to do some breathing tests at home.

Another detailed questionnaire will be sent to some people to ask about their jobs in detail. They will be chosen depending on their initial response to the first questionnaire.

Do I have to take a part?

It is up to you to decide whether to take part. You should understand that you are not obliged in any way to participate in the study. Your decision whether or not to participate is entirely private and free.

You will be free to stop taking part immediately at any time without giving a reason if you want.

Will taking part cost me anything?

I will pay your travelling costs. I will also pay you for your time or for any time you have to take off work.

What will happen if the device that I take home was lost, damaged or stolen?

I will ask you to take care of the device but I will not hold you responsible or charge you if it gets lost or damaged.

What do I have to do now?

If you decide to participate, please contact me to arrange for the breathing test. You will find my contact details (address, phone or e-mail) at the end of this sheet.

What are the possible disadvantage and risks of taking part?

I am asking for a little of your time to help with the study. There are no risks of harm from doing the breathing tests

What are the possible benefits of taking part?

The breathing tests will tell you whether you have asthma and how bad it is. I can pass the results on to your doctor and that might help him manage your condition.

The main benefit will be to others from understanding the effects of asthma in cleaners better.

What will happen if I don't want to carry on with the study?

You do not need to do anything and we will not contact you again. I will only use the information you provided on the questionnaire for our analysis.

If for some reason you become seriously unwell and are not able to inform us, I will store your personal information safely until the end of the study and then destroy it.

What happens to the information?

All your personal information will be kept in a locked cabinet at Newcastle University. The information will be coded using a secret code and then analysed on our computer.

Personal information will be destroyed as soon as the study is finished.

No-one will be able to identify you and no information about you will be passed on to anyone without your consent.

What will happen to the results at the end of the research study?

The results of the study will be reported in scientific publications and at scientific meetings. They should help those taking decisions about controlling asthma.

Will my taking part in this study be kept confidential?

Yes. No-one will be able to identify you once your personal information has been locked away and nothing about you will be passed on to anyone without your consent. Your employer will not be informed about your results. Your GP will not be informed unless you wish and agree in writing for me to do so. It will be a good idea to let your GP know the results and I recommend that you allow me to do that.

Who is organizing and funding the research?

This study organised by Newcastle University and doctors from the Royal Victoria Infirmary in Newcastle. Dr Alfajjam who is doing most of the work is funded by the Ministry of Health, Kuwait. Other work is funded by Newcastle RVI Special Trustees. The principal investigator is Dr. Chris Stenton, a respiratory consultant in Royal Victoria Infirmary

Who has reviewed the study?

The study has been reviewed by County Durham & Tees Valley Research Ethics Committee and the Research and Development department of Newcastle Upon Tyne Hospitals NHS Trust.

Thank you for taking time to read this information and to consider taking part in our research study. If you need any more information, please contact me. I will be happy to answer any questions you may have. My contact details are shown below:

Co-investigator : Dr. Shaikha Alfajjam

Institute of Health and Society, Baddiley-Clark Building

Richardson Road, Newcastle upon Tyne

NE2 4AX Telephone: 0191 222 3814-07760701322

E-mail: shaikhah.alfajjam@ncl.ac.uk

Appendix 6 Invitation letter + slip

Dear Ms

Thank you for answering the short questionnaire I sent to you recently about your chest and breathing.

I would like you to do some simple breathing tests to check whether your breathing problems are related to your work.

Could you please contact me to arrange the breathing tests at a time that is suitable for you, or, if you let me know your phone number, I will contact you.

The tests will be carried out at the RVI chest clinic and will take about one and half hours. We will pay any travel expenses.

If you can't attend the RVI, you could make some breathing measurements yourself using a small hand-held device. I would be happy to come to your work place give it to you and show you how to use it if that would help.

Thank you

Shaikhah Alfajjam

Telephone: 07760701322 – 0191 222 3814

E-mail: Shaikhah.alfajjam@ncl.ac.uk

Name:

I would like to attend the RVI? ? Yes No

I would like to have the device? Yes No

phone number:

time to call to arrange for the visit: A.M

..... P.M

Appendix 7 Instruction on how to use digital Mini Wright PEF device

Instructions for the Mini-Wright Digital Meter

When to take Readings

The readings should be taken regularly, whether at work or not for **4 weeks**. The readings should be taken **4 times a day** on **waking, lunch time, tea time and at the bed time**

It is important that you write down the times that you start and finish work each day.

