Cleaning at work and at home as related to lung health

With a focus on asthma, COPD and lung function decline, vulnerability established early in life and potential impact for the next generation

Øistein Svanes

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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At last, I am at the end of this road. And even though it is somewhat of a letdown to finally finish I am more than happy to set the final period. What tomorrow will bring is an entirely different matter.

Scientific environment

This doctoral thesis was started in 2012 and completed in 2022. In the six years from 2012 to 2018 I had a 50/50% shared university and clinical position. My scientific environments were in the Department of Clinical Science (K2), University of Bergen, and the Department of Global Public Health and Primary Care (IGS), University of Bergen, and at the Department of Occupational Medicine, Haukeland University Hospital.

Abstract

Background

Cleaning, a common everyday task for most people, means exposure to cleaning chemicals and disinfectants that might possibly be harmful to the respiratory system and cause airway disease. Asthma is the most common occupational respiratory disorder in industrialized countries and several studies have shown that cleaning exposure is associated with increased risk of asthma, whether working as an occupational cleaner or cleaning one's own home. However, at the time of initiating this thesis, most literature was from South and Middle Europe while there was limited knowledge from Northern Europe. Further, while there was evidence about short term health effects from cleaning agents and disinfectants, long-term effects were much less investigated, even though biologically plausible. One study showed associations between cleaning agents and Chronic Obstructive Pulmonary Disease (COPD), and one other study investigated a possible association between cleaning and accelerated lung function decline over time, an important indicator of general as well as respiratory health; however, a time frame of only three years made conclusions difficult.

Why do some cleaners develop disease and others not? Some literature indicates that early life disadvantage might increase susceptibility to adult harmful exposure. When new chemicals are introduced on the marked, there are strict regulation of testing with regard to toxicity, mutagenic effects etc, however, testing of germ cell effects is not mandatory. Emerging evidence suggests that parental occupational exposure before conception might influence future generations' respiratory health through germline cell impact in the parents.

Aims

The main aim of this thesis was to study how exposure to cleaning agents was associated with short- and long-term respiratory health. The secondary aims were to explore potential impact of early life disadvantage and preconception exposure.

- Paper I: Is being a cleaner associated with increased risk of asthma, airways symptoms and self-reported COPD in Northern European countries? Do factors

reflecting early life disadvantage increase the susceptibility to cleaning agents on lung health?

- Paper II: Is occupational or home cleaning associated with accelerated decline in lung function?
- Paper III: Is the use of cleaning products and disinfectants at work associated with childhood asthma in offspring?

Material and Methods

In paper I, postal questionnaire data from the RHINE study was analysed using multivariate models adjusting for central confounders to evaluate the risk of respiratory symptoms, asthma and COPD in occupational cleaners from Northern Europe, and to test interaction with an early life disadvantage score (maternal smoking, severe respiratory infection <5 years, born during winter months, maternal age at birth >35 years). In paper II, data from structured interviews and clinical examinations from the ECRHS, including spirometry performed at three time points, was used. Multivariate models accounting for change over time were used to evaluate loss of lung function over 20 years in occupational cleaners and persons cleaning at home. In paper III, data from the RHINE and RHINESSA studies were used to study the impact of maternal occupational exposure to cleaning products and disinfectants in different time windows (before conception/around the time of pregnancy/after birth) on childhood asthma and wheeze starting before age ten years.

Results

In occupational cleaners the risks of wheeze, adult-onset asthma and self-reported COPD were increased and the risk increased with the number of years in occupational cleaning. The association of wheeze with cleaning activity ≥4 years was significantly stronger for those with early life disadvantage than in those without. Both FEV_1 and FVC declined more rapidly in women responsible for cleaning at home or working as occupational cleaners, as compared to women not engaged in cleaning activities. Cleaning sprays as well as other cleaning products were associated with accelerated decline in FEV_1, however, we could not identify a dose-response trend with either. For men engaged in cleaning activities, we could not identify associations with lung function decline. Children of mothers reporting use of indoor cleaning agents starting

before conception or around conception and pregnancy, showed an increased risk of asthma and wheeze before ten years of age.

Conclusions

Women having worked as occupational cleaners had m respiratory symptoms and asthma, as well as accelerated decline in lung function. Accelerated lung function decline was also found in women who had been responsible for cleaning in their own home. Considering previous literature and biological mechanisms, it seems plausible that exposure to cleaning agents may affect long term lung health. Our findings suggest that early life disadvantage may increase an individual's vulnerability to cleaning agents in adulthood, uncovering a mechanism that might contribute to propagate health inequalities across generations. Finally, mothers' preconception exposure to cleaning agents and disinfectants at work was associated with increased offspring asthma, raising a question of potential germ cell impact.

List of publications

Paper I

Svanes Ø, Skorge TD, Johannessen A, Bertelsen RJ, Bråtveit M, Forsberg B, Gislason T, Holm M, Janson C, Jögi R, Macsali F, Norbäck D, Omenaas ER, Real FG, Schlünssen V, Sigsgaard T, Wieslander G, Zock, JP, Aasen T, Dratva J, Svanes C. *Respiratory health in cleaners in Northern Europe: Is susceptibility established in early life?* PLoS One 2015 Jul 13;10(7) :e0131959. doi: 10.1371/journal.pone.0131959. eCollection 2015.

Paper II

Svanes Ø, Bertelsen RJ, Lygre SHL, Carsin, AE, Antó JM, Forsberg B, García-García JM, Gullón JA, Heinrich J, Holm M, Kogevinas M, Urrutia I, Leynaert B, Moratella JM, Le Moual N, Lytras T, Norbäck D, Nowak D, Olivieri M, Pin I, Probst-Hensch N, Schlünssen V, Sigsgaard T, Skorge TD, Villani S, *Jarvis D, *Zock JP and *Svanes C. *Cleaning at home and at work in relation to lung function decline and airway obstruction*. Am J Respir Crit Care Med. 2018 May 1;197(9):1157-1163. doi: 10.1164/rccm.201706-1311OC.

Paper III

Tjalvin G, Svanes Ø, Igland J, Bertelsen R, Benediktsdottir B, Dharmage S, Forsberg B, Holm M, Janson C, Jogi NO, Johannessen A, Malinovschi A, Pape K, Gómez Real F, Sigsgaard T, Toren K, Vindenes H, Zock, JP, Schlünssen V, Svanes C. *Maternal preconception exposure to cleaning and disinfectant agents and offspring asthma.* J Allergy Clin Immunol. 2022;149(1):422-431. doi:10.1016/j.jaci.2021.08.025.

Contents

Abbreviations

ATS	*American Thoracic Society*
BHR	*Bronchial hyperresponsiveness*
BMRC	*British Medical Research Council*
COPD	*Chronic Obstructive Pulmonary Disease*
EAACI	*European Academy of Allergy and Clinical Immunology*
ECRHS	*European Community Respiratory Health Survey*
ECSC	*European Coal and Steel Community*
ERS	*European Respiratory Society*
FEV_1	*Forced Expiratory Volume in 1 second*
FVC	*Forced Vital Capacity*
JEM	*Job Exposure Matrix*
LF	*Lung function*
LLN	*Lower Limit of Normal*
OA	*Occupational asthma*
QAC	*Quaternary ammonium compounds*
RHINE	*Respiratory Health in Northern Europe*
RHINESSA	*Respiratory Health in Northern Europe, Spain and Australia*
SES	*Socio-economic status*
WEA	*Work exacerbated asthma*
WRA	*Work related asthma*

1. Introduction

The respiratory system, consisting of the nose and nasal cavity, pharynx, larynx, trachea, bronchi and lungs, with the lungs representing the key organs, is vital to our survival by their basic function – the exchange of oxygen and carbon dioxide between the blood and the atmosphere. It is also the first barrier in the human body that air pollutants encounter before entering the circulating system and other parts of the body [1]. With a very large interface between the alveolar surface and inspired air, the lungs are susceptible to injury caused by respiratory toxicants, either in the occupational setting, by self-inflicted injury (e.g. cigarette smoking) or during everyday activities. Since the 1970s, there has been an increase in asthma and asthma symptoms [2] Nearing the end of the 20th century, in contrast to other work-related respiratory diseases, diagnosed cases of occupational asthma were increasing, as least partly due to changing working environment with the introduction of new asthmatic agents [3]. Occupational cleaners were, in general, not recognised as a risk group. However, in an important article from 1999, Kogevinas et al [4], using data from the European health survey (ECRHS I part II), found that the risk of asthma was highest for farmers, painters, plastic workers, cleaners, spray painters and agricultural workers, and, surprisingly, the most consistent results across countries were shown for farmers and cleaners. Kogevinas followed up this finding and confirmed in a longitudinal analysis of the ECRHS that cleaners were at higher risk for asthma [5], and specific modules addressing cleaning activities at work and at home were included in the study protocol at the ECRHS II. Jan Paul Zock has then been a key person in developing this work further [6], and in subsequent years there were several published papers showing increased risk of asthma, not only for occupational cleaners, but also for those using cleaning agents in their own home. Focus was given to cleaning agents in spray form which had become increasingly common since the 1980s.

At least 372 agents that cause occupational asthma have been identified [7]. We are surrounded by chemicals in the air we breathe and there is growing concern for the possible harmful effects to the respiratory system, not least when it comes to everyday products used to keeping our homes and workplaces clean.

Emerging research suggests that epigenetic mechanisms may carry exposure effects across generations [8], and there is growing concern that chemical exposures might not only affect the health of those exposed, but also future generations, possibly due to germ cell influence. Paternal exposure to smoking and welding, [9] [10] was associated with increased risk of offspring asthma.

1.1 Lung function

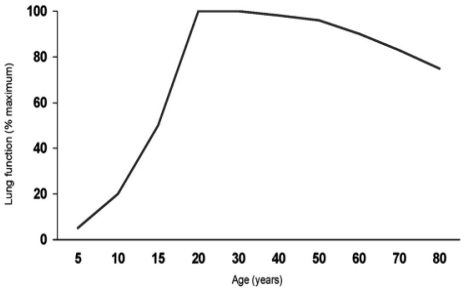
The lungs' main task is to deliver oxygen to the blood and remove carbon dioxide, and lung function tests are the tools we use to find out how well the lungs perform their task. There are different types of lung function tests, but the most common and well known is spirometry, a dynamic lung function test where lung volumes and airflow are measured. Other lung function tests include measurement of diffusion capacity, measurement of static lung volumes and cardiopulmonary exercise test.

When performing spirometry, the forced vital capacity (FVC) is measured, which is the volume of air that can be delivered during an expiration from a position of maximal inspiration made as forcefully and completely as possible. In the same manoeuvre the forced expiratory volume in one second (FEV_1) is also measured, which is the volume of air which is expired during the first second of the FVC manoeuvre. From these two measured parameters the FEV_1/FVC ratio can be calculated, and this is the proportion of air expired during the first second of the FVC manoeuvre. The FVC, FEV_1 and FEV_1/FVC ratio are (in addition to the total lung capacity, TLC) the basic parameters used to describe and interpret lung function [11].

Obstruction, or an obstructive ventilatory defect, is a disproportionate reduction of maximal airflow in relation to the total lung volume (FVC). The severity of lung function impairment is usually categorized based on FEV_1 as percent of predicted (FEV_1 % pred) [11].

During the life-course, lung function (as measured by FEV_1) increases from birth until young adulthood (18-20 years) when maximal lung function is achieved, in young

adulthood there is then a plateau-phase, after which lung function declines as a feature of normal aging [12].



It has been shown that maximal lung function is partly determined early in life and that the negative impact of early life factors (maternal asthma, paternal asthma, childhood asthma, severe respiratory infection before the age of 5 years and maternal smoking) appears to persist into adult life with permanently lower lung function and increased risk of COPD [13]. Furthermore, it has been suggested that lung function decline into old age is predicted by early life factors and a more rapid lung function decline is associated with early life disadvantages [14]. Traditionally, low lung function and development of COPD have been associated with the classic trajectory of an accelerated decline in lung function, however, it seems that also a normal decline, but starting out from a low FEV_1 in early adulthood is equally important for low lung function and development of COPD [15]. There is evidence suggesting that survival in asymptomatic adults without chronic respiratory disease or persistent respiratory symptoms is associated with the maximal forced vital capacity, FVC [16]. Additionally, both peak level and rate of decline of lung function have implications not only for lung health, but for overall health. Lower peak level and accelerated decline in lung function are associated with airflow obstruction in adult life and also comorbid conditions such as diabetes and cardiovascular disease [17].

1.2 Respiratory symptoms

"*Wheezing or whistling from the chest, breathless when wheezing, wheezing or whistling when not having a cold, woken with feeling of tightness in chest, been woken by attack of shortness of breath and been woken by attack of cough in the last 12 months*" are all respiratory symptoms of asthma [18], taken from The European Community Respiratory Health Survey (ECRHS) study questionnaire. The ECRHS study developed, when possible, questionnaires from pre-existing questionnaires already used in multinational studies. The questionnaires were tested for comprehensibility and translated, with back translation into English [2]. The questions on asthma and asthma-like symptoms were taken from the bronchial symptoms questions of the International Union Against Tuberculosis and Lung Disease (IUATLD) 1986 questionnaire [19] and the questions on chronic cough and phlegm were taken from the BMRC-ECSC questionnaires. The ECRHS questionnaire has later become extensively used in hundreds of publications, and is also validated in later studies. [20].

More generally, breathlessness or dyspnoea, chest pain and cough, which may or may not be productive of sputum, are key symptoms of respiratory disease [21]. Even without established respiratory disease such as asthma, the presence of respiratory symptoms (wheezing, dyspnoea, current cough and phlegm) have been shown to be predictors of mortality from all causes [22], although a later study found that only dyspnoea when walking was positively associated with all-cause mortality independent of lung function [23]. Chronic bronchitis is defined as daily cough and sputum production for at least three months in two consecutive years. Even though chronic bronchitis is common in patients with chronic obstructive pulmonary disease (COPD) [24], it is also found among patients without COPD, in particular in smokers. There is evidence that in younger adults (<50 years old) , chronic bronchitis may be an early marker of susceptibility to the detrimental effects of cigarette smoking; partly mediated by systemic inflammation and associated not only with increased long-term risk for developing COPD, but for all-cause mortality [25]. Even in current or ex-smokers without the airflow limitation found in obstructive pulmonary disease, the presence of respiratory symptoms (shortness of breath, chough and sputum production) is associated with exacerbations and activity limitation [26]. Thus,

respiratory symptoms are important when evaluating respiratory health also in a younger and presumably, mostly healthy, population.

1.3 Asthma

Asthma is a major noncommunicable, chronic inflammatory disease, characterized by variable respiratory symptoms. It is defined by the Global Initiative for Asthma (GINA) as a "*heterogenous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation*" [2018, Global Initiative for Asthma. Global Strategy for Asthma Management and…]. Approximately 235 million people are currently suffering from asthma and WHO estimates that on a global basis there were 383,000 deaths because of asthma in 2015 [27], and 13.8 million disability-adjusted life years lost annually due to asthma, representing 1.8% of the total global disease burden [28].

The risk of developing asthma is influenced by host (genes, obesity, sex and pre-term or small for gestational age) and environmental (allergens, occupational sensitizers and allergens, infections, microbiota, exposure to tobacco smoke, air pollution, diet and stress) factors [29], but how these factors influence asthma development and expression are both complex and interactive; genes can interact both with other genes and environmental factors, thereby determining susceptibility of asthma [30] [31]. Furthermore, there are emerging aspects of development that modify the risk of asthma in a person with a genetic susceptibility; maturation of the immune response, development of atopy, and infectious disease during the first years of life [32] However, despite intensive research on the causes of asthma, there is not a sufficient knowledge base to guide efficient public health interventions to prevent the disease with the exception of work-related asthma.

The inflammation in asthma involves multiple inflammatory cells and mediators [33], and though not well understood, is associated with early life exposures [34], bronchial

hyperresponsiveness and asthma symptoms [32]. There are structural changes (subepithelial fibrosis [35], increased airway smooth muscle mass [36], increased number and size of blood vessels in airway walls [37] and mucus hypersecretion [38]), often described as "airway remodelling" in the airways of asthma patients, some of which may result in irreversible narrowing of the airways [36] [39]. This narrowing of the airways is the final pathway in the pathophysiology of asthma that results in its symptoms and physiological changes, in addition it seems that airway narrowing itself stimulates remodelling [40]. Airway or bronchial hyperresponsiveness, linked to both inflammation and repair of the airways, is a characteristic feature of asthma and results in narrowing of the airways when a patient with asthma is exposed to a stimulus that would be harmless to a healthy person. Narrowing of the airways cause the variable airflow limitation and intermittent symptoms in an asthmatic. Though not completely understood, the mechanisms behind bronchial hyperresponsiveness include excessive contraction of respiratory muscle [41], uncoupling of airway contraction, thickening of the airway wall [36] and sensitized sensory nerves causing excessive bronchoconstriction when exposed to sensory stimuli [41].

1.4 Chronic obstructive pulmonary disease (COPD)

COPD is a noncommunicable disease defined by the Global initiative for Chronic Lung Disease (GOLD) [42] as "*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to noxious particles or gases.*" COPD is the third leading cause of death globally [43] It is estimated that 3.17 million deaths were caused by COPD in 2015 (5% of all deaths globally that year) and in 2016 a prevalence of 251 million cases were reported [44]. The airflow limitation in COPD is not fully reversible, it is slowly progressive, and it is associated with an inflammatory reaction and structural changes in the small, peripheral airways (obstructive bronchiolitis) and/or destruction of the lung parenchyma (emphysema). Extra-pulmonary manifestations and other co-morbidities are contributing to increased disease burden [42]. Co-morbidities with COPD might in

part be due to systematic effects from COPD, either because of inflammatory mediators from the lungs affecting other tissues or organs, or because inflammatory mediators from other tissues affect several different organs [45].

The pathological changes that are characteristic of COPD are present in the airways, lung parenchyma and pulmonary vasculature, and include chronic inflammation and structural changes because of repeated injury and repair [46]. The inflammation in the respiratory tract of persons with COPD is thought to be a modification of the normal response to chronic irritants such as cigarette smoke, but the mechanisms for this amplified inflammation are not yet fully understood. There are some patients with COPD that have never been exposed to cigarette smoke, but the nature of the inflammatory response in these patients is still not known. [42].

Inflammation and narrowing of peripheral airways through fibrosis and luminal exudates lead to decreased FEV_1, and their extent correlates with reduction in FEV_1 and FEV_1/FVC ratio and maybe also with the characteristic accelerated decline of FEV_1 in COPD [47]. However, it has been suggested that the accelerated decline in FEV_1 is not an obligate feature of COPD [15].

Smoking is the most important risk factor for COPD, in addition there are occupational exposures to vapour, gas, dust and fumes. Genetic disposition, perinatal conditions, lung growth and previous asthma also play a role. From foetus to old age a person is exposed to many different noxious particles, gases and chemicals and the sum of all these exposures constitutes a total risk of COPD. Additionally, there are individuals that are genetically more susceptible to such exposures and as such, COPD is an example of interaction between environmental factors and genes. It might be that even a normal decline in FEV_1 can lead to COPD in persons whose maximum attained FEV_1 in early adulthood is less than the norm of the general population [15] and adult respiratory health to a large degree originates in early life [13].

Even though treatable, COPD is not curable and an awareness of potential risk factors, both among the general population and healthcare professionals, is of uttermost importance.

1.5 Work-related asthma and COPD

The broad term work-related asthma (WRA) refers to asthma that is induced or exacerbated by exposures encountered in the workplace. WRA is further divided into occupational asthma (OA) and work-exacerbated asthma (WEA).

OA is *de novo* asthma or relapse of asthma from childhood or distant past that has been in remission, and is further classified as either sensitizer-induced OA or irritant-induced OA. Sensitizer-induced OA is caused by inhalation of a specific substance (for example a high-molecular weight (HMW) protein) or a chemical agent (low-molecular weight (LMW) agent) at work. Sensitizer-induced OA usually present with a latency period and it includes causative agents (proteins and some chemicals) for which sensitization can be shown (typically by antigen-specific IgE) in most persons with asthma caused by exposure to that specific agent. It also includes OA caused by agents (usually reactive chemicals) where an immunologic mechanism is suspected, but where an antigen-specific immune response cannot be easily tested in most affected workers [48]. Irritant-induced OA is caused by exposure to an inhaled irritant at work and can be with or without a latency period [49]. The most clear-cut form of irritant-induced OA is reactive airways dysfunction syndrome (RADS) which is an acute onset of asthma symptoms after a single exposure to very high concentrations of airway irritants [48].

WEA, on the other hand, is asthma that is triggered by various work-related factors (often irritants or non-sensitizing exposures) in workers that have a medical history of pre-existing or concurrent asthma. OA and WEA are not mutually exclusive and may coexist in the same person [48].

It has been estimated that 5-20% of new cases of adult asthma can be attributed to workplace exposures [50]. WRA is associated with a high rate of prolonged work disruption [49] [51] [5] and annual incidence numbers range from approximately 50 per million workers with reports of up to 1,300 per million in certain workplaces [52]. Occupational asthma places a substantial socioeconomic burden on both the individual worker and on society, but they are preventable and substantial reduction in incidence can be achieved by appropriate primary prevention. By early diagnosis within a few months after debut of symptoms, secondary prevention can improve both the

prognosis and financial burden [53]. Furthermore, a reliable diagnosis in an index case is important to tertiary prevention as this may reveal risk for similar exposed workers and lead to revised risk assessment, thereby reducing the risk in other exposed workers. Thus, research to identify possible causative chemicals agents and occupations at risk of exposure is important to primary, secondary and tertiary prevention.