Taking Readings

1. Place the mouthpiece into the end of the meter.
2. Stand or sit in good posture.
3. Press the button once to turn the meter on.
4. Wait until the meter beeps and the screen says "Go".
5. Take a deep breath –as deep as possible.
6. Place the mouthpiece into your mouth and close your lips around it tightly.
7. Blow out, **as fast and as hard as possible**, until you have blown out nearly all of your breath.
8. Make a note of your PEF
9. Press the button to repeat steps 4) to 8) and do this three times, the difference between the highest two readings should be within 20L/min.e.g. 480,460. Otherwise you have to do more readings until the highest two reading are within 20.
10. Hold the on button down for a short time and the meter will turn off.

Important notes

If you need to take your inhaler when it is time to carry out a peak flow reading, do the blow first, then take your inhaler.

If you forget to take reading, take one immediately and then go on to the next one as usual.

Appendix 8 PEF record

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Date							
Time Waking							
Time Starting Work							
Time Stopping Work							
Time Going To Bed							
Jobs Done							
Treatment With Times							
01.00 a.m.							
02.00 a.m.							
03.00 a.m.							
04.00 a.m.							
05.00 a.m.							
06.00 a.m.							
07.00 a.m.							
08.00 a.m.							
09.00 a.m.							
10.00 a.m.							
11.00 a.m.							
12.00 Noon							
01.00 p.m.							
02.00 p.m.							
03.00 p.m.							
04.00 p.m.							
05.00 p.m.							
06.00 p.m.							
07.00 p.m.							
08.00 p.m.							
09.00 p.m.							
10.00 p.m.							
11.00 p.m.							
12.00 Midnight							

Appendix 9 PEF records (second version)

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Date							
Time waking							
Time starting work							
Time stopping work							
Time going to Bed							
Treatment taking							
Unusual event e.g. flu, chest infection, exertion							

Appendix 10 Score proforma for the 10 cases

Dear colleague

Thank you for helping with our study about asthma in cleaners.

We have identified a cohort of cleaners with asthma (symptoms + measurable airway responsiveness) and are looking for evidence of occupational asthma from their histories, serial changes in PEFR, and changes in airway responsiveness at and away from work – generally after 2 weeks holiday.

In the next few pages I will present 11 cases. There will be a clinical history and the results of investigations for each case. Could you kindly score the probability of occupational asthma based on the history alone and then combined with the test results. To avoid biasing your opinion we have presented two sets of results, only one of which is real. Please score each.

OASYS scores were calculated conventionally on a 1-4 scale with a score of > 2.5 indicating a work-related effect. Airway responsiveness was measured using the Newcastle technique. Briefly :

- PD20 < 200-definite asthma range:

Found in 8% of an unselected population

73% have an established diagnosis of asthma

- PD20 200-1000 –possible asthma range:

Found in 12% of an unselected population

20% have an established diagnosis of asthma

- PD20 > 1000-normal range:

Found in 80% of an unselected population

4% have an established diagnosis of asthma

The measurement is normally repeatable in an individual within 1.5 doubling doses provided their clinical condition remains stable.

If you have any questions, I will happy to answer it. Could you please contact me through my e-mail address Shaikhah.alfajjam@ncl.ac.uk

Case 1

Part A: clinical history

Gender, age	Female, age 59
Family history	Negative
Childhood respiratory problems	Negative
Allergy history	Negative
Smoking status	Ex-smoker. She stopped smoking 6 years ago. Smoked on average 15 cigarettes for 35 years.
Year started work as a cleaner	2003
Onset of symptoms	2005
Diagnosis of asthma	Not diagnosed
Occupational history	Worked in : <ul style="list-style-type: none">- Print factory for 15 years.- Cleaner for 8 years until now
Main history	<p>In March 2005, she stopped smoking and started thereafter to have cough with phlegm for 2-3 months, especially in the mornings. She also noticed a wheezy chest and shortness of breath especially when climbing stairs. She had no early morning or night time symptoms.</p> <p>In June 2005, she was diagnosed as suffering from COPD and was prescribed a Ventolin inhaler to be taken PRN. She used it for about a year whenever she had attacks of breathlessness though these were infrequent. She then improved and she stopped taking Ventolin regularly though she continued to take it when she had infections. She has not been treated with inhaled corticosteroids.</p> <p>At work, she notices a wheezy chest and breathlessness after climbing stairs. Using cleaning chemicals, particularly sprays, causes coughing. She reports having a dry throat most of the time at work. Overall her breathlessness is no worse at work.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?
Please score from 0 to100.

Part 2: clinical tests

What do you think the probability is of occupational asthma considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
66	79	2.6	270	300	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
60	65	2.57	400	2250	

Case 2

Part A: clinical history

Gender, age	Female, 63 year
Family history	Negative
Childhood respiratory problem	Pneumonia at the age of 9 years. She was hospitalized at that time.
Allergy history	She has hay fever
Smoking status	Never smoked
Year started work as a cleaner	1995
Onset of symptoms	1997
Diagnosis of asthma	2011
Occupational history	She worked in shops as a salesperson for 4 years. Worked in a factory making boxes for 6 months Worked in providing meals in hospital for 6 years Then worked as a cleaner since 1995 until now
Main history	<p>In 1997, she suffered an attack of chest tightness, wheeze and loss of voice after using bleach to clean a room in the hospital. She had never experienced similar symptoms before and she has not used that product again.</p> <p>Five years ago, the hospital asked the cleaners to use actichlor tablets (bleach) for all the cleaning tasks. The patient then started to have the same symptoms (chest tightness and voice loss) at work. At home, she started to have chest tightness and cough with phlegm at nights. Her daily activities are not affected but she notices breathlessness going up hills. On holidays, she feels better and sleeps well.</p> <p>Her GP prescribed her inhaled corticosteroids and a reliever inhaler to be taken when needed. She takes it on average twice (2 puffs) when at work and not when at home. Strong smells e.g. from paint trigger chest tightness and loss of voice. She continues to use Actichlor.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100.

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
78	71	1.7	305	1030	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
97	78	2.5	850	285	

Case 3

Part A: clinical history

Gender, age	Female, 43 year
Family history	A brother had asthma
Childhood respiratory problems	Negative
Allergy history	Negative
Smoking status	Started smoking at age of 11. Still smokes on an average 20 cigarettes per day.
Year started work as a cleaner	2000
Onset of symptoms	1992
Diagnosis of asthma	Not diagnosed
Occupational history	Worked making soft furnishings (curtains and cushions) for 3 years. Worked in school catering for 5 years. Now working as a cleaner in hospital for the past 10 years. She only works at weekends.
Main history	<p>She had recurrent chest infections with wheezing when she worked in the furnishing factory. Her chest symptoms improved when she started school catering but they worsened again when she started work as a cleaner.</p> <p>She suffers wheeze and cough most days with breathlessness that stops her walking up hills. She has night-time symptoms only when she has chest infections. She was once told that she wheezes while sleeping. She hasn't sought medical advice for these symptoms and she does not use inhalers.</p> <p>She is not sure if she feels better when she is away from work, but her daughter (who was there while taking the history) reported that her mother's symptoms do improve when she is away from work.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100.

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
84	73	1.67	100	1600	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
80	69	2.85	100	1600	

Case 4

Part A: clinical history

Gender, age	Female, 66 year
Family history	Aunt and uncle have asthma.
Childhood respiratory problems	Negative
Allergy history	She has allergy to dogs, cats and foods
Smoking status	Ex-smoker. She smoked for 12 years, on average 10 cigarettes/day.
Year started work as cleaner	1991
Onset of symptoms	1981
Diagnosis of asthma	1981
Occupational history	Worked in a confectionary factory for 17 years. Worked in offices (punch card operator) for 10 years. Now working as a cleaner for the last 20 years.
Main history	She developed difficulty in breathing with wheeze 30 years ago. She sought medical advice and asthma was diagnosed. She was given an inhaled corticosteroid and ventolin to be taken when needed and her asthma was controlled with that. She hasn't used a salbutamol inhaler for the last 5 years. Her daily activities are not affected by asthma but she is not able to run. She notices no change in her chest condition whether in or out of work.