Of all COPD cases, approximately 15% could have been avoided with a clean working environment [54], and in a non-smoking population, up to 30% of COPD cases are caused by the working environment [54]. Hence, even though smoking is still the most important cause of COPD, with the declining prevalence of smoking and an aging workforce, non-smoking factors such as working conditions are becoming increasingly more important [55]; additionally, there are geographical variations and differences due to social inequalities [56] [57]. An ATS statement [12] concludes that there is sufficient evidence for a causal relationship between occupational exposures and development of COPD and that consistent associations have been shown in several epidemiological studies. Biological plausibility between occupational airway irritants and COPD is supported by data from inhalation toxicological studies demonstrating the induction of chronic bronchitis and/or emphysema in animals after exposure to agents associated with chronic bronchitis and emphysema [12].

1.6 Cleaning workers and cleaning exposure

In paper I, occupational cleaners was defined by the question "*have you ever worked as a cleaner?*" and, "*If, yes, for how many years*". In paper II, cleaning was defined by the questions "s*ince the last survey, have you been the person doing the cleaning and/or washing in your home?*" and "*since the last survey, have you worked as a cleaner?*" Persons who responded "*yes*" to either of these questions answered a specific questionnaire about types of cleaning agents etc. In paper III, exposure to cleaning products and disinfectants was a specific category defined from an occupational asthma-specific job-exposure matrix (JEM), including such exposures in

many occupations, such as cleaners, nurses and other health care workers, cooks, hair dressers, etc.

In general, persons working as cleaners often have lower educational level and low socioeconomic status [58]. There is no definitive definition of what constitutes "cleaning exposure", but in general this exposure encompasses all types of chemical agents used when cleaning. Both the components of the agents that are used, and the method of application are important with regard to possible harmful effects to the respiratory system. Several specific exposures that increases the risk of asthma have been identified; asthma symptoms or exacerbations have been found to be associated with the use of sprays, bleach, waxing and also a history of acute inhalations. A case-control study among French women found that weekly use of cleaning sprays may have a deleterious effect on asthma [59] and exposure to cleaning products in spray form has been shown to be associated with an increase in FeNO level and lower FEV_1 [60] which suggests that cleaning agents in spray form may induce inflammation. Lee et al [61] also found that among cleaning workers, respiratory symptoms were associated with exposure to spray products, carpet cleaners, solvents and multi-purpose cleaning products. That cleaning sprays have deleterious effects on respiratory health was further shown in a paper from 2015 on professional cleaners [62] –FEV_1 and PEF were lower on days when three or more sprays were used as compared to days with lower frequency of use.

Most chemicals used for cleaning have irritating effects on the airways, but there are some that can cause development of sensitization through specific immunological mechanisms [6].

The inhalation of irritants initiates an inflammatory response that cause damage to epithelial and other residential cells of the lungs. The inflammation occurs at concentrations levels that are below those that will cause tissue damage, and the level needed to elicit a response may differ from person to person. Several factors might influence how the pulmonary system reacts to irritants; intensity of exposure, physical properties (for example vapor pressure and solubility) and chemical reactivity, but noteworthy, odour is not related to toxicity [63]. The resulting biological effect then depend on the deposition of the irritant in the upper and/or lower airways. Inhalation

of airway irritants can produce damage to the bronchial epithelium, which can then result in several events; a proinflammatory response, neurogenic inflammation because of exposed nerve endings, and finally, increased lung permeability and remodelling of the airways [6]. These events are thought to be caused by stimulation of sensory nerves, epithelial cells and cells of the innate immune system. Sensory nerves are also thought to be directly activated by chemical irritants, either by stimulation of solitary chemosensory cells or by directly stimulating chemoreceptors [63].

Sensitizer-induced or immunologic OA typically involves an IgE-dependent mechanism and OA induced by IgE-dependent agents is similar to allergic asthma unrelated to work. Many occupational sensitizers, particularly HMW agents like flour and animal proteins, and some LMW agents like chlorinated platinum salts, induce asthma by producing specific IgE antibodies, but many LMW agents can cause asthma through a non-IgE-dependent mechanism [64].

Among chemical agents linked to OA, quaternary ammonium compounds (QAC) are of interest as they are extensively used as antiseptics, detergents and preservatives; for example many detergents used to clean floors and surfaces contain QAC. The mechanism by which QAC cause asthma is still not established, but thought to be either by non-immunological mechanisms or by immunological mechanisms, where they in the latter case act as haptens [65]. So far, cleaning sprays, bleach, ammonia and disinfectants have been identified as the most common agents of OA in cleaners, while specific job tasks such as kitchen cleaning and furniture polishing, cleaning windows, washing dishes, mopping/waxing the floor, spot-cleaning carpets and cleaning tiles and grout, have been identified as causes or exacerbation of asthma. Thus, WRA caused by exposure to cleaning agents are in the majority of cases preventable, and identifying specific risk factors is needed to develop effective prevention strategies. However, even though the relationship between exposure to cleaning agents and asthma have been repeatedly documented, little improvement has been made with regard to prevention [66].

Concerning long-term effects of cleaning exposure, it seems plausible that long-term exposure to different types of airway irritants from cleaning agents over time might

lead to COPD [67] [68]. In later studies, occupational cleaners, which have a known exposure to airway irritants, have been identified as one of several vocations with increased risk of COPD [69], even though in a more recent analyses cleaners were not among specific jobs associated with an increased risk of COPD [70].

1.7 Review of the literature on respiratory health outcomes as related to cleaning exposures, prior to this thesis

Short term outcomes

Up until 1999, there had been no large population-based studies on occupational asthma, but in their study based on the ECRHS I, Kogevinas et al showed that occupational cleaners, amongst other occupations, had increased risk of asthma [4]. In the last two decades, cross-sectional studies [71] [72] have shown a 50-100% higher risk of occupational asthma or respiratory symptoms in cleaners.

A PubMed search using the term (cleaning worker* OR cleaning product* OR cleaner* OR cleaning agent*) AND (asthma) AND (("1999/01/01"[PDat] : "2013/12/31"[PDat])) yielded initially 165 results, which was then narrowed down to 46 papers that was concerned with exposure to cleaning agents, either in work as a professional cleaner or in household products, and asthma.

-asthma-

In the years after Kogevinas et al's article there were several papers that well documented the increased risk of asthma associated with cleaning and exposure to cleaning agents [73] [74] [71] [75] [76] [77] [78]. In a British 1958 birth cohort, cleaning occupations plus three occupations likely to use cleaning agents were among occupations associated with adult onset asthma [79].

In a prospective study from Denmark [80], the authors found that the use of sprays in cleaning work was associated with increased risk of eye and respiratory symptoms. When they interviewed participants from the Spanish part of the ECRHS Zock et al [81] found that asthma risk was primarily related to cleaning of private homes, and

that this might in part be explained by the use of sprays plus other products in kitchen cleaning and furniture polishing.

An analysis of a joint registry of OA from outpatient clinics [82] found cleaning services to be the main reported occupation in cases with OA and cleaning products the main reported agents. The authors also found that women, as compared to men, had significantly shorter exposure duration and shorter symptoms duration in cases with OA. Furthermore, in a cross-sectional study [75], asthma was found to be more prevalent in women currently employed in domestic cleaning and also former domestic cleaning was associated with asthma. The authors pointed to that domestic cleaning might have had important public health impact, not only limited to professional cleaners, but also people undertaking cleaning tasks in their own homes were at increased risk. It might have seemed that asthma symptoms in women engaged in domestic cleaning was associated with exposure to bleach and possibly other agents with irritant properties [83] and this could have had widespread public health impact, given that the use of irritating cleaning products was common both in occupational cleaning and at home. In a follow-up of the ECRHS study [84], the risk of new-onset asthma in relation to use of common household cleaning agents was investigated. The authors found higher incidence of physician-diagnosed asthma when sprays were used at least four times per week and a dose-response relationship was apparent for the frequency of use and number of different sprays. Thus, the frequent use of common household cleaning sprays may be an important risk factor for adult asthma. As women usually were the primary persons responsible for cleaning their own home, women with asthma should be cautioned about potential respiratory effects [85]. Exposure to cleaning products was also frequently reported as triggers of asthma by workers with WRA, and the risk of contracting WRA in cleaners increased with years in non-domestic cleaning; women appeared to have higher risk than men [86]. Jakkola et al [87] summarized the recent evidence on the effect of cleaning jobs on asthma. They found strengthened evidence for increased risk of asthma in domestic and industrial cleaners. Furthermore, chemicals such as bleach were identified as specific causes of asthma, and specific job tasks were related to increased asthma risk. They pointed to the need for further research to elaborate how asthma is related to

specific sensitization to certain chemicals, and to what degree airway inflammation is induced by exposure to a mixture of irritants. A later study found that cleaning products used for common cleaning tasks contain mixtures of many chemicals including respiratory irritants and sensitizers such as quaternary ammonium compounds [88], and concluded that cleaning workers were at risk of acute and chronic inhalation exposures to volatile compounds, vapours and aerosols generated from the use of sprays. A pilot exposure assessment study found that airborne exposures from short-term cleaning tasks could remain in the air even after the cessation of cleaning, thus potentially expose anyone that entered a room shortly after it had been cleaned [89].

Though OA was associated with several occupations, cleaners were among the occupations with high rates of OA and inhalation accidents [90], and the authors re-emphasized the persistence of troublesome asthma also after withdrawal from exposure, concluding that primary and secondary preventive strategies should be directed at controlling workplace exposures and improve education of employees [91]. However, the authors pointed out that with established OA, early removal from exposure was still the appropriate treatment; up to one third of exposed workers with OA continued to remain exposed to causative agent, or, sadly, suffered prolonged work disruption, discrimination and risk of unemployment.

Female cleaners had been found to report significantly more respiratory symptoms and work-related symptoms as compared to women who do not work as cleaners, whereas male cleaners showed a non-significant trend towards more physician-diagnosed asthma and work-related symptoms compared to male controls [92]. Among men, work-related symptoms were significantly associated with specific tasks such as waxing floors, wax-stripping floors, spot-cleaning carpets and cleaning tiles. Especially cleaning work in places with high demand for disinfection, high cleaning standards and use of cleaning products containing respiratory irritants was associated with a higher risk of asthma symptoms and it seemed that irritants may play an important role in asthma related to cleaning [93]. It might have seemed that occupational cleaners exposed to a large variety of irritants and sensitizers were especially at increased risk of OA and irritant-induced asthma [94].

Using data from the RHINE study the authors confirmed an increased risk of asthma in several occupations, among them cleaners [95].
Though few experimental studies have been published, Vandeplas et al performed specific inhalation challenge (SIC) tests in workers with cleaning-related asthma symptoms in order to determine the causative agents of asthmatic reactions [96]. The authors found that a substantial proportion of the participants showed a pattern of bronchial reaction consistent with sensitizer-induced OA, and quaternary ammonium compounds appeared to be the principal cause.

-reviews-
In their review from 2004, Malo et al found that cleaners were at increased risk of developing OA, but that the causal agents were unknown.
A review from 2010 [97] found that even though studies showed an association between cleaning work and asthma the risk factors were uncertain. Cleaning workers were exposed to a large variety of cleaning products and agents, both sensitizers and irritants. Thus, onset or aggravation of asthma could be due to either mechanisms caused by exposure to irritants or specific sensitization. The authors identified disinfectants, quaternary ammonium compounds, amine compounds and fragrances to be among the main sensitizers whereas bleach, hydrochloric acid and alkaline agents were among the strongest irritants. Exposure to cleaning agents may have given rise to new-onset asthma (OA) with or without latency and WEA, but asthma-like symptoms without confirmed asthma after exposure was common. High exposures to cleaning agents may have induced RADS, whereas cleaners may have had a greater relative risk of developing asthma due to prolonged low-to-moderate exposure to airway irritants.
Also, Zock et al [98] found that although the predominant mechanism remained unclear, it may have included both specific sensitization and irritant mechanisms. Furthermore, they found in this review that new-onset asthma was associated with cleaning work, professional use of cleaning products and domestic use of cleaning sprays, and strengthened evidence of asthma and other adverse respiratory effects in cleaners.

-consensus statements-

In a position paper from 2013 Siracusa et al presented a consensus statement on asthma and exposure to cleaning products [6] when they reviewed the then to date available literature linking exposure to cleaning products and the risk of asthma. They found that both specific types of cleaning agents (cleaning sprays, bleach, ammonia, disinfectants, mixing products) and specific job tasks had been identified as causes and/or triggers of asthma and while most cleaning agents had an irritating effect on the airways, some had shown an IgE-mediated mechanism. Since cleaning was (and still is) a women-dominated occupation, and also more women than men are responsible for cleaning in their own home, this might partly have explained why there were gender differences in asthma control [6]. To minimize the risks from exposure to cleaning agents, the authors suggested several possible interventions such as substitution or minimizing the use of certain products such as cleaning sprays, ammonia and disinfectants and the use of respiratory protective devices. Furthermore, they advocated education of labour unions and consumer and public interest groups to encourage safer products, as well as information activities for the general population with the purpose of improving the knowledge of professional and domestic cleaners regarding risks and available preventive measures and to promote strict collaboration between scientific communities and safety and health agencies.

Long term outcomes

In general, up until 2013 there had been few studies on cleaners, whether occupational or cleaning at home, and long-term outcomes as COPD or decline in lung function. A PubMed search using the search term (cleaning worker* OR cleaning product* OR cleaner* OR cleaning agents*) AND (COPD) AND (("1999/01/01"[PDat] : "2013/12/31"[PDat])) identified 19 papers; of these, only one mentioned COPD and cleaning agents; cleaning agents were one of 17 individual agents, professions or work-sites with the strongest evidence to be moderately associated with occupational asthma or COPD. [99]. One study was identified that addressed occupation and lung function decline [67], however, the participants were only followed for three years,

thus it was difficult to evaluate possible effects of long-term low-grade irritant exposure on accelerated lung function decline in such a short follow-up period.

2. Objectives

Main aim

To study potential impact of exposure to cleaning agents and disinfectants on short- and long-term respiratory health, and on offspring respiratory health.

Specific research questions and a brief background for these

1. Is being a cleaner associated with increased risk of asthma, airways symptoms and self-reported COPD in Northern European countries? *Most literature is from South and Middle Europe, while cleaning habits and products might be different and possibly less harmful in North Europe.*

2. Do factors reflecting early life disadvantage increase the susceptibility to cleaning agents with regard to lung health? *Cleaners may come from a less advantageous socioeconomic background, and there is some evidence that early life factors might increase susceptibility to subsequent harmful exposures.*

3. Is occupational and home cleaning associated with accelerated decline in lung function? *Long term effects on lung health in terms of accelerated decline in lung function are biologically plausible, but are however, very challenging to investigate. It is relevant to study both persons cleaning their own home and occupational cleaners; while the first would be exposed less time during a week, the latter might be more aware of the need to select less harmful products and protect themselves through government health agencies and labour unions.*

4. Are children of mothers exposed to occupational cleaning agents and disinfectants at increased risk of asthma? *One may suspect that preconception germline cell exposure to cleaning products and disinfectants could have an impact on respiratory health in offspring.*

3. Methods

3.1 The ECRHS study

3.1.1 Study design

- ECRHS I
  - Stage 1
    - Cohort established 1992-1994
    - Randomly selected population-based sample
    - ≈150,000 participants aged 20-44 years
    - Postal screening questionnaire
  - Stage 2
    - ≈22,000 participants
    - 20% random sample from stage 1
    - Additional symptomatic sample
    - Clinical examination including forced spirometry
- ECRHS II
  - 1998 - 2002
  - Participants from ECRHS I stage 2 invited
  - ≈ 11,000 participants
  - ≈ 7,700 performed forced spirometry
- ECRHS III
  - 2010 – 2012
  - Participants from ECRHS II invited
  - ≈ 6,000 participants
  - ≈ 4,800 performed forced spirometry

The European Community Respiratory Health Survey (ECRHS) is an international prospective multi-centre population-based study with three study waves; ECRHS I from 1992 to 1994, ECRHS II from 1998 to 2002 and ECRHS III from 2010 to 2012 (details can be found at www.ecrhs.org). The cohort was established in stage 1 of the ECRHS I when randomly selected men and women aged 20 to 44 years from 56 participating centres in 25 countries were sent a screening questionnaire. In stage 2, a smaller random sample of subjects who had completed the postal questionnaire were invited to a more detailed interviewer-led questionnaire as well as a clinical examination. Additionally, subjects not included in the random sample but having symptoms suggesting asthma in stage 1, were invited to participate in the clinical stage 2 [2] [100].

All persons who completed stage 1 of ECRHS I and who, having been selected for stage 2, had at least their smoking status recorded were invited to participate in the ECRHS II [101] by a short screening questionnaire. Those who responded were invited to a clinical examination (blood samples, lung function testing and bronchial

responsiveness) and structured interview (respiratory symptoms and medical history, medication and use of medical services, smoking and exposure to environmental tobacco smoke, occupation, home environment and air pollution); 29 centres from 14 countries participated. Among those 29 study centres, 22 centres completed a protocol on occupational exposure; this protocol included questionnaire modules on cleaning at home and occupational cleaning.

In the third follow-up, the ECRHS III, participants from 29 centres in 14 countries who took part in the clinical stage of ECRHS I were sent a short screening questionnaire; in 27 of the centres those who responded were once more invited for a clinical examination and structured interview.

A fourth follow-up, ECRHS IV, is planned to take place 2021-2022.

3.1.2 Participants

The number of participants in the ECRHS I stage 1 questionnaire survey, comprised 200,682 men and women aged 20 to 44 years [102]. In stage 2 there were 18,811 subjects in the random sample and 2,998 subjects in the symptomatic sample, totalling 21,809 participants in the clinical part of ECRHS I [100]. In ECRHS II 11,219 individuals participated in a clinical examination and in the third study wave approximately 8834 individuals participated [103].

3.1.3 Interview

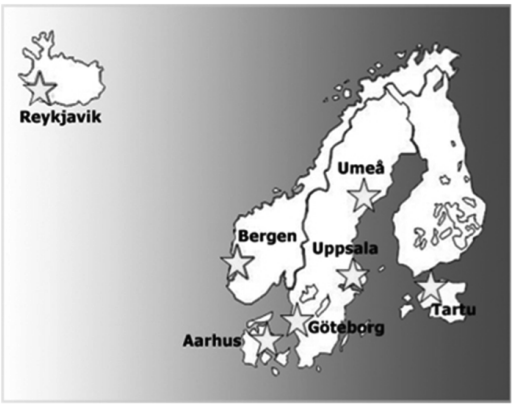
All participants in ECRHS I stage 2 and ECRHS II and III underwent a detailed questionnaire administered by an interviewer. The initial questions for assessment of respiratory symptoms was identical in all three study waves. Furthermore, the questionnaire covered medical history, smoking and exposure to environmental tobacco smoke, occupation, home environment, air pollution and medication amongst other [101].

In ECRHS II, all occupations held since ECRHS I were recorded. Additionally, in 22 centres participants who reported having worked as a cleaner, and persons who

reported having been responsible for cleaning and washing in their own home, were asked to complete an occupational module providing detailed information on, amongst others, length of employment/years of exposure, the use of different types of cleaning agents and frequency of use. Likewise, participants having worked as a nurse or metal worker, and persons who had soldered, welded or used disinfectants at home or at work, were asked for more detailed information about workplace activities [101]. Cleaning activities were further recorded in the main questionnaire in ECRHS III, but in much less detail than in the occupational modules of ECRHS II.

3.2 The RHINE study

3.2.1 Study design



- RHINE
  - 1999 – 2001
  - Follow-up of participants from the Nordic and Baltic centres in ECRHS I stage 1
  - Born 1945 - 1973
  - Postal questionnaire
  - >20,000 invited, ≈ 16,000 responders
  - Timing corresponded with ECRHS II =>RHINE II
- RHINE III
  - 2010 - 2012
  - Postal questionnaire
  - Participants from RHINE II invited
  - ≈ 13,500 responders

The first stage of the ECRHS I stage 1 was conducted from 1990 to 1994 when participants were invited to a postal screening questionnaire. The Respiratory Health in Northern Europe (RHINE) study is a postal questionnaire follow-up of the participants from the seven Nordic and Baltic centres in the ECRHS I stage 1. The RHINE study was conducted between 1999 and 2001 and as the timing corresponded with the second follow-up of the ECRHS (ECRHS II) it is often referred to as RHINE II. The next stage of the RHINE study, named RHINE III, took place from 2010 to 2012. RHINE IV is currently being planned to take place spring 2021.

3.2.2 Participants

The participants of the ECRHS I stage 1 were randomly selected population-based samples of men and women aged 20 to 44 years; of these 21,659 participants were from the seven Nordic and Baltic centres (Bergen in Norway; Umeaa, Gothenburg and Uppsala in Sweden; Aarhus in Denmark; Reykjavik in Iceland; Tartu in Estonia), and 16,106 (75%) responded to the RHINE questionnaire. The follow-up (RHINE III) included 13,499 responders, 62% of the original sample [104].

3.2.3 Postal questionnaire

Both questionnaires from RHINE and RHINE III included standard questions on respiratory symptoms from the ECRHS questionnaire (see www.ecrhs.org for wording). Respiratory symptoms such as wheezing were reported as 12 months prevalence while respiratory diseases such as adult asthma and COPD were reported as lifetime prevalence. Furthermore, the questionnaires included questions on rhinitis, bronchitis, smoking, indoor environment, early life disorders, sleep disorders and occupation, but only in RHINE III the participants were asked about whether they had ever worked as a cleaner and duration in years of such occupation.

3.3 The RHINESSA study

3.3.1 Study design and participants

In all study centres G2 (RHINE/ECRHS study participants) and G3 (RHINESSA 3rd generation study participants) have been investigated, including 1607 offspring-parent pairs in a clinical study and 10133 offspring parent-pairs in a questionnaire study. In the Bergen study centre also G1 and G4 have been investigated as well as the G2 parent not participating in RHINE/ECRHS.

The Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) is a generation study examining the offspring of the participants in the ECRHS and RHINE studies (www.rhinessa.net). Each participant in RHINESSA is an offspring who had (at least) one parent that has participated in the ECRHS/RHINE study. RHINESSA has ten study centres [105], including the seven RHINE centres in five Nordic countries and three additional ECRHS centres (Melbourne in Australia, Huelva and Albacete in Spain). The protocols of the RHINESSA study were harmonised with those of the ECHRS and RHINE. Offspring with parental questionnaire data from RHINE/ECRHS were included in a questionnaire study, and offspring with parental clinical data from the ECRHS were included in a clinical study.

3.3.2 Questionnaire and clinical study

A postal questionnaire based on the ECRHS I and RHINE, including similar questions as those their parents answered, addressed, among others, respiratory symptoms, asthma, occupation, socio-demographic characteristics, childhood and family. Questionnaires were sent to all adult offspring (>18 years) in the ten RHINESSA

centres. The sub-sample of offspring responding to the questionnaire study, having a parent with clinical data from ECRHS and lived in the area of the study centre, were invited to face-to-face interviews and clinical examinations [106]. The detailed interviewer-led questionnaire at the clinical investigation included questions on respiratory symptoms, asthma, smoking, socio-demographic characteristics, occupational history, general health and co-morbidities relevant for airway disease.

3.4 Spirometry

At the clinical examination the participants were asked for respiratory symptoms during the last weeks and days prior to the examination, and for possible exclusion criteria to performing spirometry. Height, weight, sex, age and time of day were recorded. Subjects were advised to avoid smoking for one hour, using a β_2-agonist or anticholinergic inhaler for four hours or oral medication (β_2-agonist , theophylline or antimuscarinic) for eight hours before the test [107]. Spirometry was then carried out according to a study protocol consistent with 1995 ATS guidelines on spirometry [108]. The maximum Forced Vital Capacity (FVC) and the maximum Forced Expired Volume in one second (FEV_1) of up to five technically acceptable tests were determined. Spirograms were not to be rejected solely on the basis of poor reproducibility as elimination of data from subjects who failed to meet ATS reproducibility criteria could result in population bias by excluding participants with abnormal lung function. In ECRHS I and II subjects were also tested for bronchial hyperresponsiveness with methacholine, whereas bronchodilator test, a repeated spirometry after administration of two puffs of Salbutamol (100 mcg per puff), was performed at ECRHS III.

3.5 Classification of occupations and job exposure matrix

The International Standard Classification of Occupations (ISCO) is a system for organizing information on jobs into a clearly defined set of groups according to the

tasks and duties undertaken in the jobs [109]. Each job or job title is classified by a numeric variable which describes the different task and duties of jobs.

As a detailed history of work exposure is often difficult to obtain in large population-based studies, exposure assessment are often rather crudely based on self-reported exposure or job title, i.e. “Have you ever worked as a cleaner?” To improve the occupational exposure classification, job-exposure matrices (JEM) have been developed, in which each job title is translated into exposures to specific agents [110] [111]. The use of a JEM also has the advantage that jobs with similar exposures, but different job titles also will be included in the exposure category; i.e. nurses in hospitals exposed to cleaning agents and disinfectants.

4. Synopsis of papers

4.1 Paper I

Respiratory health in cleaners in Northern Europe: Is susceptibility established in early life?

Svanes Ø, Skorge TD, Johannessen A, Bertelsen RJ, Bråtveit M, Forsberg B, Gislason T, Holm M, Janson C, Jögi R, Macsali F, Norbäck D, Omenaas ER, Real FG, Schlünssen V, Sigsgaard T, Wieslander G, Zock, JP, Aasen T, Dratva J, Svanes C PLoS One 2015 Jul 13;10(7) :e0131959. doi: 10.1371/journal.pone.0131959. eCollection 2015.

Cleaners have more asthma and airway symptoms than a general population [4] [5] and exposure to different types of airway irritants from cleaning agents might over time lead to COPD among cleaners. [67] [68]. However, most literature on asthma in cleaners were from South and Middle Europe and there was in general little literature on the risk of COPD in cleaners. A previous analysis had shown that persons with characteristics reflecting early life disadvantages were more susceptible to harmful effects from adult smoking [14]. We hypothesized that cleaners from Northern Europe are at increased risk of asthma and COPD and that early life disadvantage factors may modify adult responses to occupational exposures such as cleaning agents. The aim of the study was to investigate respiratory symptoms, asthma and self-reported COPD as related to working as a cleaner in Northern Europe, and whether early life factors influenced susceptibility to occupational cleaning's unhealthy effects.
Using data from the RHINE study, 2138 (16%) cleaners (N=13,283) were investigated. From reported number of years working as a cleaner a categorical exposure variable was built: never exposed, exposed ≤1 year, >1 to <4 years, ≥4 years. Standardized questions from the ECRHS study were used to assess respiratory symptoms and disease; participants reporting at least one of four factors (maternal smoking in childhood, severe respiratory infection before 5 years of age, being born during winter months and/or maternal age at delivery above 35 years) were defined as having early life disadvantage. Multiple logistic regression models were used to evaluate possible associations between occupational cleaning and respiratory health,

adjustments were made for age, sex, smoking habits, educational level, parents' educational level, BMI and participating centre. Analyses of associations between occupational cleaning ≥4 years and respiratory health outcomes were stratified by the dichotomous variable early life disadvantage. Potential interaction between early life disadvantages and cleaning status was analysed by including an interaction term of occupational cleaning ≥4 years and early life disadvantage in effects on respiratory outcomes.

Among 2138 ever-cleaners the risks of wheeze (OR 1.4, 95% CI 1.3-1.6), adult-onset asthma (1.5 [1.2-1.8]) and self-reported COPD (1.7 [1.3-2.2]) were increased. The risk increased with years in occupational cleaning (adult-onset asthma: ≤1 year 0.9 [0.7-1.3]; 1-4 years 1.5 [1.1-2.0]; ≥4 years 1.6 [1.2-2.1]). The association of wheeze with cleaning activity ≥4 years was significantly stronger for those with early life disadvantage than in those without (1.8 [1.5-2.3] vs. 1.3 [0.96-1.8]; $p_{interaction}$ 0.035). In conclusion, this paper found increased asthma, respiratory symptoms and self-reported COPD in people from Northern Europe having worked as an occupational cleaner. The risk was particularly increased among persons with early life disadvantage, suggesting that early life disadvantage might increase individual susceptibility to an adult occupational exposure.

4.2 Paper II

Cleaning at home and at work in relation to lung function decline and airway obstruction

Svanes Ø, Bertelsen RJ, Lygre SHL, Carsin, AE, Antó JM, Forsberg B, García-García JM, Gullón JA, Heinrich J, Holm M, Kogevinas M, Urrutia I, Leynaert B, Moratella JM, Le Moual N, Lytras T, Norbäck D, Nowak D, Olivieri M, Pin I, Probst-Hensch N, Schlünssen V, Sigsgaard T, Skorge TD, Villani S, *Jarvis D, *Zock JP and *Svanes C Am J Respir Crit Care Med. 2018 May 1;197(9):1157-1163. doi: 10.1164/rccm.201706-1311OC.
*Contributed equally

Cleaning tasks are associated with exposure to several chemical agents with potential harmful effects to the respiratory system [112] and excess risk of asthma and respiratory symptoms among professional cleaners and in persons cleaning their own home have been reported in several studies [4] [84] [113]. However, the long-term consequences of cleaning agents on respiratory health was not well described, but it seemed biologically plausible that exposure to cleaning chemicals could result in accelerated lung function decline. Therefore, the aim of the study was to investigate the long-term effects of occupational cleaning and cleaning at home on lung function decline and airway obstruction.

Data from the multi-centre ECRHS study was used, providing information about occupational cleaning and cleaning at home as well as spirometry performed at three time points. Possible associations of cleaning exposure with decline in lung function were analysed with mixed effect models with adjustments for potential confounders [age at baseline and age squared, number of years from baseline to each follow-up, height, BMI, life-time pack-years at each time point, age at completed education, spirometer type, and centre]. Associations between cleaning exposure and airway obstruction were analysed with multiple logistic regression with adjustments for potential confounders. The study population included 6,235 participants, mean age at baseline was 34 years and 53% were women. Of the 3,298 female participants, 85.1% reported to be the one who usually was cleaning at home, as compared to 46.5% of

2,932 male participants. 293 women and 57 men reported working with occupational cleaning.

As compared to women not engaged in cleaning (ΔFEV_1=-18.5 ml/year), FEV_1 declined more rapidly in women responsible for cleaning at home (-22.1 ml/year, p=0.01) and occupational cleaners (-22.4 ml/year, p=0.03). The same was found for decline in FVC (ΔFVC=-8.8 ml/year; -13.1, p=0.02 and -15.9, p=0.002 respectively). Both cleaning sprays and other cleaning agents were associated with accelerated FEV_1 decline (-22.0 ml/year, p=0.04 and -22.9 ml/year, p=0.004, respectively). Cleaning was not significantly associated with lung function decline in men, or with FEV_1/FVC-decline or with airway obstruction.

In conclusion, this paper found that women cleaning at home or working as occupational cleaners have accelerated decline in lung function, suggesting that exposures related to cleaning activities may constitute a risk to long-term respiratory health. A causal effect might be biologically plausible, since cleaning agents have known irritative effects and potential for causing inflammatory changes in the airways [6].

4.3 Paper III

Maternal preconception exposure to cleaning and disinfection agents and offspring asthma

Tjalvin G, Svanes Ø, Igland J, Bertelsen R, Benediktsdottir B, Dharmage S, Forsberg B, Holm M, Janson C, Jogi NO, Johannessen A, Malinovschi A, Pape K, Gómez Real F, Sigsgaard T, Toren K, Vindenes H, Zock, JP, Schlünssen V, Svanes C. Submitted manuscript.

Since the 1980s, there has been a marked increase in childhood asthma prevalence in many countries [34]. Though the reasons still remain mostly unknown, suggested mechanisms have included events occurring early in life, both before and after birth. Furthermore, there might be windows of susceptibility to environmental exposures in the parental generation before conception or even in previous generations [9] [10] [8] [114]. A registry study found that several parental occupations were associated with increased hospitalization for childhood asthma in offspring [115] and future parents' exposure to chemicals might affect both their somatic and germ cells [116]. A possible hypothesis is that occupational exposure before conception impact offspring's health through germline cell exposure. The aim of the study was to investigate risk of asthma in children of mothers that had been occupationally exposed to indoor cleaning agents starting before or around the time of conception.

Data from the RHINE and RHINESSA studies were analysed for associations between maternal exposure to cleaning agents and offspring outcomes before the age of ten (childhood asthma, childhood asthma with nasal allergies and childhood wheezing and/or asthma) using mixed effects logistic regression with adjustment for maternal education; for stratified analyses ordinary logistic regression were used. Based on an occupational asthma-specific JEM and the year exposure started, maternal exposure was defined as 1) medium exposure, starting the birthyear or before, 2) high exposure, starting the birthyear or before, 3) medium exposure, only after birthyear, and 4) high exposure, only after birthyear. Of 3318 adult offspring in the study population, 1307 had a mother who's employment for at least six months involved exposure to indoor

cleaning agents; 2011 had a mother who had no exposure to cleaning agents, but had held at least one job for six months.

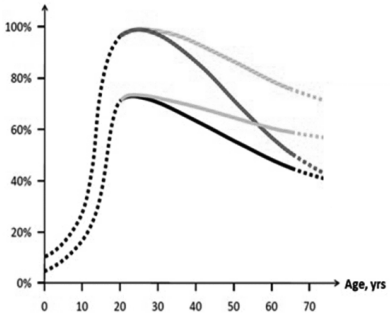
Children of mothers whose occupational exposure to indoor cleaning agents started before conception and continued had an increased risk for all outcomes. There also seemed to be an increased risk of offspring outcomes in children where maternal exposure started around the time of conception or pregnancy. Stratified analyses suggested a dose-response pattern as maternal exposure before or around conception and pregnancy appeared to be more strongly associated with asthma in offspring, if the exposure level had been high as compared to medium.

In conclusion, this paper found an association between pre-conception maternal occupational exposure to cleaning products and disinfectants and childhood asthma in offspring. This further adds up to the growing concern about health risks from cleaning agents and underlines the need for further mechanistic research and replication in human studies.

5. Discussion

"*Life-course epidemiology is the study of long-term effects on later health and disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood, and later adult life. The aim is to elucidate the underlying biological, behavioural, and psychosocial processes that operate across an individual's life-course or across generation*" [117].

In this thesis factors that might have an impact on lung function through life have been studied, from conception and the first few years of life (early life disadvantage), in adult life (cross-sectional studies with asthma and COPD as outcomes) and aging of the lungs (lung function decline) How lung function might vary throughout life is illustrated in the figure to the right, showing four possible trajectories for lung function from birth and to old age. In addition, this thesis includes preconception exposure into the "life-course" perspective, a novel field that goes beyond the definition of life-course epidemiology given above.



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F1000Research

5.1 Methodological considerations

-study design and population-

The RHINE, ECRHS and RHINESSA studies are multi-centre prospective studies, where the initial ECRHS study population consisted of random samples from available population registers. Initial recruitment and invitation to follow-up studies were conducted by postal questionnaires; in the ECRHS and RHINESSA the responders to the questionnaires were subsequently invited to a clinical examination at a local study centre. One disadvantage to such multi-centre studies is that the estimates is weakened

by the heterogeneity in measurements between different centres – even though great care is taken to standardize all clinical observations and measurements between centres, some differences will still exist. However, it is more likely that observed associations are due to homogenous biological phenomena and not heterogeneous socio-cultural factors and errors in measurement between different study centres. Each of the three studies (RHINE, ECRHS and RHINESSA) include several thousand participants. The RHINE study had sufficient number of participants to analyse a potential interaction between occupational cleaning and early life disadvantage. The ECRHS study had clinical data including measurements of lung function from several thousand of participants at each study wave. The RHINESSA study made it possible to study health effects of occupational exposure through generations by providing data from offspring of mothers that participated in the RHINE and ECRHS studies. Indeed, the population-based design of the studies, the large number of participants, the substantial data available for each participant, the multicentred structure and the inclusion of two generations are among their strengths, as the results are being relevant for the general public and not only select groups due to the random design.

-exposure assessment-

The assessment of exposure in paper I and II is rather crude; in paper I participants were asked "*Have you ever worked as a cleaner?*" and in paper II "*Are you the person doing the cleaning and /or washing at home?*" and "*Have you worked as a cleaner?*" This might give rise to differential bias causing spurious effects, or non-differential bias diminishing true associations. It seems improbable that the former would be the case; for example at the timing of the RHINE III study (2010-2012), work as a cleaner had little focus in the general media in the Nordic countries and thus it seems unlikely that reporting as an occupational cleaner would be different for symptomatic and asymptomatic participants. With the crude exposure assessment, it is possible that other vocations also exposed to cleaning agents, for example industrial cleaners and homecare takers [84], are included in the reference group. Furthermore, it is likely that the reference group also included other occupations with known increased risk of asthma, for example farmers, mechanics and textile workers [71] [118]. As a result,

this could lead to an underestimation of the true negative impact from occupational cleaning.

In the study population of paper II, the exposure of cleaning one's own home may have had differential associations across centres in different countries. For example, it is likely that having someone to clean at home (e.g. a homecare taker) varies between countries. However, this possible social-cultural difference was accounted for in the analyses by using centre as an adjustment variable and the multicultural structure of the study thus made it possible to adjust for heterogenous cultural differences between centres.

In paper III, occupational exposure was based on job title and a JEM and not limited to employment as a cleaner. The JEM used was validated and designed for this kind of study [119] and included a specific category for the exposure of interest, indoor cleaning products and disinfectants. The use of a JEM does increase the risk of a Berkson type error and while this will not attenuate risk estimates, statistical power is reduced [120]. The maternal generation provided a full occupational history with the year starting and the year stopping for each job and the JEM classified all reported jobs with regard to occupational exposure to indoor cleaning agents.

-outcomes-

In paper I, COPD was based on self-reported, doctor's diagnosed COPD ("*Have a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)?*") which gives the lowest prevalence estimates [121] [122], and as shown in another paper, COPD is in its early stage under-diagnosed [123]. There were relatively few participants in RHINE with self-reported COPD, in part this is likely due to the study population being relatively young, and the low numbers can explain the less consistent results on analyses of COPD. Spirometric airway obstruction in paper II was defined as a FEV_1/FVC ratio less than the lower limit of normal (LLN). According to the Global Initiative for Chronic Obstructive Disease (GOLD) [42] spirometric obstruction is defined as a fixed FEV_1/FVC ratio < 0.70. But, using this fixed cut-off value as a definition of airway obstruction rises concern that cases of obstruction can be misdiagnosed as the FEV_1/FVC ratio is not a fixed number, but rather varies with age, height and gender [124]. Hence, using the fixed ratio may result in over-diagnosis of

spirometric obstruction in the elderly patients as lung volumes may be reduced as a result of the normal aging process and not as part of development of COPD.

-bias-

by selection

As with all postal questionnaires, one disadvantage is non-response or loss to follow-up, which might reduce the effective sample size and may introduce bias [125]. However, Johannessen et al concluded in their paper from 2014 [104] that even though follow-up populations should be interpreted with some caution in future reports from RHINE and the Italian part of the ECRHS (I-ECRHS), exposure-outcome associations were mainly unchanged by loss to follow-up, and although response rates varied between studies, their results indicated high validity in the data from the RHINE and I-ECRHS study. Even though a similar study has not been undertaken for all the centres in the ECRHS or in the RHINESSA study, the participants of all these studies were recruited and invited to follow-up in the same way, answered the same questionnaires and the clinical examination were performed after the same protocol. Furthermore, although a response rate below 100% gives room for selection, it seems improbable that the association between cleaning and asthma in non-responders would differ from the responders, i.e. that cleaning and exposure to cleaning agents have positive respiratory health effects for this group. Therefore, one could argue that there is good reason to expect that the data from the ECRHS and RHINESSA have high validity. There is a possibility that persons with respiratory symptoms are more likely to quit a cleaning job than asymptomatic subjects, thus creating a “healthy worker effect” that may further underestimate the negative impact of working as a cleaner [126]. This could also explain why the results from paper I did not show a stronger tendency of increased risk of respiratory disease with more years having worked as a cleaner.

by misclassification

In paper II, there is the possibility of differential misclassification of occupational cleaning, leading to either positive or negative confounding. Even so, a reporting error in whether or not having worked as a cleaner is more likely to give non-differential bias. By the use of a validated JEM in paper III, misclassification in exposure is likely

to be non-differential and true effects attenuated, hence the results are unlikely to be caused by information bias. Even though there is a possibility that other occupational exposures are correlated to exposure to cleaning products and disinfectants and thereby explain at least in part the results, this does not seem plausible as exposure to cleaning agents were found in many different occupations.

-confounding-

by smoking

Smoking habits is an important confounder to account for as smoking is known to have harmful effects on the respiratory system [127].

In paper I, however, sensitivity analyses of never-smokers gave results that were consistent with results from the whole study population, which suggest that the results were not due to rest confounding by smoking.

In paper II, it was not apparent in the study population that occupational cleaning might be related to an unhealthy lifestyle, in particular with smoking. Even so, smoking, in terms of pack-years, was used as an adjustment variable in the analyses and additionally age at attained education was used to account for possible confounding by socio-economic status. Smoking, in terms of pack-years, was further included in the analyses as a time-varying variable so as to take into account the effect from smoking on lung function decline over time. As smoking is a known cause of accelerated decline in FEV_1 and thereby could cause residual confounding on accelerated decline in FEV_1 a sensitivity analysis with an interaction term between pack-years and time was performed. This model did not change the estimates of annual decline in FEV_1 or the confidence intervals in the two exposure groups – cleaning at home and working as an occupational cleaner. Furthermore, as the findings in paper III were consistent also in offspring of never-smoking mothers, rest confounding by smoking seems unlikely.

by socioeconomic status

The reference group of women in paper II, those neither cleaning their own home nor working as an occupational cleaner, was small (n=197), and might be a select socio-economic group that in general have a healthier lifestyle. Adjustment for age at

attained education in the main analysis did not attenuate the results and secondly, socio-economic status itself was not a significant predictor for decline in lung function. Furthermore, sensitivity analyses with adjustments for mother's and father's educational level did not alter the findings of accelerated lung function decline with cleaning exposure and parental educational level were not associated with lung function decline. Another sensitivity analysis, using the occupational based socio-economic variable, based on "UK social class", did not alter the associations. Further, the social class variable was not a significant, independent predictor for accelerated decline in FEV_1 or FVC. In paper III, exposure to cleaning agents was found in many different occupations, thus the variation in occupation reduced the risk for rest confounding by social class.

by asthma

Asthma among female participants in paper II was more prevalent in the two groups exposed to cleaning agents (12.3% and 13.7% versus 9.6% respectively). Previous studies have shown that asthmatics, regardless of sex and smoking status, have a greater decline in FEV_1 than people without asthma [128]. But, when taking this into account and adjusting for ever having had asthma in either of the three study waves of the ECRHS, sensitivity analysis did not change the associations between exposure to cleaning agents and accelerated decline in lung function. Moreover, when participants with asthma were excluded from the analyses, the effects on lung function decline were similar. Thus, it seems reasonable to believe that the observed accelerated decline in lung function is not in general mediated by asthma. Furthermore, as suggested by this sensitivity analysis, asthma medication did not limit, meditate or confound the associations with cleaning exposure.

5.2 Discussion of main results

5.2.1 Risk of asthma and COPD in cleaners

Specific research question 1: Is being a cleaner associated with increased risk of asthma, airways symptoms and self-reported COPD in Northern European

countries? *Most literature is from South and Middle Europe, while cleaning habits and products might be different and possibly less harmful in North Europe.*

The results on respiratory symptoms and asthma in paper I are in agreement with what has been shown in several other studies, thus, findings in Northern Europe did not differ from other studies areas. The results confirm that occupational cleaners are at increased risk of respiratory health hazards, described previously in data from the ECRHS [4] [84] [5] [98] and from other study populations [75] [98] [113] [59].

We could not identify heterogeneity between the study centres in RHINE, this support that the results are more likely to be due to biological mechanisms that would be similar across centres, rather than confounding by socio-cultural factors, which are likely to differ between study centres.

The analyses from paper I show increased risk of prevalent self-reported COPD in cleaners. In general, there are relatively few papers that address COPD in cleaners, however, our findings are in agreement with analyses from the UK Biobank cohort study that also showed increased prevalence of COPD in industrial as well as domestic cleaners [69]. An increased risk for occupational COPD have been described for a range of other occupations, including occupations with low-grade exposure to airways irritants accumulated over time [129] [130].

Cleaning chemicals have inflammatory effects [6] and a person using cleaning agents at work is thus exposed repeatedly over time to low-grade airways irritants. This could cause remodelling of the airways, leading both to asthma and to long-term damage to the airways. Thus, our findings both of asthma and respiratory symptoms in cleaners, and between long-term exposure to cleaning agents and COPD, are biologically plausible.

In Paper II we analysed incident COPD, defined as spirometric chronic airway obstruction with FEV_1/FVC ratio less than LLN. [124]. However, there were relatively few new cases of COPD in this study population that was substantially smaller than the study population in paper I, and an association between cleaning exposures and incident COPD did not reach statistical significance. Furthermore, paper II did not find any difference in yearly decline in FEV_1/FVC between the three exposure groups

which in part might be due to the study population being relatively young and thus, airway obstruction has not yet progressed as far as to manifest as spirometric changes. On the other hand, that we could not find significant associations with reduced FEV1/FVC ratio is in accordance with our analyses that suggested a steeper decline in FVC than in FEV_1 in relation to cleaning exposures. FVC appears to be a most important marker of general health; in asymptomatic adults, without a diagnosis of chronic respiratory disease or persistent respiratory symptoms, survival has been shown to be associated with FVC rather than FEV_1 or the FEV_1/FVC ratio [16].

5.2.2 Susceptibility to occupational hazards like cleaning

Specific research question 2: Do factors reflecting early life disadvantage increase the susceptibility to cleaning agents with regard to lung health? *Cleaners may come from a less advantageous socioeconomic background, and there is some evidence that early life factors might increase susceptibility to subsequent harmful exposures.*

The Barker hypothesis on early life programming, described in Barkers publication in 1990 of «The foetal and infant origins of adult disease» [131] implies that childhood or early life disadvantage factors may have long-term health consequences. Early life events have also been suggested to influence respiratory health [13] [132]. The first paper of this thesis found effect modification of exposure to cleaning agents in adult life by a defined "early life disadvantage" score. The variable "early life disadvantage" was defined as the reporting of at least one out of the following four factors: maternal smoking in childhood, severe respiratory infection before 5 years of age, being born during winter months, and/or maternal age at delivery after age 35 years. The choice of these four factors was based on biological plausibility and previous knowledge [133] [134], and the early life disadvantage score therefore conveys a concept that is general and beyond each of the individual components. Another analysis found that an early life disadvantage factor increased an individual's susceptibility to the harmful effects from cigarette smoking with regard to airflow limitation [135]. Dratva et al. found accelerated decline in FEV_1 among subjects reporting one or more factors reflecting early life disadvantage (born during winter season, of older mothers, of smoking mothers or with younger siblings), and that this early life disadvantage factors modified responses to adult exposures. For example, maternal smoking appeared to enhance harmful effects of personal smoking on lung function decline [14]. Another analysis [13] found substantially lower lung function level, higher accelerated lung function decline and higher risk of COPD in persons with early life disadvantage; in this paper early life disadvantage factors were defined as maternal or paternal asthma, childhood asthma, maternal smoking and childhood respiratory disease. Even though the individual components reflecting early life disadvantage varied somewhat between the papers referred above, these papers suggest that the first

years of life are important for how we later in life are able to tolerate harmful exposures to the respiratory system. Our finding that early life disadvantage modified the association of cleaning with respiratory symptoms, supports this notion, that a disadvantageous early life development could increase the susceptibility to subsequent harmful exposures. With regard to potential mechanisms for how early life disadvantage might influence the susceptibility to adverse exposures in adult life, we speculate that poor early life development could hamper molecular repair mechanisms, hence reducing the ability in later life to cope with repeated insults from harmful exposures. Cleaners would often come from a less advantageous background, and we raise the question whether enhanced susceptibility to subsequent hazards would contribute to propagate health inequalities across generations.

5.2.3 Accelerated decline in lung function as related to cleaning

Specific research question 3: Is occupational and home cleaning associated with accelerated decline in lung function? *Long term effects on lung health in terms of accelerated decline in lung function are biologically plausible, but are however, very challenging to investigate. It is relevant to study both persons cleaning their own home and occupational cleaners; while the first would be exposed less time during a week, the latter might be more aware of the need to select less harmful products and protect themselves through government health agencies and labour unions.*

Paper II of this thesis found that women exposed to cleaning chemicals, either when cleaning their own home or when working as a professional cleaner, had accelerated decline in FEV_1 and FVC when compared to women not regularly engaged in cleaning activities. In an attempt to address groups of specific cleaning agents, we found that women who used sprays or other cleaning agents at least once per week had accelerated decline in FEV_1, and that use of cleaning products other than sprays at least once per week was significantly associated with accelerated decline in FVC. More detailed investigation of specific products was not possible in this already complex study of exposure over time in relation to change in lung function over time.

A similar accelerated decline in lung function could not be identified for men in association with exposure to cleaning, whether the exposure was from an occupational or home setting, or whether sprays or other cleaning products were used.

The findings in paper II were consistent and robust when performing sensitivity analyses. Tobacco smoking is a well-known cause of greater annual lung function decline [127]. However, accounting for smoking over time by inclusion of an interaction term between pack-years and time, did not alter the estimates of cleaning as related to accelerated decline in FEV_1. The reference group of women not engaged in cleaning activities was small and could be suspected to be a selected socioeconomic group. We addressed potential confounding by socioeconomic status (SES) using various approaches: Adjustment for SES did not alter the observed association. Smoking is a characteristic of low SES, and adjustment for smoking did not influence the results, further speaking against substantial confounding by SES. Furthermore, we adjusted for mother's and for father's educational level, characteristics of the study participant's childhood SES, and such adjustment did not alter the observed associations. Finally, selection into the reference group would differ between study centres, and study centre was accounted for in the analysis. Different misclassification between study centres could contribute to attenuating true associations. Thus, while rest-confounding cannot be ruled out, it seems unlikely that this is an important driver of the results.

Asthmatics have greater decline in FEV_1 than non-asthmatics, independent of sex and smoking. However, even though asthma was more prevalent in the exposed groups, adjustment for ever had asthma did not affect the associations. Neither did excluding asthmatics from the analyses alter the results. Thus, while a link between occupational exposure to cleaning agents and poorer respiratory health outcomes agree with previous studies on asthma related to cleaning [4] [5], the associations of cleaning with accelerated lung function decline was not mediated by cleaning-related asthma.

Women cleaning at home had an excess decline in FEV_1 of 3.6 ml/year and in FVC of 4.3 ml/year, whereas the corresponding numbers for women engaged in occupational cleaning was 3.9 and 7.1 ml/year, respectively. However, because of the multi-centre study design with 22 participating centres, each with different technical personnel

assisting in lung function measurements and use of different spirometer models, there is reason to argue that the absolute decline in lung function over time more likely is underestimated [136]. Thus, this might have diminished true differences between exposure groups and secondly, our study would have lower sensitivity to pick up smaller changes. To compare with a different exposure – smoking- and using similar models with the same adjustments as in the model on cleaning, we found an excess decline in FEV_1 of 6.1 ml/year and in FVC 8.9 ml/year in heavy smokers (>20 pack-years), thus the effect of working as an occupational cleaner on accelerated lung function decline was in the magnitude of smoking somewhat less than 20 pack-years. There is, to our knowledge, no other study in the literature on lung function decline as related to cleaning exposures – it is difficult to study decline in lung function in a study population large enough to address a specific occupation, and the exposure "cleaning" is also difficult. However, our results are plausible considering literature on biological mechanisms. Cleaning agents and chemicals are described to have irritant effects on the mucous membranes of the airways [97] [6]. A person using cleaning agents is exposed to repeated low-grade irritants over time, and this might constitute one possible mechanism for the accelerated decline in lung function in cleaners. Additionally, there are cleaning agents that have sensitizing properties through specific immunological mechanisms such as quaternary ammonium compounds which have known airway sensitizer properties as well as irritant effects [97]. Repeated exposure to cleaning agents over time could, due to allergic inflammation, cause remodelling of the airways leading to an accelerated decline in lung function. Furthermore, it is possible that exposure to airway irritants over years, for example ammonia and bleach which is used when cleaning at home, could lead to irreversible either fibrotic or other interstitial changes in the lung tissue, which could cause more pronounced decline in FVC than in FEV_1 [137]. Even as there are several methodological challenges in the analyses in paper II, as also discussed in the previous sections, most of the errors are more likely to have attenuated true associations than causing spurious associations and leading to the finding that women cleaning at home or working as an occupational cleaner had accelerated decline in FEV_1 and FVC. Though difficult to achieve in

human studies, the results should be replicated in other large cohorts with longitudinal data on lung function and exposure.

5.2.4 Risk of respiratory symptoms in offspring of mothers occupationally exposed to cleaning agents and disinfectants

Specific research question 4: Are children of mothers exposed to occupational cleaning agents and disinfectants at increased risk of asthma? *One may suspect that preconception germline cell exposure to cleaning products and disinfectants could have an impact on respiratory health in offspring.*

The third paper found an association between mother's exposure to cleaning agents and disinfectants at work before conception, and increased risk of childhood asthma in the offspring. Sensitivity analyses suggested a dose-response pattern with higher risk related to higher than medium intensity exposure, and that results remained reasonably consistent with additional adjustment for maternal educational level, asthma and smoking status. The risk estimates were similar regardless of the offspring's sex. In a real-life scenario, women go in and out of jobs with the exposure of interest. Thus, four time windows of exposure was defined: 1) only preconception exposure, 2) exposure starting at least 3 months before conception, 3) exposure starting during the two-year period around conception (birth year minus 1 year, thus including 3-15 months preconception, 9 months intrauterine and 0-12 months postnatal), and 4) exposure starting after birth. Exposure scenarios 2 and 4 had large numbers of women, and gave solid, consistent results with regard to offspring asthma: Exposure scenario 2, starting before conception, showed consistent association with higher offspring asthma risk; exposure scenario 4, starting after birth of the child, showed no increase in offspring asthma. Exposure before conception, which implies transfer of risk through germ cell impact, could not be accurately separated from exposure *in utero*, which means direct exposure to the foetus. Exposure scenario 2 could reflect both mechanisms. Exposure scenario 1, only before conception with mean time for quitting exposure 7 years before conception, showed a similar risk estimate as scenario 2, supporting an interpretation of a role of preconception exposure. The association did not reach statistical significance, possibly because there was a smaller number of

women in this exposure group. A role of more immediate preconception exposure or exposure to the foetus was suggested by a borderline statistically significant association with exposure starting during the 2-year time interval around conception of the offspring, a relatively small exposure group. The consistent finding of no increased risk with only postnatal exposure, a large exposure group, disfavours an effect of shared environment. Further, this adds strength to the results on the other exposure scenarios, post-natal exposure could be seen as a different reference group with similar potential confounding factors as the other scenarios.

That notion that preconception exposure plays a role in childhood asthma is supported in a Swedish study where participants probably would have been exposed to cleaning agents and where their offspring had increased risk of hospitalization for childhood asthma [138]. However, even though there are studies that support an association between a mother's occupational exposure to cleaning and asthma in offspring, these studies could not specifically investigate the period before conception [139] [140] [141].

With regard to publications of other parental occupational exposures and offspring health, Pape et al [114] in another analysis of RHINE/RHINESSA, studied 20 specific asthmogenic agents, divided into four exposure groups; microorganisms, pesticides, allergens and reactive chemicals. The JEM category "exposure to indoor cleaning agents and disinfectants" was not investigated in this study. Further, the reference group and exposure time windows were defined differently from in our study. Pape et al. found mostly negative results, not showing associations of parental occupational exposure with offspring asthma, but the study did identify an association of mother's occupational exposure to "allergens and reactive chemicals" before and after the child's year of birth, with the child's risk of early-onset asthma. Reactive chemicals have some properties that are common with cleaning chemicals, and the findings thus to some extent are in line with our finding on cleaners. Another paper that investigated father's preconception occupational exposure to welding and metal fumes [9], found increased risk of asthma in offspring; offspring asthma risk was doubled if the father had worked with welding 10 or more years before conception of the offspring.

5.3 Causality

Observational epidemiological studies such as the ECRHS, RHINE and RHINESSA give the opportunity to study multiple exposures in a real-life setting, and due to their broader inclusion criteria (and few exclusion criteria) than the randomised clinical trial, their results can be more applicable to the general public [142]. While it also has been suggested that it is not possible in a cohort study to establish causal effects [142], already in 1965, Sir Austin Bradford Hill argued in favour of epidemiological studies and causality and described nine criteria to provide epidemiological evidence of a causality between a suspected exposure or cause and an outcome or effect [143]. Nevertheless, confounders, even if adjusted for in the analyses, will remain a possible source to misinterpretation of results in cohort studies [142]. A recent publication by editors of respiratory journals argues for how causality can be approached in observational studies [144].

-consistency-

As has been shown in earlier paragraphs of this thesis, the results on increased risk of respiratory symptoms and asthma in occupational cleaners in the Nordic countries agree with previous literature and also literature published after this thesis was started [145]. There is literature supporting the results from paper III, but to the authors knowledge this is the first study to address maternal preconception occupational exposure and possible health impact in offspring. Even so, the results agree with an emerging understanding of intergenerational inheritance where for example occupational exposures might cause epigenetic changes in germ cells which then might be transmitted to offspring [8] [146].

-specificity-

Though limited to a specific occupation (cleaning) and activity (cleaning one's own home), the exposure assessment in both paper I and II is rather crude, but this is more likely to have attenuated true associations and in both papers there are more specific outcomes. In paper III a more detailed exposure assessment was achieved as a full

occupational job history was obtained with start -and stop year for each job and the JEM classified each job with respect to occupational exposure to indoor cleaning agents.

-temporality-

In paper I, the questions on occupational cleaning activity were only included in RHINE III (the last survey) and then with limited detail, thus is was not possible to establish a temporal relationship between start of occupational cleaning and development of asthma and COPD. Likewise, it was not possible to in greater detail explore susceptibility windows in adulthood as timing of neither exposure nor development of disease was established. In paper II, participants were asked for information on cleaning activities between the first and second study wave and thus a temporal relationship between exposure and outcome was established. In paper III it was not possible to separate the immediate preconception time window from the intrauterine time window, additionally the modelling of time windows was limited by the time resolution (one year) in the duration of each job held and year of birth of offspring.

-biological gradient-

The participants in paper I were asked for length of exposure (how long they had worked as a cleaner), but even though there was a trend towards increased risk with more years of exposure for most outcomes, a biological gradient was not clearly established. This might in part be explained by the rather short time spent as a cleaner (median 2 years, mean 5.7 years). In paper II, a clear dose-response relationship was not established while in paper III a biological gradient was suggested as higher-level exposure starting before birth was associated with higher risk of asthma in offspring than lower-level exposure.

-biological plausibility-

Most chemicals used for cleaning tasks have irritating effects on the airways, but there are some that can cause development of true sensitization through an immunologic

mechanism [6]. Though the pathophysiological mechanisms behind asthma and COPD are not completely understood, there is a clear association between exposure to irritants and asthma and COPD. Likewise, long-term, repeated exposure to respiratory irritants (as found in cigarette smoke) is associated with accelerated decline in lung function.

Siracusa et al [6] have earlier described irritant effects as well as specific immunological effects as possible mechanisms, but even so, no study have robustly investigated exposure to cleaning products or ingredients along with asthma risk. Thereby the determination of causal relationships between asthma and specific products or ingredients have been limited, and there is also a lack of robust animal models for toxicological assessment of asthma [145].

There are several studies showing an association between an unfavorable intrauterine environment and increased risk of the development of disease in later life [147] [148], thus supporting a biological plausibility for the increased risk for offspring asthma related to maternal exposure during pregnancy.

-coherence-

The possibility of increased susceptibility to the harmful effects from cleaning agents due to early life disadvantage factors as shown in paper I is supported by other studies. Though some differences as to which factors that have been included as early life disadvantage, there is good reason to suspect that events occurring early in life are associated with poorer lung health as an adult [149].

Finally, there is a possibility of reversed causality, i.e. that asthma and respiratory symptoms could be the reason for working as a cleaner or keeping one's home spotlessly clean. However, this notion seems unlikely and to our knowledge, all available literature shows increased respiratory symptoms or worsening of asthma with exposure to cleaning agents.

Thus, while not all of Hill's criteria are fulfilled, we believe that each of the three papers suggest causality between exposure (cleaning) and outcome (adverse respiratory effects), and that the findings presented in this thesis constitute a valuable

and important contribution to the knowledge basis that allows for drawing conclusions between cleaning exposure and respiratory health.

Hill's criteria with brief comments to each of the criteria for the three papers in the thesis.

	Paper I	Paper II	Paper III
Strength of the association – a strong association supports causality	Adjusted OR 1.4 for wheeze, 1.7 for asthma symptoms and 1.5 for adult onset asthma in ever occupational cleaners	Strong association – comparable with smoking which is a well-documented cause of accelerated lung function decline	OR 1.6 for offspring's childhood asthma, 1.8 for childhood asthma with nasal allergies and 1.7 for childhood wheeze and/or asthma when mother exposed to occupational indoor cleaning
Consistency – causation more likely if results from various research studies consistent	-findings on respiratory symptoms and asthma consistent with previous literature - findings on interaction of chemical exposure with early life factor also found for smoking/maternal smoking	- consistent with association with study on other long-term respiratory outcome - COPD	-no previous literature on this exposure, but consistent with previous studies on other chemical exposures – preconception smoking and offspring asthma
Specificity – causation more likely if a specific outcome is related to a specific exposure	-crude exposure assessment (cleaner), more specific outcome (respiratory symptoms, asthma, COPD)	- crude exposure assessment (cleaner), more specific outcome (decline in FVC and FEV_1)	- detailed exposure assessment using JEM - specific exposure windows before/during pregnancy markedly different from exposure window after birth –includes specific outcome (asthma before ten years of age)
Temporality – exposure must occur before outcome	-temporal relationship between exposure and outcome (asthma and COPD) not confirmed	-temporal relationship between exposure and outcome established	-temporal relationship established with high time-resolution, - not possible to fully disentangle exposure only before conception from exposure before and after

Biological gradient – causality more likely with a dose-response relationship	-trend toward higher risk with longer years worked as a cleaner (dose-response relationship)	-data did not allow for exploration of a biological gradient (years of exposure and accelerated loss of lung function)	-a biological gradient suggested (higher exposure associated with higher risk)
Biological plausibility – a conceivable mechanism for causation between outcome and exposure should exist	-biological plausibility between cleaning exposure and respiratory outcomes (symptoms, asthma, COPD)	-biological plausibility between cleaning and accelerated loss of lung function	-biological plausibility between maternal occupational exposure before birth of offspring and disease in offspring
Coherence – current association should not be contradicted by previous knowledge	-results agree with previous knowledge	-no known previous studies on exposure (cleaning) and outcome (long-term lung function decline) when paper published	-to our knowledge there is no previous literature that contradicts the current association
Experiment – experimental evidence enhances probability of causation	-no experimental evidence	- no experimental evidence	-no experimental evidence
Analogy – existing similar associations supports causation	-effect modification by early life factors supported by other studies	-the greater impact seen in women reported for other exposures (cigarette smoke) and other occupations	-father's exposure to welding and metal fumes before conception showed increased asthma in offspring

6. Conclusions

Persons having worked as occupational cleaners have increased risk of respiratory symptoms, asthma and COPD. The results were consistent for different adjustments, between study centres and between subgroups (sex, smoking status, body weight). In particular, we found that people expressing one or more factors associated with having early life disadvantage – maternal smoking in childhood, severe respiratory infection before 5 years of age, born during winter months and/or maternal age at delivery above 35 years – had increased risk of respiratory symptoms and disease. This suggests that early life disadvantage might increase an individual's susceptibility to harmful occupational exposures in adult life, uncovering a mechanism whereby health inequalities may be propagated across generations.

Further, we found that women cleaning at home and/or working as occupational cleaners had accelerated decline in FVC and FEV_1, but not apparent accelerated decline in the FEV_1/FVC ratio. The results were consistent when adjusting for smoking, which is a known cause of accelerated lung function. Likewise, adjusting for socio-economic status (SES) did not alter the associations, nor was SES in itself a significant predictor for decline in lung function. Thus, while the reference group of women not cleaning at home or working as occupational cleaner was small, sensitivity analyses discouraged the notion that the results could be explained by confounding by socioeconomic status. This suggest that women cleaning either at home or working as cleaners are at higher risk of deteriorating respiratory health due to both increased risk of asthma as have been shown earlier, but also in terms of long-term impact on lung function decline and accelerated lung function decline with loss of dynamic lung volume. The accelerated decline advocates for further prevention from harmful airway exposure when performing cleaning activities, notably, both at home and as an occupational cleaner.

Finally, we found that mothers' preconception exposure to cleaning agents and disinfectants at work was associated with increased offspring asthma. The use of a validated JEM made it unlikely that the results were caused by information bias, and there were several different occupations with exposure to cleaning agents, which

reduced the risk for confounding by social class. Further, the results were consistent in offspring of never-smoking mothers, thus, confounding by smoking is unlikely. The results thereby raise a question of potential germ cell impact of cleaning agents and disinfectants.