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100.

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC %	OASYS score	PD20 at work	PD20 off work	Score :
100	75	1.43	320	130	

Scenario 2

FEV1%	FEV1/FVC %	OASYS score	PD20 at work	PD20 off work	Score :
82	65	2.13	410	730	

Case 5

Part A: clinical history

Gender, age	Female, 63 year
Family history	Negative
Childhood respiratory problem	Negative
Allergy history	Negative
Smoking status	Ex-smoker. Stopped smoking around 6 years ago. She smoked for 45 years on average 20 cigarettes per day.
Year started work as cleaner	1974
Onset of symptoms	1990
Diagnosis of asthma	1990
Occupational history	Worked in a paper factory for 3 years then in a food factory (sausage) for 2 years and a sweet factory for 1 year. Has worked as a cleaner in the university for the past 37 years.
Main history	<p>She developed breathing problems acutely at the age of 41. She was diagnosed with asthma and was given Ventolin and corticosteroid inhalers. She had four severe attacks of asthma that required admission to hospital in the first year. Serevent was then added to her treatment regimen and her asthma was better controlled. More recently she has taken Seretide. She has had no asthma attacks in the last 5 years and her daily activities are not affected by her asthma.</p> <p>At work, she complains of watery eyes when she uses bleach but no chest symptoms. She does not use her inhaler more often at work.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100

Part 2: clinical tests

What do you think the probability is of occupational asthma considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
100	58	1.17	46	320	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
68	75	3.1	180	100	

Case 6

Part A: clinical history

Gender, age	Female, 55 year
Family history	Negative
Childhood respiratory problem	Negative
Allergy history	Negative
Smoking status	Ex-smoker stopped 2011 smoked 40 cigarette/ day for 24 yr
Year started work as cleaner	1981
Onset of symptoms	1986
Diagnosis of asthma	2004
Occupational history	She worked as a barmaid for 5 years, as a cleaner in paper shops for 3.5 years then again as a barmaid. She has worked as a cleaner in the university since 1981, and as a part-time barmaid.
Main history	<p>In 1986, she developed chest tightness and breathlessness after a fire in her house. She didn't seek medical advice until 2004 when she started to have severe panic attacks after her husband died. She was given ventolin and corticosteroid inhalers. She continued to have frequent attacks but these were probably mostly panic. She had only infrequent and mild asthma that was controlled by reliever inhalers. She never had a severe attack and she was never hospitalized. She didn't have any night time symptoms. She becomes more chesty with winter infections.</p> <p>Her chest symptoms are not worsened by anything at work and her use of medication is the same at and away from work.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
89	76	2.2	100	100	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
100	80	1.5	1400	960	

Case 7

Part A: clinical history

Gender, age	Female, 55 year
Family history	Negative
Childhood respiratory problem	Negative
Allergy history	Negative
Smoking status	Ex-smoker since 2005. Smoked for 35 years on average 15 cigarette /day.
Year started work as cleaner	1999
Onset of symptoms	1998
Diagnosis of asthma	1998
Occupational history	She worked as a cashier for 20 years and in a printing shop for 4 years. Cleaner in a hospital from 1999.
Main history	<p>In 1998, she had a chest infection that was accompanied by chest tightness. She was diagnosed with asthma and she was prescribed salbutamol which she used it for a short period. Her symptoms were controlled until 1999 when she started work as a cleaner. She was in charge of MRSA rooms which required her to clean intensively using actichlor tablets (bleach). Her symptoms worsened in that she increased the number of puffs taken daily to relieve her symptoms. In 2003 she started to use oral and inhaled corticosteroids to control her asthma and she was moved to work that involved less use of bleach.</p> <p>She has been stable since then with no symptoms at early morning or night times. Currently, she is using inhaled corticosteroids and salbutmol.</p> <p>Currently she complains of occasional cough at work. She feels better at weekends and on long holidays in that she does not cough as much compared to working days.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient if you also consider the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
78	85	2.8	450	390	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
82	81	3.29	100	560	