7. Perspectives

7.1 Impact of results - translating research to changes in behaviour and industry

While it is one thing to have a research result that could have significant implications for public health, the next question is how best to translate the results to action; who to inform and how to inform them. As a result of our paper on lung function decline [150], showing that exposure to cleaning products was associated with accelerated lung function decline in women, this motion was tabled 14 May 2018 in the British House of Commons [151]: *"That this House notes research by the Department of Clinical Science at Bergen University which shows that exposure to some cleaning products can be as damaging to lung function as smoking 20 cigarettes a day; further notes the occupational health risks faced by people who work as cleaners; expresses dissatisfaction at the current regulation of cleaning products; and calls on the Government to bring forward proposals for labelling of cleaning products to warn of the health risks, to work with the industry to make such products as safe as possible, and to bring forward regulations to minimise health risks.*" Following the motion, my supervisor Cecilie Svanes participated in a meeting held in the UK Parliament between trade unions, health and safety executives and MPs.

This article also sparked a lot of attention in the media around the globe, there were hundreds of newspaper articles and several radio interviews on the topic, in European languages, but also Hindu, Chinese etc. The news story went viral, and still there are new online references to this, in medical as well as popular channels.

Furthermore, the Norwegian Labour Inspection Authority has issued fact sheets in Norwegian, Polish and English warning about the use of cleaning sprays and increased risk of asthma and COPD in cleaners, and advocating the use of dry or damp cleaning methods.

As to who to inform, Cecilie Svanes presented at the main European conference on cleaning products about the research findings to industry leaders (Cleaning Products Europe 2019).

In conclusion, I would like to think that there have been some positive changes due to our findings presented in this thesis. It appears to be a shift of habits and an awareness in the public. People have a focus on potential harmful effects of cleaning agents, and in the following doctors are warning against the effects of using cleaning products, or at least using adequate protective gear and ensuring circulating fresh air when cleaning (https://www.spokesman.com/stories/2019/jul/13/ask-the-doctors-your-clean-house-could-be-hurting-/).Focusing on workplace interventions, such as optimal air quality and access to adequate personal protective equipment, particularly among persons with early life disadvantage, might better ensure an adequate prevention to respiratory diseases. Lilleborg AS, one of the largest manufacturers of cleaning products in Norway for both the professional and home marked, have changed the nozzles on spray bottles to increase the size of droplets from cleaning sprays, thereby reducing the "fog" of cleaning chemicals that can be inhaled.

7.2 Future perspectives

Since experimental studies in humans would not be feasible and also unethical, causality cannot finally be proved in humans, and the observational data are of major

importance. Seen together, the observational studies linking various measures of exposure to cleaning products and disinfectants with a range of respiratory health outcomes, constitutes fairly strong evidence that cleaning products cause impaired respiratory health. The results of this thesis, in general, give strong support to this notion. When it comes to the specific topics of the thesis, the long-term effects on lung function decline, vulnerability in those with developmental disadvantage early in life, and suggested impact on future offspring, our studies are unique – and need confirmative studies. The availability of data to replicate the findings is a major problem both when studying life-span impact and impact across generations, and there is a need to support with experimental studies, in particular animal studies when it comes to addressing potential effects across generations. However, there is also a lack of robust animal models for toxicological assessment of asthma [145]. There is no legislation requiring testing for germline effects when new chemical products enter the marked, and our study together with emerging mechanistic understanding supports the need for this.

In 2020 the world faced a new pandemic, the new corona virus (SARS-CoV-2) which has, amongst other alterations in our lives, led to extreme cleanliness. As advised by governments and health authorities, we use more disinfectants and cleaning agents to avoid infection and spreading of the virus. Based on the results of this thesis we question, might the increased use of airway irritants increase asthma, even in future offspring? And, we speculate, could the irritant effects from cleaning agents have an impact on susceptibility to Covid-19?

8. References

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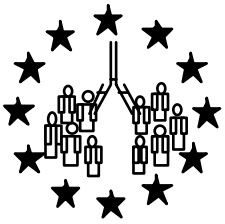
Appendix

THE EUROPEAN COMMUNITY RESPIRATORY HEALTH SURVEY II



ECRHS II

MAIN QUESTIONNAIRE

Project Leaders:
Prof Peter Burney
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www.ecrhs.org

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Centre number
Personal number
Sample
Date DAY MONTH YEAR

I AM GOING TO ASK YOU SOME QUESTIONS. AT FIRST THESE WILL BE MOSTLY ABOUT YOUR BREATHING. WHEREVER POSSIBLE, I WOULD LIKE YOU TO ANSWER 'YES' OR 'NO'.

1. Have you had wheezing or whistling in your chest at any time in the last ***12 months***? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 2, IF 'YES':

1.1 Have you been at all breathless when the wheezing noise was present? NO ☐ YES ☐

1.2. Have you had this wheezing or whistling when you did ***not*** have a cold? NO ☐ YES ☐

2. Have you woken up with a feeling of tightness in your chest at any time in the last ***12 months***? NO ☐ YES ☐

3. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last ***12 months***? NO ☐ YES ☐

4. Have you had an attack of shortness of breath that came on ***following*** strenuous activity at any time in the last ***12 months***? NO ☐ YES ☐

5. Have you been woken by an attack of shortness of breath at any time in the last ***12 months?*** NO ☐ YES ☐

IF NO GO TO Q6, IF YES

5.1 Have you been woken by an attack of shortness of breath in the last ***3 months***? NO ☐ YES ☐

IF NO GO TO Q6, IF YES

5.1.1 ***On average*** have you been woken by an attack of shortness of breath ***at least once a week*** *in the* ***last 3 months?*** NO ☐ YES ☐

IF NO GO TO Q6, IF YES

5.1.1.1 How many times a week ***on average*** have you been woken by shortness of breath in the ***last 3 months***? TIMES ☐☐

6. Have you been woken by an attack of coughing at any time *in the last* ***12 months***? NO ☐ YES ☐

7. Do you ***usually*** cough first thing in the morning in the winter? NO ☐ YES ☐
[IF DOUBTFUL, USE QUESTION 8.1 TO CONFIRM]

8. Do you ***usually*** cough during the day, or at night, in the winter? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 9, IF 'YES':

8.1 Do you cough like this on most days for as much as three months each year? NO ☐ YES ☐

9. Do you ***usually*** bring up any phlegm from your chest first thing in the morning in the winter? NO ☐ YES ☐

[IF DOUBTFUL, USE QUESTION 10.1 TO CONFIRM]

10. Do you ***usually*** bring up any phlegm from your chest during the day, or at night, in the winter? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 11, IF 'YES':

10.1 Do you bring up phlegm like this on most days for as much as three months each year? NO ☐ YES ☐

11. Do you ever have trouble with your breathing? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 12, IF 'YES':

11.1 Do you have this trouble — TICK ONE BOX ONLY

a) continuously so that your breathing is never quite right? 1 ☐

b) repeatedly, but it always gets completely better? 2 ☐

c) only rarely? 3 ☐

12. Are you disabled from walking by a condition ***other than*** heart or lung disease? NO ☐ YES ☐

IF 'YES' STATE CONDITION _____ AND GO TO QUESTION 13, IF 'NO':

12.1 Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 13, IF 'YES':

12.1.1 Do you get short of breath walking with other people of your own age on level ground? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 13, IF 'YES':

12.1.1.1 Do you have to stop for breath when walking at your own pace on level ground? NO ☐ YES ☐

13. ***FOR WOMEN ONLY - MEN GO TO Q14***

Have you ever noticed that you had respiratory symptoms (such as wheeze, tightness in your chest or shortness of breath) at a particular time of your monthly cycle? — TICK ONE BOX ONLY

yes, in the week before my period	1	☐
yes, during my period	2	☐
yes, in the week after my period	3	☐
yes, another time of the month	4	☐
does not apply to me (i.e., amenorrhoeal)	5	☐
No	6	☐

NO YES

14. Have you ever had asthma? ☐☐

IF 'NO' GO TO QUESTION 15, IF 'YES':

	NO	YES
14.1 Was this confirmed by a doctor?	☐	☐

	YEARS
14.2 How old were you when you had your first attack of asthma?	☐☐
14.3 How old were you when you had your most recent attack of asthma?	☐☐

14.4.1-6 Which months of the year do you usually have attacks of asthma?

	NO	YES
14.4.1 January / February	☐	☐
14.4.2 March / April	☐	☐
14.4.3 May / June	☐	☐
14.4.4 July / August	☐	☐
14.4.5 September / October	☐	☐
14.4.6 November / December	☐	☐

	NO	YES
14.5 Have you had an attack of asthma in the last ***12 months***?	☐	☐

IF NO GO TO 14.8, IF YES

	ATTACKS
14.6 How many attacks of asthma have you had in the last ***12 months***?	☐☐
14.7 How many attacks of asthma have you had in the last ***3 months***?	☐☐

14.8 How many times have you woken up because of your asthma in the last ***3 months?*** TICK ONE BOX ONLY

every night or almost every night	1 ☐
more than once a week, but not most nights	2 ☐
at least twice a month, but not more than once a week	3 ☐
less than twice a month	4 ☐
not at all	5 ☐

14.9. How often have you had trouble with your breathing because of your asthma in the last ***3 months?*** TICK ONE BOX ONLY

continuously	1 ☐
about once a day	2 ☐
at least once a week, but less than once a day	3 ☐
less than once a week	4 ☐
not at all	6 ☐

	NO	YES
14.10 Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?	☐	☐
14.11 Do you have a peak flow meter of your own?	☐	☐

***IF 'NO' GO TO QUESTION 14.12 , IF 'YES'*:**

14.11.1 How often have you used it over the last 3 months? TICK ONE BOX ONLY

never 1 ☐
some of the days 2 ☐
most of the days 3 ☐

14.12 Do you have written instructions from your doctor on how to manage your asthma if it gets worse or if you have an attack? NO ☐ YES ☐

14.13. ***FOR WOMEN ONLY - MEN GO TO Q15***

Have you ever noticed that your asthma got worse with your monthly cycle? TICK ONE BOX ONLY

Yes, in the week before my period 1 ☐
Yes, during my period 2 ☐
Yes, in the week after my period 3 ☐
Yes, another time of the month 4 ☐
Does not apply to me (i.e., amenorrhoeal) 5 ☐
No 6 ☐

NO YES

14.14 Have you been pregnant (at least 25 weeks) since your asthma started? ☐ ☐

IF NO GO TO Q15, IF YES

14.14.1.What happened to your asthma during your pregnancies? TICK ONE BOX ONLY

got better 1 ☐
got worse 2 ☐
stayed the same 3 ☐
not the same for all pregnancies 4 ☐
don't know 5 ☐

NO YES

15. Do you have any nasal allergies, including hay fever? ☐ ☐

IF NO GO TO Q16, IF YES

YEARS

15.1 How old were you when you first had hay fever or nasal allergy? ☐☐

16. Have you ever had a problem with sneezing, or a runny or a blocked nose when you did not have a cold or the flu? NO ☐ YES ☐

IF NO GO TO Q17, IF YES

16.1.Have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu ***in the last 12 months***? NO ☐ YES ☐

IF NO GO TO Q17, IF YES

16.1.1. Has this nose problem been accompanied by itchy or watery eyes? NO ☐ YES ☐

16.1.2. In which months of the year did this nose problem occur? NO YES

January ☐ ☐
February ☐ ☐
March ☐ ☐
April ☐ ☐
May ☐ ☐
June ☐ ☐
July ☐ ☐

August
September
October
November
December

17. ***Since the last survey*** have you used any medication to treat nasal disorders? NO YES

IF NO GO TO Q18, IF YES

17.1 Have you used any of the following nasal sprays for the treatment of your nasal disorder? NO YES

{SHOW LIST OF STEROID NASAL SPRAYS}

IF NO GO TO Q17.2, IF YES

17.1.1 How many years have you been taking this sort of nasal spray? YEARS

17.1.2 Have you used any of these nasal sprays ***in the last 12 months?*** NO YES

17.2 Have you used any of the following pills, capsules, or tablets for the treatment of your nasal disorder? NO YES

{SHOW LIST OF ANTIHISTAMINES}

IF NO GO TO Q18, IF YES

17.2.1 How many years have you been taking these sort of pills, capsules or tablets? YEARS

17.2.2 Have you used any of these pills, capsules or tablets ***in the last 12 months?*** NO YES

18. Have you ***ever*** had eczema or any kind of skin allergy? NO YES

19. Have you ***ever*** had an itchy rash that was coming and going for at ***least 6 months***? NO YES

IF 'NO' GO TO QUESTION 20, IF 'YES': NO YES

19.1.. Have you had this itchy rash ***in the last 12 months?***

IF 'NO' GO TO QUESTION 20, IF 'YES':

19.1.1. Has this itchy rash ***at any time*** affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles under the buttocks or around the neck, ears or eyes NO YES

20. Have you ever had any difficulty with your breathing after taking medicines? NO YES

IF 'NO' GO TO QUESTION 21, IF 'YES':

20.1-2 Which medicines? _____ 20.1. 20.1.2

21. How old was your mother when you were born? YEARS

22. How many times did you move house during the first five

years of your life? TICK ONE BOX ONLY

None	1 ☐
Once	2 ☐
more than once	3 ☐

NO YES

23. Were you hospitalised before the age of two years for lung disease? ☐ ☐

YEARS

24. At what age did you first attend a school, play school, day care or nursery? ☐

25. How many ***other*** children regularly slept in your bedroom before ***you were five years old?*** CHILDREN ☐

I would now like to ask you some questions on the type of jobs that you have done.

I am interested in each one of the jobs that you have done for more than 3 consecutive months since the time we last contacted you (in 1991/2). These jobs may be outside the house or at home, full time or part time, paid or not paid, including self employment, for example in a family business. Please include part time jobs only if you had been doing them for more than 8 hours per week.

Q26. Are you currently

TICK ONE BOX ONLY

Employed (including military service)	1 ☐
Self employed	2 ☐
Unemployed, looking for work	3 ☐
Not working because of poor health	4 ☐
Full-time house-person	5 ☐
Full time student	6 ☐
Retired	7 ☐
Other	8 ☐

IF EMPLOYED OR SELF EMPLOYED OR A FULL TIME HOURSEPERSON GO TO Q28

27. Have you been employed in any job for three continuous months or longer since the last survey? NO ☐ YES ☐

IF YES NOW GO TO OCCUPATIONAL MATRIX

Centre number
Personal number
Sample
Date DAY MONTH YEAR

Q 28. If you had more than one job in the same company, or if you were doing more than one job at the same time, we would like to talk about them separately. Please start with your current or last job.

JOB	Q28.1. What is (was) the title of your current (last) job? *OCCUPATION*	Q28.2. What did the firm, company or organisation do or what services did it provide? INDUSTRY	Q28.3. In what month and year did you start working in this job? MONTH YEAR	Q28.4. In what month and year did you stop working in this job? MONTH YEAR
JOB 1				
JOB 2				
JOB 3				
JOB 4				
JOB 5				
JOB 6				
JOB 7				
JOB 8				
JOB 9				
JOB 10				

29. Have any of these jobs ever made your chest tight or wheezy? NO ☐ YES ☐

IF YES, (tick no or yes for each job)

	NO	YES
Job 1?	☐	☐
Job 2?	☐	☐
Job 3?	☐	☐
Job 4?	☐	☐
Job 5?	☐	☐
Job 6?	☐	☐
Job 7?	☐	☐
Job 8?	☐	☐
Job 9?	☐	☐
Job 10?	☐	☐

30. Have you had to leave any of these jobs because they affected your breathing? NO ☐ YES ☐

IF YES, (tick no or yes for each job)

	NO	YES
Job 1?	☐	☐
Job 2?	☐	☐
Job 3?	☐	☐
Job 4?	☐	☐
Job 5?	☐	☐
Job 6?	☐	☐
Job 7?	☐	☐
Job 8?	☐	☐
Job 9?	☐	☐
Job 10?	☐	☐

31.Since the last survey have you been involved in an accident at home, work or elsewhere that exposed you to high levels of vapours, gas, dust or fumes? NO ☐ YES ☐

IF YES,

31.1 Did you experience respiratory symptoms immediately following this exposure? NO ☐ YES ☐

IF YES

31.1.1 Could you describe to me what it was? _____

Centres performing the extra occupational modules should at this point introduce the modular introductory questionnaire and complete modules as appropriate.

32. At what age did you complete full time education? YEARS ☐☐

If full time student enter 88

33. How often do you usually exercise so much that you get out of breath or sweat? TICK ONE BOX ONLY

every day	1 ☐
4-6 times a week	2 ☐
2-3 times a week	3 ☐
once a week	4 ☐
once a month	5 ☐
less than once a month	6 ☐
never	7 ☐

34. How many hours a week do you usually exercise so much that you get out of breath or sweat? TICK ONE BOX ONLY

none	1 ☐
about ½ hr	2 ☐
about 1 hour	3 ☐
about 2-3 hours	4 ☐
about 4-6 hours	5 ☐
7 hours or more	6 ☐

NO ☐ YES ☐

35. Do you avoid taking vigorous exercise because of wheezing or asthma?

YEAR ☐☐☐☐

36. When was your present home built?

NO ☐ YES ☐

37. Do you live in the same home as when you were last surveyed?

IF YES GO TO QUESTION 38, IF NO

TIMES ☐☐

37.1. How many times have you moved since you were last surveyed?

YEARS ☐☐

37.2. How many years have you lived in your current home?

37.3 Where do you currently live? TICK ONE BOX ONLY

a different home, but still in the study sampling area	1 ☐
outside the sampling area but still in the same country	2 ☐
a different country	3 ☐

37.3.1. **IF A DIFFERENT COUNTRY** Which country? ☐☐☐

37.4 Which best describes the building in which you live? TICK ONE BOX ONLY

a) a mobile home or trailer?	1 ☐
b) a one family house detached from any other house?	2 ☐
c) a one family house attached to one or more houses?	3 ☐
d) a building for two families?	4 ☐
e) a building for three or four families?	5 ☐
f) a building for five or more families?	6 ☐
g) a boat, tent or van	7 ☐
e) other: _____	8 ☐

38. Does your home have any of the following?

	NO	YES
38.1 central heating	☐	☐
38.2 ducted air heating (forced air heating)	☐	☐
38.3 air conditioning	☐	☐

39. Which of the following appliances do you use for heating or for hot water?

	NO	YES
39.1 open coal, coke or wood fire	☐	☐
39.2 open gas fire	☐	☐
39.3 electric heater	☐	☐
39.4 paraffin heater	☐	☐
39.5 gas-fired boiler	☐	☐
39.6 oil-fired boiler	☐	☐
39.7 portable gas heater	☐	☐
39.8 other: _____	☐	☐

40. What kind of stove do you ***mostly*** use for cooking? TICK ONE BOX ONLY

a) coal, coke or wood (solid fuel)?	1 ☐
b) gas (gas from the mains)?	2 ☐
c) electric?	3 ☐
d) paraffin (kerosene)?	4 ☐
e) microwave	5 ☐
f) gas (gas from bottles or other non-mains source)	6 ☐
g) other: _____	7 ☐

40.1 IF YOU USE GAS FOR COOKING Which of the following do you have?

	NO	YES
40.1.1 gas hob	☐	☐
40.1 2.gas oven	☐	☐

41. What kind of stove was mostly used for cooking in the home you lived in when you were five years old? TICK ONE BOX ONLY

a) coal, coke or wood (solid fuel)?	1 ☐
b) gas (gas from the mains)?	2 ☐
c) electric?	3 ☐
d) paraffin?	4 ☐
e) gas (gas from bottles or other non-mains source)	5 ☐
f) don't know	6 ☐
g) other: _____	7 ☐

MINUTES

42. ***On average*** how long have you spent cooking with your stove each day over the ***last four weeks***? ☐☐☐

43. ***Over the last four weeks*** when you were cooking did you have a door or window to the outside air open — TICK ONE BOX ONLY

- a) most of the time 1 ☐
- b) some of time 2 ☐
- c) rarely (or only occasionally) 3 ☐
- d) I do not have a door or window that opens to the outside in my kitchen 4 ☐

	NO	YES	DK
44. Do you have an extractor fan over the cooker?	☐	☐	☐

***IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 45, IF 'YES'*:**

44.1 When cooking, do you use the fan — TICK ONE BOX ONLY

- a) all of the time? 1 ☐
- b) some of the time? 2 ☐
- c) none of the time? 3 ☐

	NO	YES	DK
44.2 Does the fan take the fumes outside the house?	☐	☐	☐

45. Does the room which you use most at home during the day	NO	YES
45.1 have fitted carpets covering the whole floor?	☐	☐
45.2 contain rugs?	☐	☐
45.3 have double glazing?	☐	☐

46 How old is the oldest carpet or rug in the room which you use most at home during the day? , — TICK ONE BOX ONLY

- a) less than one year 1 ☐
- b) 1-5 years old 2 ☐
- c) more than 5 years old 3 ☐

47 On what floor is the room which you use most at home during the day? ☐☐
(The lowest floor of a building is 00)

48. Does your bedroom	NO	YES
48.1 have fitted carpets covering the whole floor?	☐	☐
48.2 contain rugs?	☐	☐
48.3 have double glazing?	☐	☐

49 How old is the oldest carpet or rug in your bedroom — TICK ONE BOX ONLY

- a) less than one year ☐
- b) 1-5 years old ☐
- c) more than 5 years old ☐

TICK ONE BOX ONLY

50 How old is your mattress
- a) less than one year ☐
- b) 1-5 years old ☐
- c) more than 5 years old ☐

51 What floor of the building is your bedroom on? (lowest=00) ☐☐

	NO	YES
52. Do you sleep with the windows open at night during winter?	☐	☐

IF 'NO' GO TO QUESTION 53, IF 'YES':

52.1 Do you sleep with the windows open — TICK ONE BOX ONLY
- a) all of the time? 1 ☐
- b) sometimes? 2 ☐
- c) only occasionally? 3 ☐

	NO	YES	DK
53. Has there been any water damage to the building or its contents, for example, from broken pipes, leaks or floods?	☐	☐	☐
IF YES	NO	YES	DK
53.1 Has there been any water damage in the last 12 months	☐	☐	☐

	NO	YES
54. ***Within the last 12 months*** have you had wet or damp spots on surfaces inside your home other than in the basement (for example on walls, wall paper, ceilings or carpets)?	☐	☐

	NO	YES	DK
55. Has there ever been any mould or mildew on any surface, other than food, inside the home?	☐	☐	☐

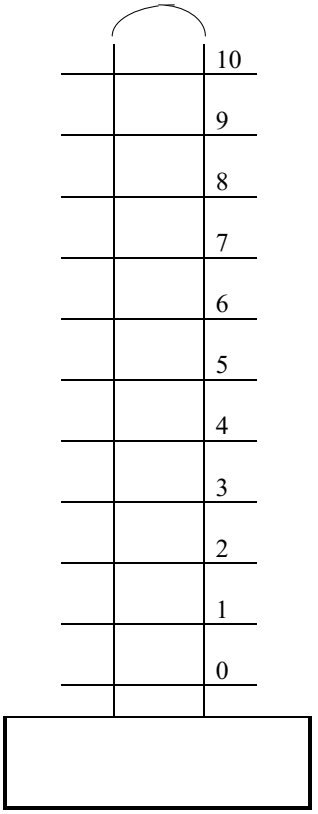
IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 56, IF 'YES':

	NO	YES
55.1.1-6 Which rooms have been affected?		
55.1.1 bathroom(s)	☐	☐
55.1.2 bedroom(s)	☐	☐
55.1.3 living area(s)	☐	☐
55.1.4 kitchen	☐	☐
55.1.5 basement or attic	☐	☐
55.1.6 other: _____	☐	☐

	NO	YES
55.2 Has there been mould or mildew on any surfaces inside the home in the last ***12 months***?	☐	☐

'This scale looks like a thermometer; it allows you to rate your personal opinion regarding the following question on annoyance from air pollution. You can indicate your level of annoyance on this scale between 0 and 10 where 0 mean does not annoy at all' and 10 means intolerable annoyance.'

56 . How much are you annoyed by outdoor air pollution (from traffic, industry, etc.) if you keep the windows open?



THOSE WHO HAVE NOT MOVED HOME SINCE LAST SURVEY (Check with response to question 37)

GO TO QUESTION 58

THOSE WHO HAVE MOVED SINCE LAST SURVEY – answer 57

57. How much were you annoyed by outdoor air pollution (from traffic, industry, etc.) in your previous home, if you kept the windows open?

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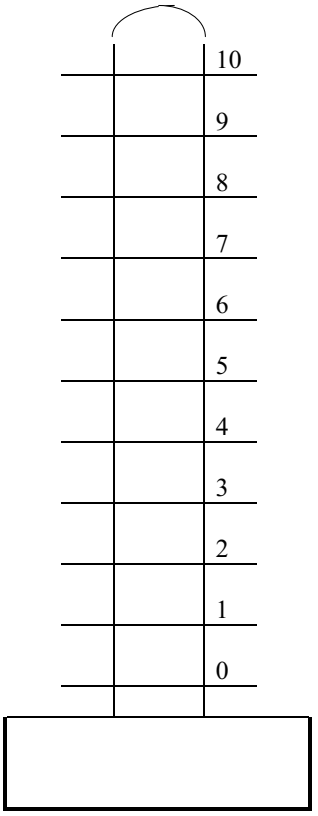

58. How often do cars pass your house? TICK ONE BOX ONLY

a) constantly 1
b) frequently 2
c) seldom 3
d) never 4

59. How often do heavy vehicles (e.g. trucks/buses) pass your house? TICK ONE BOX ONLY

a) constantly 1 ☐
b) frequently 2 ☐
c) seldom 3 ☐
d) never 4 ☐

60. Have you taken any of the following measures to reduce allergen or exposure to allergen in your home since the last survey?

	NO	YES
60.1 changed from carpet to a wooden or other smooth surface on floor of the room you use most	☐	☐
60.2 changed from carpet to a wooden or to a smooth surface on floor of your bedroom	☐	☐
60.3 bought a new carpet for the room you use most	☐	☐
60.4 bought a new carpet for your bedroom	☐	☐
60.5 used antidust-mite sprays	☐	☐
60.6 put an allergy-proof cover on your mattress	☐	☐
60.7 sold, given away or destroyed a pet dog or cat	☐	☐

	NO	YES
61. Do you keep a cat?	☐	☐
IF 'NO' GO TO QUESTION 62, IF 'YES'	NO	YES
61.1 Is your cat (are your cats) allowed inside the house?	☐	☐
61.2 Is your cat (are your cats) allowed in the bedroom?	☐	☐
	NO	YES
62. Do you keep a dog?	☐	☐
IF 'NO' GO TO QUESTION 63, IF 'YES':	NO	YES
62.1 Is your dog (are your dogs) allowed inside the house?	☐	☐
62.2 Is your dog (are your dogs) allowed in your bedroom?	☐	☐
	NO	YES
63. Do you keep any birds?	☐	☐
IF 'NO' GO TO QUESTION 64, IF 'YES':	NO	YES
63.1 Are any of these birds kept inside the house?	☐	☐

	NO	YES	DK
64. Was there a cat in your home?			
64.1 during your first year of life	☐	☐	☐
64.2 when you were aged 1 to 4 years	☐	☐	☐
64.3 when you were aged 5-15 years	☐	☐	☐

	NO	YES	DK
65. Was there a dog in your home?			
65.1 during your first year of life	☐	☐	☐
65.2 when you were aged 1 to 4 years	☐	☐	☐
65.3 when you were aged 5-15 years	☐	☐	☐

	NO	YES	DK
66. Was there a bird in your home?			
66.1. during your first year of life	☐	☐	☐
66.2 when you were aged 1 to 4 years	☐	☐	☐
66.3 when you were aged 5-15 years	☐	☐	☐

67. What term best describes the place you lived most of the time when you were under the age of five years? TICK ONE BOX ONLY

a) farm	1	☐
b) village in a rural area	2	☐
c) small town	3	☐
d) suburb of a city	4	☐
e) inner city	5	☐

68. When you are near animals, such as cats, dogs or horses, do you ***ever***

	NO	YES
68.1 start to cough?	☐	☐
68.2 start to wheeze?	☐	☐
68.3 get a feeling of tightness in your chest?	☐	☐
68.4 start to feel short of breath?	☐	☐
68.5 get a runny or stuffy nose or start to sneeze?	☐	☐
68.6 get itchy or watering eyes?	☐	☐

69. When you are in a dusty part of the house, or near pillows or duvets do you ***ever***

	NO	YES
69.1 start to cough?	☐	☐
69.2 start to wheeze?	☐	☐
69.3 get a feeling of tightness in your chest?	☐	☐
69.4 start to feel short of breath?	☐	☐
69.5 get a runny or stuffy nose or start to sneeze?	☐	☐
69.6 get itchy or watering eyes?	☐	☐

70. When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ***ever***

	NO	YES
70.1 start to cough?	☐	☐
70.2 start to wheeze?	☐	☐
70.3 get a feeling of tightness in your chest?	☐	☐
70.4 start to feel short of breath?	☐	☐
70.5 get a runny or stuffy nose or start to sneeze?	☐	☐
70.6 get itchy or watering eyes?	☐	☐

IF 'YES' TO ANY OF THE ABOVE:

70.7.1-4 Which time of year does this happen?	NO	YES
70.7.1 winter	☐	☐
70.7.2 spring	☐	☐
70.7.3 summer	☐	☐
70.7.4 autumn	☐	☐

71. How often do you eat pre-packaged food, such as tinned food or pre-prepared frozen meals? TICK ONE BOX ONLY

a) every day or most days	1	☐
b) at least once a week	2	☐
c) less than once a week	3	☐

NO YES

72 Do you take snacks between meals? ☐ ☐

IF 'NO' GO TO QUESTION 73, IF 'YES':

72.1.1-3 Which of the following would you have as a snack at least ***once a week***? NO YES

72.1.1 savoury biscuits or crisps ☐ ☐

72.1.2 sweets, chocolates or sweet biscuits ☐ ☐

72.1.3 fruit or vegetables ☐ ☐

73. Have you ever had an illness or trouble caused by eating a ***particular*** food or foods? NO YES ☐ ☐

IF 'NO' GO TO QUESTION 74, IF 'YES':

73.1 Have you nearly always had the same illness or trouble after eating this type of food? NO YES ☐ ☐

***IF 'NO' GO TO QUESTION 74, IF 'YES'*:**

73.1.1 What type of food was this? [List up to 3]

_____ ☐☐

_____ ☐☐

_____ ☐☐

73.1.2.1-6 Did this illness or trouble include NO YES

73.1.2.1 a rash or itchy skin? ☐ ☐

73.1.2.2 diarrhoea or vomiting? ☐ ☐

73.1.2.3 runny or stuffy nose? ☐ ☐

73.1.2.4 severe headaches? ☐ ☐

73.1.2.5 breathlessness? ☐ ☐

73.1.2.6 other: _____ ☐ ☐

NO YES

74. Have you ever smoked for as long as a year? ☐ ☐

['YES' means at least 20 packs of cigarettes or 12 oz (360 grams) of tobacco in a lifetime, or at least one cigarette per day or one cigar a week for one year]

IF 'NO' GO TO QUESTION 75, IF 'YES':

YEARS

74.1 How old were you when you started smoking? ☐☐

NO YES

74.2 Do you **now** smoke, as of ***one month ago***? ☐ ☐

***IF 'NO' GO TO QUESTION 74.3, IF 'YES'*:**

74.2.1-4 How much do you ***now*** smoke on average? NUMBER

74.2.1 number of cigarettes per day ☐☐

74.2.2 number of cigarillos per day ☐☐

74.2.3 number of cigars a week ☐☐

74.2.4 pipe tobacco in a) ounces / week ☐☐

b) grams / week ☐☐☐

NO YES

74.3 Have you stopped or cut down smoking? ☐ ☐

IF 'NO' GO TO QUESTION 74.4, IF 'YES': YEARS

74.3.1 how old were you when you stopped or cut down smoking? ☐☐

74.3.2.1-4 ***on average*** of the entire time you smoked, before you stopped or cut down, how much did you smoke? NUMBER

74.3.2.1 number of cigarettes per day ☐☐

74.3.2.2 number of cigarillos per day ☐☐

74.3.2.3 number of cigars a week ☐☐

74.3.2.4 pipe tobacco in a) ounces / week ☐☐

b) grams / week ☐☐☐

NO YES

74.4 Do you or did you inhale the smoke? ☐ ☐

75. Have you been **regularly** exposed to tobacco smoke in the last ***12 months***? ['Regularly' means on most days or nights] NO YES ☐ ☐

IF 'NO' GO TO QUESTION 76, IF 'YES':

75.1. Not counting yourself, how many people in your household smoke regularly? NUMBER ☐☐

NO YES

75.2 Do people smoke regularly in the room where you work? ☐ ☐

75.3 How many hours per day are you exposed to ***other people's*** tobacco smoke? HOURS ☐☐

75.4 Please provide more information.

How many hours per day, are you exposed to other peoples tobacco smoke in the following locations? HOURS

at home ☐☐

at workplace ☐☐

in bars, restaurants, cinemas or similar social settings ☐☐

elsewhere ☐☐

76. Have you used any **inhaled** medicines to help your breathing at any time in the last ***12 months***? NO YES ☐ ☐

IF NO' GO TO QUESTION 77, IF 'YES':

Which of the following have you used in the last ***12 months***? NO YES

76.1 <u>short acting</u> **beta-2-agonist inhalers** ☐ ☐

(Please include combinations that include beta 2 and steroids in section 76.5)

76.1.1 If used, which one? _____ ☐☐

76.1.2 What type of inhaler do you use? ☐

NUMBER

76.1.3. What is the dose per puff (in micrograms)? ☐☐☐☐

76.1.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐

b) in short courses 2 ☐

c) continuously 3 ☐

d) not at all 4 ☐

If answer to 76.1.4 is <u>when needed</u>: NUMBER

76.1.5 Number of puffs per month ☐☐

If answer to 76.1.4 is <u>in short courses</u> NUMBER

76.1.6 number of courses ☐☐
76.1.7 number of puffs per day ☐☐
76.1.8 average number of days per month ☐☐

If answer to 76.1.4 <u>is continuously</u> NUMBER

76.1.9 number of puffs per day ☐☐

NO YES

76.2 **long acting beta-2-agonist inhalers** ☐ ☐
(Please include combinations that include beta 2 and steroids in section 76.5)

76.2.1 If used, which one? _____ ☐
76.2.2 What type of inhaler do you use? ☐

NUMBER

76.2.3. What is the dose per puff (in micrograms)? ☐☐

76.2.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 76.2.4 is <u>when needed</u>: NUMBER
76.2.5 Number of puffs per month ☐☐

If answer to 76.2.4 is <u>in short courses</u> NUMBER

76.2.6 number of courses ☐☐
76.2.7 number of puffs per day ☐☐
76.2.8 average number of days per month ☐☐

If answer to 76.2.4 is <u>continuously</u> NUMBER

76.2.9 number of puffs per day ☐☐

NO YES

76.3 **non-specific adrenoreceptor agonist inhalers** ☐ ☐

76.3.1 If used, which one? _____ ☐☐

NO YES

76.4 **anti-muscarinic inhalers** ☐ ☐

76.4.1 If used, which one? _____ ☐☐
76.4.2 What type of inhaler do you use? ☐

NUMBER

76.4.3. What is the dose per puff (in micrograms)? ☐☐☐

76.4.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 76.4 .4 is <u>when needed</u>: NUMBER

76.4.5 Number of puffs per month ☐☐

If answer to 76.4.4 is <u>short courses</u> NUMBER

76.4.6 number of courses ☐☐
76.4.7 number of puffs per day ☐☐
76.4.8 average number of days per month ☐☐

If answer to 76.4.4 is <u>continuously</u> NUMBER

76.4.9 number of puffs per day ☐☐

NO YES

76.5 **inhaled steroids** ☐ ☐

(***if combined B2 and steroid please insert inhaled steroid dose***)

76.5.1 If used, which one? _____ ☐☐
76.5.2 What type of inhaler do you use? ☐

NUMBER

76.5.3. What is the dose per puff (in micrograms)? ☐☐☐☐

76.5.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 76.5.4 is <u>when needed</u>: NUMBER

76.5.5 Number of puffs per month ☐☐

If answer to 76.5.4 is in <u>short courses</u> NUMBER

76.5.6 number of courses ☐☐
76.5.7 number of puffs per day ☐☐
76.5.8 average number of days per month ☐☐

If answer to 76.5.4 is <u>continuously</u> NUMBER

76.5.9 number of puffs per day ☐☐

NO YES

76.6 **inhaled cromoglycate/nedocromil** ☐ ☐

76.6.1 If used, which one? _____ ☐☐

NUMBER

76.6.2. What is the dose per puff (in milligrams)? ☐☐

76.6.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 76.6.3 is <u>when needed</u>: NUMBER

76.6.4 Number of puffs per month ☐☐

If answer to 76.6.3 is in <u>short courses</u> NUMBER

76.6.5 number of courses ☐☐
76.6.6 number of puffs per day ☐☐
76.6.7 average number of days per month ☐☐

If answer to 76.6.3 is <u>continuously</u> NUMBER

76.6.8 number of puffs per day ☐☐

NO YES

76.7 **inhaled compounds** ☐ ☐

76.7.1 If used, which one? _____ ☐☐
76.7.2 What type of inhaler do you use? ☐

NUMBER

76.7.3. What is the dose per puff (in micrograms)? ☐☐☐

77. Have you used any **pills**, **capsules**, **tablets** or **medicines**, other than inhaled medicines, to help your breathing at any time in the last ***12 months***? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 78, IF 'YES':
Which of the following have you used in the last ***12 months***?

NO YES

77.1 **oral beta-2-agonists** ☐ ☐

77.1.1 If used, which one? _____ ☐☐
77.1.2 what dose of tablet ☐☐

77.1.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 77.1.3 is <u>when needed</u>: NUMBER

77.1.4 number of tablets per month ☐☐

If answer to 77.1.3 is in <u>short courses</u> NUMBER

77.1.5 number of courses ☐☐
77.1.6 tablets per day ☐☐
77.1.7 average number of days per month ☐☐

If answer to 77.1.3 is <u>continuously</u> NUMBER

77.1.8 tablets per day ☐☐

NO YES

77.2 **oral methylxanthines** ☐ ☐

77.2.1 if used, which one? _____ ☐☐

77.2.2 what dose of tablet ☐☐☐

77.2.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐

b) in short courses 2 ☐

c) continuously 3 ☐

d) not at all 4 ☐

If answer to 77.2.3 is <u>when needed</u>: NUMBER

77.2.4 number of tablets per month ☐☐

If answer to 77.2.3 is in <u>short courses</u> NUMBER

77.2.5 number of courses ☐☐

77.2.6 tablets per day ☐☐

77.2.7 average number of days per month ☐☐

If answer to 77.2.3 is <u>continuously</u> NUMBER

77.2.8 tablets per day ☐☐

NO YES

77.3 **oral steroids** ☐ ☐

77.3.1 If used, which one? _____ ☐☐

77.3.2 what dose of tablet ☐☐.

77.3.3. In the last 12 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐

b) in short courses 2 ☐

c) continuously 3 ☐

If answer to 77.3.3 is <u>when needed</u>: NUMBER

77.3.4 number of tablets per month ☐☐

If answer to 77.3 3 is in <u>short courses</u> NUMBER

77.3.5 number of courses ☐☐

77.3.6 tablets per day ☐☐

77.3.7 average number of days per month ☐☐

If answer to 77.3.3 is <u>continuously</u> NUMBER

77.3.8 tablets per day ☐☐

NO YES

77.3.9. Have you used them in the last ***3 months***? ☐ ☐

NO YES

77.4 oral anti-leukotrienes ☐ ☐

77.4.1 If used, which one? _____ ☐☐
77.4.2 what dose of tablet ☐☐

77.4.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 77.4.3 is <u>when needed</u>: NUMBER
77.4.4 number of tablets per month ☐☐

If answer to 77.4.3 is <u>short courses</u> NUMBER
77.4.5 number of courses ☐☐
77.4.6 tablets per day ☐☐
77.4 .7 average number of days per month ☐☐

If answer to 77.4.3 is <u>continuously</u> NUMBER
77.4.8 tablets per day ☐☐

NO YES

77.5 **ketotifen** ☐ ☐

77.5.1 If used, which one? _____ ☐☐
77.5.2 what dose of tablet ☐

77.5.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 77.5.3 is <u>when needed</u>: NUMBER
77.5.4 number of tablets per month ☐☐

If answer to 77.5.3 is in <u>short courses</u> NUMBER
77.5.5 number of courses ☐☐
77.5.6 tablets per day ☐☐
77.5.7 average number of days per month ☐☐

If answer to 77.5.3 is <u>continuously</u> NUMBER
77.5.8 tablets per day ☐☐

NO YES

78. Since the last survey have you ever used inhaled steroids (show list)? ☐ ☐
IF NO GO TO QUESTION 79 YEARS
78.1. How old were you when you first started to use inhaled steroids? ☐☐

NO YES

78.2. Have you used inhaled steroids ***every year*** since the last survey? ☐ ☐

IF NO GO TO QUESTION 78.3, IF YES MONTHS

78.2.1. On average how many months each year have you taken them? ☐☐

NOW GO TO Q79

78.3 How many of the years since the last survey have you taken inhaled steroids? YEARS ☐☐

78.4. On average how many months of each of these years have you taken them? MONTHS ☐☐

NO YES DK

79. Have you been vaccinated for allergy since the last survey? ☐ ☐ ☐

IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 80, IF 'YES':

NO YES

79.1 Have you been vaccinated for allergy in the last ***12 months***? ☐ ☐

80. Have you had any other **injections** to help your breathing at any time in the last ***12 months***? NO YES ☐ ☐

IF 'NO' GO TO QUESTION 81, IF 'YES':

80.1 What injections? _____ ☐

_____ ☐

81. Have you had any suppositories to help your breathing at any time in the last ***12 months***? NO YES ☐ ☐

IF 'NO' GO TO QUESTION 82, IF 'YES':

81.1 What suppositories? _____ ☐

_____ ☐

82 . Have you used any other **remedies** to help your breathing at any time in the last ***12 months***? NO YES ☐ ☐

***IF 'NO' GO TO QUESTION 83 IF 'YES'*:**

82.1. What remedies? _____ ☐

_____ ☐

_____ ☐

83. Has your doctor ever prescribed medicines, including inhalers, for your breathing? NO YES ☐ ☐

IF 'NO' GO TO QUESTION 84, IF 'YES':

83.1 If you are prescribed medicines for your breathing, do you ***normally*** take TICK ONE BOX ONLY

a) all of the medicine? 1 ☐

b) most of the medicine? 2 ☐

c) some of the medicine? 3 ☐

d) none of the medicine? 4 ☐

83.2 ***When your breathing gets worse***, and you are prescribed medicines for your breathing, do you normally take — TICK ONE BOX ONLY

a) all of the medicine?	1 ☐
b) most of the medicine?	2 ☐
c) some of the medicine?	3 ☐
d) none of the medicine?	4 ☐

83.3 Do you think it is bad for you to take medicines all the time to help your breathing? — NO ☐ YES ☐

83.4 Do you think you should take as much medicine as you need to get rid of ***all*** your breathing problems? — NO ☐ YES ☐

84. Since the last survey have you visited a hospital casualty department or emergency room because of breathing problems? — NO ☐ YES ☐

IF NO GO TO Q85, IF YES

84.1 Have you visited a hospital casualty department or emergency room because of breathing problems in the ***last 12 months***? — NO ☐ YES ☐

IF NO GO TO 85, IF YES — NO ☐ YES ☐

84.1.1 Was this due to asthma, shortness of breath or wheezing?

84.1.2 How many times ***in the last 12 months*?** — TIMES ☐☐

85. Since the last survey have you spent a night in hospital because of breathing problems? — NO ☐ YES ☐

IF NO GO TO Q86 IF YES

85.1 Have you spent a night in hospital because of breathing problems in the ***last 12 months***? — NO ☐ YES ☐

IF NO GO TO Q86, IF YES — NO ☐ YES ☐

85.1.1 Was this due to asthma, shortness of breath or wheezing?

85.1.2 How many nights have you spent on each of the following types of ward in ***the last 12 months?*** — NUMBER

General	☐☐
Chest medicine	☐☐
Rehabilitation	☐☐
Intensive care unit	☐☐
Other	☐☐

86. Since the last survey have you been seen by a doctor because of breathing problems or because of shortness of breath? — NO ☐ YES ☐

IF NO GO TO Q87, IF YES

86.1 Have you been seen by a general practitioner because of breathing problems or shortness of breath in the ***last 12 months?*** — NO ☐ YES ☐

IF NO GO TO Q86.4, IF YES — NO ☐ YES ☐

86.2.Was this due to asthma, shortness of breath or wheezing?