Case 8

Part A: clinical history

Gender, age	Female, 61 year
Family history	Negative
Childhood respiratory problem	Negative
Allergy history	hay fever
Smoking status	Smoker for 49 years 10-15 cigarettes/day
Year started work as cleaner	1996
Onset of symptoms	2006
Diagnosis of asthma	Not diagnosed
Occupational history	Cleaner for 15 years in universities
Main history	<p>She developed shortness of breath with wheeze 4-5 years ago especially when lying down and after walking short distances. She didn't seek medical advice and she has just added more pillows to relieve symptoms.</p> <p>After 1 year she had a heart attack and she was given a nitrolingual spray to relieve chest pain. After the heart attack she was more breathless eg after walking a shorter distance. She also noticed that hot weather triggered chest tightness.</p> <p>She does not have an established diagnosis of asthma and she is on no asthma treatment.</p> <p>Working does not make her symptoms worse and she does not feel a difference when she is away in a long holiday.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
80	69	2.0	450	1250	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
100	76	1.15	75	70	

Case 9

Part A: clinical history

Gender, age	Female, 59 year
Family history	Mother had asthma
Childhood respiratory problem	Negative
Allergy history	She has hay fever and eczema
Smoking status	Current smoker from the age of 23 till now. She smokes 15-20 cigarettes/day.
Year started work as cleaner	1986
Onset of symptoms	1989
Diagnosis of asthma	1991
Occupational history	Cleaner of a dog kennels for 19yr, shop assistant for 2yr. Worked as a cleaner in university since 1986
Main history	<p>Developed a 'chest infection' in 1989 and was diagnosed with asthma after that. Treated with ventolin and inhaled corticosteroids. Her asthma has been variable over the years, generally controlled by varying the doses of inhalers. In the last year, she has had one or two attacks a month.</p> <p>Her work sometimes triggers acute symptoms especially if she is in dusty areas or if there are strong smells e,g perfumes. Overall she feels no worse at work and taking a long holiday does not make her symptoms any better.</p>

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
93	79	2.15	50	220	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
71	66	2.7	75	310	

Case 10(the last case)

Part A: clinical history

Gender, age	Female, 39 year
Family history	Her mother has asthma
Childhood respiratory problem	Negative
Allergy history	Negative
Smoking status	Smoker for 22 years. She smokes on average 3 cigarettes per day.
Occupational history	She worked in shops and restaurants for 4 years, in an office for 8 years and as a hotel receptionist and barmaid for 7 years In hospital as a cleaner since 2008
Year started work as a cleaner	2009
Onset of symptoms	2010
Diagnosis of asthma	Not diagnosed
Main history	One year ago, the patient noticed being out of breath after running. No other symptoms. She does not have an established diagnosis of asthma and she is on no treatment. At work, she experiences a transient cough when she opens containers of actichlor tablets. She has a runny nose and sneezes after using a sanitizer powder for toilet cleaning. She does not suffer from breathlessness at work.

Based on the history, what do you think the probability is of this person having occupational asthma?

Please score from 0 to100.

Part 2: clinical tests

What do you think the probability is of occupational asthma of the patient considering also the results of the serial airway-responsiveness and peak flow measures?

I will present two scenarios, Could you please score from 0-100 for each scenario.

Scenario 1

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
76	82	2.6	260	320	

Scenario 2

FEV1%	FEV1/FVC%	OASYS score	PD20 at work	PD20 off work	Score :
100	81	1.7	105	270	

THANK YOU FOR YOUR PARTICIPATION

Appendix 11 Conference publications

1. The prevalence of Asthma among Cleaners in United Kingdom. (Abstract). *Thorax*. 2011; **66**; (Suppl 4):A6. (British thoracic society winter meeting, London, UK, December 2011).
2. The prevalence of Asthma among Cleaners in United Kingdom. (poster presentation). Association of Physicians Meeting, Newcastle upon Tyne, UK, March 2012.
3. The prevalence of Asthma among Cleaners in United Kingdom. (oral presentation). Society of Occupational Medicine annual scientific meeting, Gateshead, UK, June 2012).
4. The prevalence and risk factors of asthma among cleaners in United Kingdom. (Abstract). 21st World Congress of Asthma, Québec, Canada, August 2012.
5. Identifying occupational asthma among a cohort of cleaners in the North East England. (Abstract). *Thorax* . 2012;**67**:A62 (British thoracic society winter meeting, London, UK, December 2012).