86.3 How many times have you been seen by your general practitioner because of breathing problems or shortness of breath in each of these locations over the last 12 months?

	NUMBER
at home (excluding emergency visits)	
in his surgery	
at home in an emergency	
at another location	

86.4 Have you seen a specialist (chest physician, allergy specialist, internal medicine specialist, ENT doctor) because of your breathing problems or shortness of breath ***in the last 12 months***?

NO ☐ YES ☐

IF NO GO TO Q87 IF YES

86.4.1 How many times? NUMBER ☐☐

87. Are you given regular appointments to be seen by a doctor (or nurse) for your asthma, wheezing or shortness of breath?

NO ☐ YES ☐

IF NO GO TO Q88 IF YES

87.1.Are you given regular appointments with a hospital doctor? NO ☐ YES ☐

87.2 Are you given regular appointments with your general practitioner? NO ☐ YES ☐

87.3. Are you given regular appointments with a nurse? NO ☐ YES ☐

88. How many times have you visited the following because of breathing problems or shortness of breath ***in the last 12 months?***

	NUMBER
88.1 nurse	
88.2 physiotherapist	
88.3 practitioner of 'alternative' medicine	

89. Have you had any clinical or laboratory tests because of asthma wheezing or shortness of breath ***in the last 12 months***?

NO ☐ YES ☐

IF NO GOT Q90 ,IF YES

89.1. How many times have you had the following ***in the last 12 months?***

	NUMBER
Breathing test in a laboratory specially for lung function measures	
Skin test for allergy	
Blood test for allergy	
x-rays	

90. Are you currently working? NO ☐ YES ☐

IF NO GO TO Q90.2 IF YES

90.1. How many days of work have you lost because of asthma, shortness of breath or wheezing in the last **12 months?** NUMBER ☐☐☐

90.2. Were you forced to **give up working** because of asthma, wheezing or shortness of breath in the last **12 months?** NO ☐ YES ☐

IF NO GO TO 91. IF YES DAY MONTH YEAR
91.2.1. When? ☐☐ ☐☐ ☐☐

91. Have there been any days when you have had to **give up activities other than work** (e.g. looking after children, the house, studying) because of your asthma, wheezing or shortness of breath in the ***last 12 months?*** NO ☐ YES ☐

IF NO YOU HAVE FINISHED THE QUESTIONNAIRE IF YES
91.2. How many days on average each month? ☐☐

M F
Subjects Gender ☐ ☐

DAY MONTH YEAR
Subjects Date of Birth ☐☐ ☐☐ ☐☐

INTERVIEW TYPE? TICK ONE BOX ONLY
a) At centre face to face 1 ☐
b) At home face to face 2 ☐
c) By telephone 3 ☐
d) Self completed at home 4 ☐

END FIELDWORKER NUMBER ☐

ECRHS III MAIN Q - MAY VERSION

Centre number
Personal number
Sample
Date

You were last seen as part of this survey in _____ (month) _____ (year)

I AM GOING TO ASK YOU SOME QUESTIONS. AT FIRST THESE WILL BE MOSTLY ABOUT YOUR BREATHING. WHEREVER POSSIBLE, I WOULD LIKE YOU TO ANSWER 'YES' OR 'NO'.

1. Have you had wheezing or whistling in your chest at any time in the last ***12 months***? NO YES

IF 'NO' GO TO QUESTION 2, IF 'YES':

1.1 Have you been at all breathless when the wheezing noise was present? NO YES

1.2. Have you had this wheezing or whistling when you did ***not*** have a cold? NO YES

1.3 How old were you when you first had wheezing or whistling in your chest? YEARS
(If started 'as a baby' enter '01')

1.4 How frequently have you had wheezing or whistling in the last 12 months? TICK ONE BOX ONLY
- everyday 1
- at least once a week, but not everyday 2
- occasionally 3

2. Have you woken up with a feeling of tightness in your chest at any time in the last ***12 months***? NO YES

3. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last ***12 months***? NO YES

IF 'NO' GO TO QUESTION 4, IF 'YES':

3.1 How old were you when you first had an attack of shortness of breath that came on during the day when you were at rest? YEARS

4. Have you had an attack of shortness of breath that came on ***following*** strenuous activity at any time in the last ***12 months***? NO YES

5. Have you been woken by an attack of shortness of breath at any time in the last ***12 months?*** NO YES

6. Have you been woken by an attack of coughing at any time *in the last* ***12 months***? NO YES

7. How often have you experienced bouts or spasms of coughing in the last 12 months? TICK ONE BOX ONLY
- less than once a month 1
- every month, but less than every week 2
- every week, but not every day 3
- every day 4

NO YES

8. Do you ***usually*** cough first thing in the morning in the winter? ☐☐
[IF DOUBTFUL, USE QUESTION 9.1 TO CONFIRM]

NO YES

9. Do you ***usually*** cough during the day, or at night, in the winter? ☐☐

IF 'NO' GO TO QUESTION 10, IF 'YES':

9.1 Do you cough like this on most days for as much as three months each year? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 10, IF 'YES':

9.2 How many years have you had this problem (coughing on most days for as much as three months each year? YEARS ☐☐

10. Do you ***usually*** bring up any phlegm from your chest first thing in the morning in the winter? NO ☐ YES ☐
[IF DOUBTFUL, USE QUESTION 11.1 TO CONFIRM]

11. Do you ***usually*** bring up any phlegm from your chest during the day, or at night, in the winter? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 12, IF 'YES':

11.1 Do you bring up phlegm like this on most days for as much as three months each year? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 12, IF 'YES':

11.2 How many years have you had this problem (of bringing up phlegm from your chest on most days for as much as three months each year)? YEARS ☐☐

IF 'NO' TO QUESTIONS <u>3-11</u> GO DIRECT TO QUESTION 13;
IF 'YES' TO ANY OF QUESTIONS <u>3-11</u> PLEASE COMPLETE QUESTION 12

12. In the last ***12 months***, have you had any episodes/times when your symptoms (cough, phlegm, shortness of breath) were a lot worse than usual? NO ☐ YES ☐

IF 'NO' TO QUESTION 12 GO TO QUESTION 13; IF 'YES'

In the last ***12 months***:

12.1 How many times have these episodes occurred? TIMES ☐☐

12.2 How many times have these episodes forced you to consult your doctor? TIMES ☐☐

12.3 How many times was your therapy changed after these episodes? TIMES ☐☐

12.4 How many times have you visited a hospital casualty department or emergency room or have you spent a night in hospital after these episodes? TIMES ☐☐

NO YES

13. Do you ever have trouble with your breathing? ☐☐

IF 'NO' GO TO QUESTION 14, IF 'YES':

13.1 Do you have this trouble TICK ONE BOX ONLY

a) continuously so that your breathing is never quite right?	1	☐
b) repeatedly, but it always gets completely better?	2	☐
c) only rarely?	3	☐

14. Are you disabled from walking by a condition ***other than*** heart or lung disease? NO ☐ YES ☐

IF 'YES' STATE CONDITION _____ AND GO TO QUESTION 15, IF 'NO':

14.1 Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 14.2, IF 'YES':

14.1.1 Do you get short of breath walking with other people of your own age on level ground? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 14.2, IF 'YES':

14.1.1.1 Do you have to stop for breath when walking at your own pace on level ground? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 14.2, IF 'YES':

14.1.1.1.1 Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 14.2, IF 'YES':

14.1.1.1.1.1 Are you too short of breath to leave the house OR short of breath on dressing or undressing? NO ☐ YES ☐

14.2 How much shortness of breath are you having right now? Please indicate by marking the height of the column. If you are not experiencing any shortness of breath at present circle the marker at the bottom of the column

☐☐☐

Height in mm
(NB total height =100mm)

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15. Have you ever had asthma? NO YES

IF 'NO' GO TO QUESTION 16, IF 'YES':

15.1 Was this confirmed by a doctor? NO YES

15.2 How old were you when your asthma was confirmed by a doctor? YEARS

15.3 How old were you when you had your first attack of asthma? YEARS

15.4 How old were you when you had your most recent attack of asthma? YEARS

15.5.1-6 Which months of the year do you usually have attacks of asthma?

	NO	YES
15.5.1 January / February		
15.5.2 March / April		
15.5.3 May / June		
15.5.4 July / August		
15.5.5 September / October		
15.5.6 November / December		

15.6 Have you had an attack of asthma in the last ***12 months***? NO YES

IF 'NO' GO TO 15.9, IF YES

15.7 How many attacks of asthma have you had in the last ***12 months***? ATTACKS

15.8 How many attacks of asthma have you had in the last ***3 months***? ATTACKS

15.9 How many times have you woken up because of your asthma in the last ***3 months?*** TICK ONE BOX ONLY

every night or almost every night	1
more than once a week, but not most nights	2
at least twice a month, but not more than once a week	3
less than twice a month	4
not at all	5

15.10. How often have you had trouble with your breathing because of your asthma in the last ***3 months?*** TICK ONE BOX ONLY

continuously	1
about once a day	2
at least once a week, but less than once a day	3
less than once a week	4
not at all	5

15.11 Are you currently taking any medicines including inhalers, aerosols or tablets for asthma? NO YES

15.12 Do you have a peak flow meter of your own? NO YES

IF 'NO' GO TO QUESTION 15.13 , IF 'YES':

15.12.1 How often have you used it over the last 3 months? TICK ONE BOX ONLY

never	1
some of the days	2
most of the days	3

15.13 Do you have written instructions from your doctor on how to manage your asthma if it gets worse or if you have an attack? NO ☐ YES ☐

16. Has a doctor ever told you that you have chronic bronchitis? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 17, IF 'YES':

16.1 How old were you when you first had a diagnosis of chronic bronchitis? YEARS ☐☐

17. Has a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 18, IF 'YES

17.1 How old were you when you first had a diagnosis of COPD? YEARS ☐☐

18. Has a doctor ever told you that you have emphysema? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 19, IF 'YES':

18.1 How old were you when you first had a diagnosis of emphysema? YEARS ☐☐

19. Have you ever been diagnosed with any **other** lung disease (excluding asthma, chronic bronchitis, COPD and emphysema)? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 20, IF 'YES':

19.1 What is that lung disease called?_____ CODE ☐☐

20. Do you have any nasal allergies, including hay fever? NO ☐ YES ☐

IF 'NO' GO TO Q21, IF' YES':

20.1 How old were you when you first had hay fever or nasal allergy? YEARS ☐☐

21. Have you ***ever*** had a problem with sneezing, or a runny or a blocked nose when you did not have a cold or the flu? NO ☐ YES ☐

IF 'NO' GO TO Q22, IF 'YES':

21.1. Have you had a problem with sneezing or a runny or a blocked nose when you did not have a cold or the flu ***in the last 12 months***? NO ☐ YES ☐

IF 'NO' GO TO Q22, IF' YES':

21.1.1. Has this nose problem been accompanied by itchy or watery eyes? NO ☐ YES ☐

21.1.2. In which months of the year did this nose problem occur? NO YES

21.1.2.1. January/February	☐	☐
21.1.2.2. March/April	☐	☐
21.1.2.3. May/June	☐	☐
21.1.2.4. July/August	☐	☐
21.1.2.5. September/October	☐	☐
21.1.2.6 November/December	☐	☐

NO YES

21.1.3 Have you had this problem for **more than 4 days in any one week** in the last 12 months? ☐ ☐

IF 'NO' GO TO Q21.1.4, IF' YES':

NO YES

21.1.3.1 Did this happen for **more than 4 weeks consecutively?** ☐ ☐

21.1.4. For **each** of the following problems, please indicate how important it has been ***over the last 12 months***. *(SHOW A CARD WITH THE FOLLOWING OPTIONS)*

1. No problem (symptom not present)
2. A problem that is/was present but not disturbing
3. A disturbing problem but not hampering day time activities or sleep
4. A problem that hampers certain activities or sleep

		CODE ***Please enter code 1-4 in each of the five boxes***
21.1.4.1	a watery runny nose	☐
21.1.4.2	a blocked nose (feeling of being unable to breath through your nose)	☐
21.1.4.3	an itchy nose	☐
21.1.4.4	sneezing, especially violent and in bouts	☐
21.1.4.5	watery, red itchy eyes	☐

NO YES

22. ***Since the last survey*** have you used any medication to treat nasal disorders? ☐ ☐

IF NO GO TO Q23, IF YES

NO YES

22.1 Have you used any of the following nasal sprays for the treatment of your nasal disorder? **{SHOW LIST OF STEROID NASAL SPRAYS**} ☐ ☐

IF NO GO TO Q22.2, IF YES

YEARS

22.1.1 How old were you when you first started to use **this sort of nasal spray**? ☐☐

YEARS

22.1 2 How many years have you been taking this sort of nasal spray? ☐☐

NO YES

22.1.3 Have you used any of these nasal sprays ***in the last 12 months?*** ☐ ☐

NO YES

22.1.4. Have you used this sort of nasal spray ***every year*** in the last 5 years? ☐ ☐

IF 'NO' GO TO QUESTION 22.2 IF 'YES'

MONTHS

22.1.4.1 On average how many months each year have you taken them ? ☐☐

NO YES

22.2 Have you used any of the following pills, capsules, or tablets for the treatment of your nasal disorder? **{SHOW LIST OF ANTIHISTAMINES**} ☐ ☐

IF 'NO' GO TO Q23, IF 'YES'

NO YES

22.2.1 Have you used any of these pills, capsules or tablets in the last 12 months**?** ☐ ☐

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23. Has your nose been blocked **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

24. Have you had pain or pressure around the forehead, nose or eyes **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

25. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

26. Has your sense of smell been reduced or absent **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

27. Has a doctor ***ever*** told you that you have

	NO	YES
27.1.1 **chronic** sinusitis?	☐	☐
27.1.2 nasal polyps?	☐	☐

IF 'NO' TO Q27.1 and 27.2 GO TO Q 28, IF 'YES'

	YEARS
27.2 How old were you when a doctor told you had chronic sinusitis?	☐☐
27.3 How old were you when a doctor told you had nasal polyps?	☐☐

(enter 00 if question not applicable)

28. Have you ***ever*** had eczema or any kind of skin allergy? NO ☐ YES ☐

IF 'NO' TO Q28 GO TO Q 29, IF 'YES'

28.1 How old were you when you first had eczema or skin allergy? YEARS ☐☐

28.2 Did/does your eczema or skin allergy affect your hands? NO ☐ YES ☐

28.3 Have you noticed that contact with certain materials, chemicals or anything else **in your work** makes your eczema worse? NO ☐ YES ☐ DON'T KNOW ☐

29. Have you ***ever*** had an itchy rash that was coming and going for at ***least 6 months***? NO ☐ YES ☐

***IF 'NO' GO TO QUESTION 30, IF 'YES'*:** NO ☐ YES ☐

29.1.. Have you had this itchy rash ***in the last 12 months?***

IF 'NO' GO TO QUESTION 30, IF 'YES':

29.1.1. Has this itchy rash ***at any time*** affected any of the following places:

	NO	YES
the folds of the elbows, behind the knees, in front of the ankles	☐	☐
under the buttocks or around the neck, ears or eyes	☐	☐
29.1.2 Has this itchy rash affected your hands at any time in the last 12 months?	☐	☐

30. What was the highest level of education your mother had? TICK ONE BOX ONLY

a) Up to the minimum school leaving age	☐ 1
b) Secondary school/technical school past the minimum age	☐ 2
c) College or University	☐ 3

31. What was the highest level of education your father had? TICK ONE BOX ONLY

a) Up to the minimum school leaving age	☐ 1
b) Secondary school/technical school past the minimum age	☐ 2
c) College or University	☐ 3

32. Were you delivered by Caesarean section? NO ☐ YES ☐ DK ☐

33. Is your biological mother still alive? NO ☐ YES ☐ DK ☐

IF 'NO' GO TO QUESTION 33.2

IF 'DON'T KNOW'' GO TO QUESTION 34, IF 'YES':

33.1 How old is your mother now? YEARS ☐☐

NOW GO TO QUESTION 34

33.2 How old was your mother when she died ? YEARS ☐☐

34. Is your biological father still alive? NO ☐ YES ☐ DK ☐

IF 'NO' GO TO QUESTION 34.2

IF 'DON'T KNOW'' GO TO QUESTION 35, IF 'YES':

34.1 How old is your father now? YEARS ☐☐

NOW GO TO QUESTION 35

34.2 How old was your father when he died? YEARS ☐☐

35. Did your biological parents ever suffer from any of the following?

	MOTHER NO	MOTHER YES	MOTHER DK		FATHER NO	FATHER YES	FATHER DK
35.1.1 Asthma	☐	☐	☐	35.1.2	☐	☐	☐
35.2.1 Chronic bronchitis, emphysema and/or COPD	☐	☐	☐	35.2.2	☐	☐	☐
35.3.1 Heart disease	☐	☐	☐	35.3.2	☐	☐	☐
35.4.1 Hypertension	☐	☐	☐	35.4.2	☐	☐	☐
35.5.1 Stroke	☐	☐	☐	35.5.2	☐	☐	☐
35.6.1 Diabetes	☐	☐	☐	35.6.2	☐	☐	☐

36. How many children do you have? NUMBER ☐☐

IF ANSWER TO Q36 INDICATES PARTICIPANT HAS CHILDREN GO TO Q36.1; If NO CHILDREN GO TO QUESTION 37

	Please start with first born	Year of birth (eg 1995)				Did this child have asthma before the age of ten years?		Did this child have asthma after the age of ten years?		Has this child ever had nasal allergies, including hay fever?		Has this child ever had eczema or atopic dermatitis?		Was this child a boy or girl (Boy=1, Girl=2)
						NO	YES	NO	YES	NO	YES	NO	YES	Sex
36.1	Child 1													
36.2	Child 2													
36.3	Child 3													
36.4	Child 4													
36.5	Child 5													
36.6	Child 6													
36.7	Child 7													
36.8	Child 8													

ECRHS III MAIN Q - MAY VERSION

You took part in the last survey in **[month]** in **[year]**. At that time you described your job as **['current' job from last occupational matrix]**

37. I would like to ask you to list all jobs that you have had since the last survey. I am interested in each one of the jobs that you have done for three months or more. These jobs may be outside the house or at home, **excluding homemaking or housework**, full time or part time, paid or unpaid, including self employment, for example in a family business. Please include part time jobs only if you had been doing them for 20 or more hours per week. Please start with your current or last held job.

Job	Occupation – Job Title: *Please provide a detailed description of the job*	Industry / Branch: *What does (did) your firm or employer make or what services does (did) it provide?*	Start month		Start year				End month		End year *(If current job please enter CURRENT)*			
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														

IF JOBS ARE GIVEN GO TO QUESTION 37.1; IF NO JOBS GIVEN GO TO Q38

NO YES

37.1 Have you had to change or leave any of these jobs because it affected your breathing? ☐ ☐

IF 'NO' GO TO QUESTION 38; IF 'YES':

37.1.1-10 Please indicate which job(s) you had to change or leave (use numbers from question 37).

	NO	YES
37.1.1 Job 1	☐	☐
37.1.2 Job 2	☐	☐
37.1.3 Job 3	☐	☐
37.1.4 Job 4	☐	☐
37.1.5 Job 5	☐	☐
37.1.6 Job 6	☐	☐
37.1.7 Job 7	☐	☐
37.1.8 Job 8	☐	☐
37.1.9 Job 9	☐	☐
37.1.10 Job 10	☐	☐

38. What best describes your current main activity? TICK ONE BOX ONLY

Employed (including employed by temping agencies)	1	☐
Self-employed (entrepreneur, freelance or other)	2	☐
Full time student	3	☐
Full time housewife/househusband	4	☐
Unemployed looking for work	5	☐

Unemployed not looking for work	6	☐
Retired	7	☐
Other	8	☐

IF NOT 'EMPLOYED' OR NOT 'SELF-EMPLOYED' GO TO QUESTION 38.1
IF 'EMPLOYED' OR SELF-EMPLOYED' GO TO QUESTION 38.2;

38.1 Were you forced to give up working all together because of asthma, wheezing shortness of breath or other respiratory or lung problems? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 39, IF 'YES':

38.1.1 When did this occur? MONTH ☐☐ YEAR ☐☐☐☐

NOW GO TO QUESTION 39

38.2 In your current job, are you regularly exposed to vapours, gas, dust or fumes? NO ☐ YES ☐

38.3 . Does being at your current workplace ever cause breathing problems (chest tightness,wheezing, coughing)? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 38.4 , IF 'YES':

38.3.1-5 Can you indicate what gives you breathing problems in your current workplace?

	NO	YES
38.3.1 Physical exertion	☐	☐
38.3.2 Exposure to mist, hot or cold temperature	☐	☐
38.3.3 Exposure to vapours gas dust or fumes	☐	☐
38.3.4 Other peoples cigarette smoke	☐	☐
38.3.5 Stress	☐	☐

38.3.6 Do these breathing problems diminish or stop during the weekend or during holidays? NO ☐ YES ☐

38.4. Within the last 12 months have there been wet or damp spots on surfaces in the room where you usually work (for example on walls, wall paper, ceilings or carpets)? NO ☐ YES ☐

38.5. Within the last 12 months has there been mould or mildew on any surfaces in the room where you usually work? NO ☐ YES ☐

38.6. At any time in the last 12 months have you noticed the odour of mould or mildew (not from food) in the room where you usually work? NO ☐ YES ☐

38.7. Do you regularly use cleaning products or disinfectants in your current job? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 39, IF 'YES':

38.7.1-13 In the last 12 months, on how many days a week have you used the following products at work? (SHOW CARD WITH FOLLOWING OPTIONS)

1. Never
2. <1 day/week
3. 1-3 days/week
4. 4-7 days/week

CODE
Enter code 1-4 for all boxes

38.7.1 Bleach
38.7.2 Ammonia
38.7.3 Stain removers or other solvents
38.7.4 Acids (including decalcifiers, liquid scale removers, vinegar, hydrochloric acid, …)
38.7.5 Floor polish or floor wax
38.7.6 Liquid or solid furniture polish or wax
38.7.7 Furniture sprays (atomisers or aerosols)
38.7.8 Sprays for mopping the floor
38.7.9 Glass cleaning sprays (atomisers or aerosols)
38.7.10 Degreasing sprays including oven cleaning sprays (atomisers or aerosols)
38.7.11 (Ethyl) alcohol
38.7.12 Soaps or foams or any other chemical product for disinfecting hands
38.7.13 Any other chemical disinfectant (for example, glutaraldehyde, formaldehyde, chloramine-T, quaternary ammonium compounds)

NO YES

39 Have you ever been involved in an incident at home, work or elsewhere that exposed you to high levels of vapours, gases, dusts or fumes?

IF 'NO' GO TO QUESTION 40, IF 'YES':

YEAR

39.1 When did this occur?

In case of more than one incident, please report on the most recent incident.

39.2. Could you please classify this incident — TICK ONE BOX ONLY

A fire or an explosion	1
A leakage or spill	2
An inhalation related to mixing of cleaning products	3
Something else	4

39.3. Where did this happen? — TICK ONE BOX ONLY

In your own home	1
In your workplace	2
Somewhere else indoors	3
Outdoor	4

NO YES

39. 4 Did you experience respiratory symptoms within 24 hours following this incident?

IF 'NO' GO TO QUESTION 40, IF 'YES':

NO YES

39.4.1 Did you seek medical treatment for these symptoms?

40. How often do you usually exercise so much that you get out of breath or sweat ? — TICK ONE BOX ONLY

every day	1
4-6 times a week	2
2-3 times a week	3
once a week	4
once a month	5
less than once a month	6

never 7 ☐

41. How many hours a week do you usually exercise so much that you get out of breath or sweat? TICK ONE BOX ONLY

none	1 ☐
about ½ hr	2 ☐
about 1 hour	3 ☐
about 2-3 hours	4 ☐
about 4-6 hours	5 ☐
7 hours or more	6 ☐

	NO	YES
42. Do you avoid taking vigorous exercise because of breathing problems?	☐	☐

43. When was your present home built? YEAR ☐☐☐☐

44. How many years have you lived in your current home? YEARS ☐☐

45. Which best describes the building in which you live? TICK ONE BOX ONLY

a) a one family house detached from any other house?	2 ☐
b) a one family house attached to one or more houses?	3 ☐
c) a building for two families?	4 ☐
d) a building for three or four families?	5 ☐
e) a building for five or more families?	6 ☐
f) other: _____	8 ☐

NB THERE IS NO CODE 1 and NO CODE 7

46. How many rooms does your home have? (exclude kitchen, bathroom, toilet, laundry) NUMBER ☐☐

47. How many people live in your home? NUMBER ☐☐

48 Does your home have any of the following?	NO	YES
48.1 central heating	☐	☐
48.2 ducted air heating (forced air heating)	☐	☐
48.3 air conditioning	☐	☐

49. Which of the following appliances do you use for heating or for hot water?	NO	YES
49.1 open coal, coke or wood fire	☐	☐
49.2 open gas fire	☐	☐
49.3 electric heater	☐	☐
49.4 paraffin heater	☐	☐
49.5 gas-fired boiler(located inside the home)	☐	☐
49.6 oil-fired boiler	☐	☐
49.7 portable gas heater	☐	☐
49.8 gas fired boiler (located outside the home eg: balcony)	☐	☐
49.9 fully enclosed wood/coal burning stove	☐	☐
49.10 other: _____	☐	☐

50. What kind of stove do you ***mostly*** use for cooking? TICK ONE BOX ONLY

a) coal, coke or wood (solid fuel)?	1 ☐
b) gas (gas from the mains)?	2 ☐
c) electric?	3 ☐
d) paraffin (kerosene)?	4 ☐
e) microwave	5 ☐
f) gas (gas from bottles or other non-mains source)	6 ☐
g) other: _____	7 ☐

50.1 IF YOU USE GAS FOR COOKING Which of the following do you have? NO YES

50.1.1 gas hob (the area on top for heating for example saucepans) ☐ ☐

50.1 2.gas oven (the enclosed area used, for example, for baking or for roasting) ☐ ☐

MINUTES

51 . ***On average*** how long have you spent cooking with your cooker (hob or oven) ***<u>each day</u>*** over ***<u>the last four weeks</u>***? ☐☐☐

52. ***Over the last four weeks*** when you were cooking did you have a door or window to the outside air open TICK ONE BOX ONLY

a) most of the time 1 ☐

b) some of the time 2 ☐

c) rarely (or only occasionally) 3 ☐

d) I do not have a door or window that opens to the outside in my kitchen 4 ☐

e) never 5 ☐

NO YES DK

53. Do you have an extractor fan over the cooker? ☐ ☐ ☐

***IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 54, IF 'YES'*:**

53.1 When cooking, do you use the fan TICK ONE BOX ONLY

a) all of the time? 1 ☐

b) some of the time? 2 ☐

c) none of the time? 3 ☐

NO YES DK

53.2 Does the fan take the fumes outside the house? ☐ ☐ ☐

54. Has there been any water damage to the building or its contents, for example, from broken pipes, leaks or floods? NO ☐ YES ☐ DK ☐

***IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 55, IF 'YES'*:** NO YES DK

54.1 Has there been any water damage in the last 12 months? ☐ ☐ ☐

55. ***Within the last 12 months*** have you had wet or damp spots on surfaces inside your home other than in the basement (for example on walls, wall paper, ceilings or carpets)? NO ☐ YES ☐

56. Has there ever been any mould or mildew on any surface, other than food, inside the home? NO YES DK ☐ ☐ ☐

IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 57, IF 'YES'

56.1. Has there ever been any mould or mildew on any surface inside the home in the last ***12 months***? NO YES DK ☐ ☐ ☐

***IF 'NO' OR 'DON'T KNOW' GO TO QUESTION 57, IF 'YES'*:**

56.1.1-6 Which rooms have been affected? NO YES

56.1.1 bathroom(s) ☐ ☐

56.1.2 bedroom(s) ☐ ☐

56.1.3 living area(s) ☐ ☐

56.1.4 kitchen ☐ ☐

56.1.5 basement or attic ☐ ☐

56.1.6 other: _____ ☐ ☐

NO YES

57. Have you noticed the odour of mould or mildew (not from food) in your home at any time in the last 12 months? ☐ ☐

58. Does the room which you use most at home during the day — NO / YES
- 58.1 have fitted carpets covering the whole floor?
- 58.2 contain rugs?
- 58.3 have double glazing/triple glazing?
- 58.4 have visible wet or damp spots?
- 58.5 have an airbrick or open chimney?

59. On what floor is the room which you use most at home during the day? — FLOOR
(Basement = 00 ,Ground floor=1, First floor=2, Second floor=3 etc)

60. Does your bedroom — NO / YES
- 60.1 have fitted carpets covering the whole floor?
- 60.2 contain rugs?
- 60.3 have double glazing/triple glazing
- 60.4 have visible wet or damp spots
- 60.5 have an airbrick or open chimney
- 60.6 have radiators that are the main source of room heating
- 60.7 get condensation on the window especially in the winter

61. On what floor is the room in which you sleep? — FLOOR
(Basement = 00 ,Ground floor=1, First floor=2, Second floor=3 etc)

62 How old is the mattress you currently sleep on?? — YEARS

63. Do you sleep with the windows open at night during winter? — NO / YES

IF 'NO' GO TO QUESTION 64, IF 'YES':

63.1 Do you sleep with the windows open — TICK ONE BOX ONLY
- a) all of the time? 1
- b) sometimes? 2
- c) only occasionally? 3

64. Do you keep a cat? — NO / YES

IF 'NO' GO TO QUESTION 65, IF 'YES' — NO / YES
- 64.1 Is your cat (are your cats) allowed inside the house?
- 64.2 Is your cat (are your cats) allowed in the bedroom?

65. Do you keep a dog? — NO / YES

IF 'NO' GO TO QUESTION 66, IF 'YES': — NO / YES
- 65.1 Is your dog (are your dogs) allowed inside the house?
- 65.2 Is your dog (are your dogs) allowed in your bedroom?

66. Do you keep any birds? — NO / YES

IF 'NO' GO TO QUESTION 67, IF 'YES': — NO / YES
- 66.1 Are any of these birds kept inside the house?

67. In the last 12 months, how often have you done any of the cleaning in your own home? — TICK ONE BOX ONLY
- a) Never 1
- b) On less than 1 day per week 2
- c) On 1 to 3 days per week 3
- d) On 4 to 7 days per week 4

IF 'NEVER' GO TO 68, IF 'EVER':

67.1 In the last 12 months, on how many days a week have you personally used the following cleaning products in your own home? (SHOW CARD WITH FOLLOWING OPTIONS)

1. Never
2. <1 day/week
3. 1-3 days/week
4. 4-7 days/week

CODE
Enter code 1-4 for all boxes

67.1.1 Bleach *(NOT bleach used for laundry)*
67.1.2 Ammonia
67.1.3 Stain removers or other solvents
67.1.4 Acids (including decalcifiers, liquid scale removers, vinegar, hydrochloric acid, …)
67.1.5 Floor polish or floor wax
67.1.6 Liquid or solid furniture polish or wax
67.1.7 Furniture sprays (atomisers or aerosols)
67.1.8 Sprays for mopping the floor
67.1.9 Glass cleaning sprays (atomisers or aerosols)
67.1.10 Degreasing sprays including oven cleaning sprays (atomisers or aerosols)

68. How often are the following used in your home? (SHOW CARD WITH FOLLOWING OPTIONS)

1. Never
2. <1 day/week
3. 1-3 days/week
4. 4-7 days/week

CODE
Enter code 1-4 for all boxes

68.1 Liquid or solid perfumes or scents
68.2 Plug-in or other **electric** air fresheners
68.3 Air refreshing sprays (atomisers or aerosols)

IF NEVER USE AIR FRESHENER SPRAYS GO TO QUESTION 69: IF USE AIR FRESHENER CODE
Enter code 1-4

68.4 How often do you use air freshening sprays(atomisers or aerosols) **yourself** inside your home?

69. How often are the following used in your home? (SHOW CARD WITH FOLLOWING OPTIONS)

1. Never
2. Sporadically
3. Depending on the season
4. The whole year round

CODE
Enter code 1-4 for all boxes

69.1 Insecticides or other pesticides in powder form
69.2 Plug-in or other **electric** insecticides/pesticides
69.3 Insecticides or other pesticides in spray form

IF NEVER USE SPRAY INSECTICIDES GO TO QUESTION 70:IF USE SPRAY INSECTICIDES CODE
Enter code 1-4

69. 4 How often do you use insecticides or other pesticides in spray form **yourself** inside your home?

ECRHS III MAIN Q - MAY VERSION

70. We would like to know where you have lived since January 1990.

Please give the address, including postcode, of all homes you have lived in **for at least one year since 1990, starting with your current address**

House number	Street name	City	Postcode	Moved in	Lived there until (YEAR)
					current

All centres please note: this information will be used for your centre staff to geocode residence.
Please do not attempt to send these data to the coordinating centre.

The variables needed within each centre ultimately will be (rh=residential history)

rh70.1.1 CURRENT Year moved in
rh70.1.2 CURRENT Year moved out
rh70.1.3 CURRENT Geocode
rh70.2.1 HOUSE 1 Year moved in
rh70.2.2 HOUSE 1 Year moved out
rh70.2.3 HOUSE 1 Geocode

Further instructions will follow

70.1 How often do cars pass your house? TICK ONE BOX ONLY

a) more than 80 per hour	1 ☐
b) between 21 and 80 per hour	2 ☐
c) between 5 and 20 per hour	3 ☐
d) less than 5 per hour	4 ☐

70.2 How often do heavy vehicles (trucks/buses) pass your house? TICK ONE BOX ONLY

a) more than 80 per hour	1 ☐
b) between 21 and 80 per hour	2 ☐
c) between 5 and 20 per hour	3 ☐
d) less than 5 per hour	4 ☐

71. How many days per week do you commute to work — NUMBER ☐

IF '0' GO TO QUESTION 72; IF ONE OR MORE DAYS

71.1 On average, how much time do you spend travelling to and from work each day (total for both directions)? — MINUTES ☐☐☐

71.2 What is your main method of commuting? TICK ONE BOX ONLY

a) Walking or cycling	1 ☐
b) In a private car	2 ☐
c) Bus	3 ☐
d) Train	4 ☐
e) Other	5 ☐

72. Have you ever had an illness or trouble caused by eating a ***particular*** food or foods? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 73, IF 'YES':

72.1 Have you nearly always had the same illness or trouble after eating this type of food? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 73, IF 'YES':

72.2 Was this food any of the following?

	NO	YES
72.2.1 Cow's milk*	☐	☐
72.2.2 Hen's eggs	☐	☐
72.2.3. Fish	☐	☐
72.2.4 Shrimp or Lobster	☐	☐
72.2.5 Peanut	☐	☐
72.2.6 Hazelnut	☐	☐
72.2.7 Walnut	☐	☐
72.2.8 Peach	☐	☐
72.2.9 Apple	☐	☐
72.2.10 Kiwi fruit	☐	☐
72.2.11 Bananas	☐	☐
72.2.12 Melon	☐	☐
72.2.13. Tomato	☐	☐
72.2.14 Celery	☐	☐
72.2.15 Carrot	☐	☐
72.2.16 Soybean	☐	☐
72.2.17 Lentils	☐	☐
72.2.18 Wheat**	☐	☐

72.2.19 Buckwheat		
72.2.20 Corn		
72.2.21 Rice		
72.2.22 Sesame seed		
72.2.23 Mustard seed		
72.2.24 Sunflower seed		
72.2.25 Poppy seed		

* Including other cow's milk products such as butter, cheese, yoghurt, crème fraiche, fromage frais….
** Including wheat products such as bread and breakfast cereals

	NO	YES
72. 3 Have you had any problems eating any other food or foods?		

IF 'NO' GO TO QUESTION 72.4, IF 'YES PLEASE LIST THESE FOODS:

CODE

72.3.1 Food 1_____

CODE

72.3.2 Food 2_____

CODE

72.3.3 Food 3_____

72.4 Please answer each of these questions for the three foods causing the main problems. Please identify the food from the list of foods given (q72.2.1-25). If than three foods are given in the list provide information on foods in 72.3.1-3. Please list in order of the most severe reaction

FOOD ONE

CODE

72.4.1 Please confirm the name of this food _____

72.4.2-11 Did this illness or trouble include	NO	YES
72.4.2 a rash or itchy skin?		
72.4.3 diarrhoea or vomiting?		
72.4.4 runny or stuffy nose?		
72.4.5 severe headaches?		
72.4.6 breathlessness?		
72.4.7 itching, tingling or swelling in the mouth, lips or throat?		
72.4.8 difficulty swallowing?		
72.4.9 fainting or dizziness?		
72.4.10 symptoms so severe you had an emergency injection from a doctor, or had to use an epipen		
72.4.11 other_____		

72.4.12 . How soon after eating this food did you get the first symptoms? TICK ONE BOX ONLY

a) Less than half an hour	1	
b) Half an hour to one hour	2	
c) One hour to two hours	3	
d) Two hours to four hours	4	
e) More than four hours	5	

YEARS

72.4.13 How old were you when you first had this attack?

YEARS

72.4.14 How old were you when you last had this attack?

NUMBER

72.4.15 How many times has this occurred during your life? [ ][ ]

FOOD TWO

CODE

72.5.1 Please confirm the name of this food _____ [ ][ ][ ]

	NO	YES
72.5.2-11 Did this illness or trouble include		
72.5.2 a rash or itchy skin?	☐	☐
72.5.3 diarrhoea or vomiting?	☐	☐
72.5.4 runny or stuffy nose?	☐	☐
72.5.5 severe headaches?	☐	☐
72.5.6 breathlessness?	☐	☐
72.5.7 itching, tingling or swelling in the mouth, lips or throat?	☐	☐
72.5.8 difficulty swallowing?	☐	☐
72.5.9 fainting or dizziness?	☐	☐
72.5.10 symptoms so severe you had an emergency injection from a doctor, or had to use an epipen	☐	☐
72.5.11 other_____	☐	☐

72.5.12 . How soon after eating this food did you get the first symptoms? TICK ONE BOX ONLY

a) Less than half an hour	1 ☐
b) Half and hour to one hour	2 ☐
c) One hour to two hours	3 ☐
d) Two hours to four hours	4 ☐
e) More than four hours	5 ☐

YEARS

72.5.13 How old were you when you first had this attack? [ ][ ]

YEARS

72.5.14 How old were you when you last had this attack? [ ][ ]

NUMBER

72.5.15 How many times has this occurred during your life? [ ][ ]

FOOD THREE

CODE

72.6.1 Please confirm the name of this food _____ [ ][ ][ ]

	NO	YES
72.6.2-11 Did this illness or trouble include		
72.6.2 a rash or itchy skin?	☐	☐
72.6.3 diarrhoea or vomiting?	☐	☐
72.6.4 runny or stuffy nose?	☐	☐
72.6.5 severe headaches?	☐	☐
72.6.6 breathlessness?	☐	☐
72.6.7 itching, tingling or swelling in the mouth, lips or throat?	☐	☐
72.6.8 difficulty swallowing?	☐	☐
72.6.9 fainting or dizziness?	☐	☐
72.6.10 symptoms so severe you had an emergency injection from a doctor, or had to use an epipen	☐	☐
72.6.11 other_____	☐	☐

72.6.12 . How soon after eating this food did you get the first symptoms? TICK ONE BOX ONLY

a) Less than half an hour	1 ☐

b) Half and hour to one hour 2
c) One hour to two hours 3
d) Two hours to four hours 4
e) More than four hours 5

72.6.13 How old were you when you first had this attack? YEARS

72.6.14 How old were you when you last had this attack? YEARS

72.6.15 How many times has this occurred during your life? NUMBER

73. When you are near animals, such as cats, dogs or horses, do you ***ever***

	NO	YES
73.1 start to cough?		
73.2 start to wheeze?		
73.3 get a feeling of tightness in your chest?		
73.4 start to feel short of breath?		
73.5 get a runny or stuffy nose or start to sneeze?		
73.6 get itchy or watering eyes?		

IF NO TO ALL SYMPTOMS GO TO QUESTION 74;IF YES TO ONE OR MORE SYMPTOMS

73.7.1-4 Do you have such symptom/s when you are near	NO	YES
73.7.1 cat?		
73.7.2 dog?		
73.7.3 horse?		
73.7.4 other?		

74. When you are in a dusty part of the house, or near pillows or duvets do you ***ever***

	NO	YES
74.1 start to cough?		
74.2 start to wheeze?		
74.3 get a feeling of tightness in your chest?		
74.4 start to feel short of breath?		
74.5 get a runny or stuffy nose or start to sneeze?		
74.6 get itchy or watering eyes?		

75. When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ***ever***

	NO	YES
75.1 start to cough?		
75.2 start to wheeze?		
75.3 get a feeling of tightness in your chest?		
75.4 start to feel short of breath?		
75.5 get a runny or stuffy nose or start to sneeze?		
75.6 get itchy or watering eyes?		

IF 'YES' TO ANY OF THE ABOVE:

75.7.1-4 Which time of year does this happen?	NO	YES
75.7.1 winter		
75.7.2 spring		
75.7.3 summer		
75.7.4 autumn		

	NO	YES
76. Have you ever smoked for as long as a year?		

['YES' means at least 20 packs of cigarettes or 12 oz (360 grams) of tobacco in a lifetime, or at least one cigarette per day or one cigar a week for one year]

IF 'NO' GO TO QUESTION 77, IF 'YES':

76.1 How old were you when you started smoking? — YEARS

76.2 How old were you when you started smoking daily? — YEARS

Never smoked daily please enter 88

76.3 Do you **now** smoke, as of ***one month ago***? — NO YES

IF 'NO' GO TO QUESTION 76.4, IF 'YES':

76.3.1-4 How much do you ***now*** smoke on average? — NUMBER

- 76.3.1 number of cigarettes per day
- 76.3.2 number of cigarillos per day
- 76.3.3 number of cigars a week
- 76.3.4 pipe tobacco in a) ounces / week
  b) grams / week

76.4 Have you stopped or cut down smoking? — NO YES

IF 'NO' GO TO QUESTION 76.5, IF 'YES':

76.4.1 Did you stop or cut down due to breathing problems? — NO YES

76.4.2 How old were you when you stopped or cut down smoking? — YEARS

76.4.3.1-4 ***On average*** of the entire time you smoked, before you stopped or cut down, how much did you smoke? — NUMBER

- 76.4.3.1 number of cigarettes per day
- 76.4.3.2 number of cigarillos per day
- 76.4.3.3 number of cigars a week
- 76.4.3.4 pipe tobacco in a) ounces / week
  b) grams / week

76.5 Do you or did you inhale the smoke? — NO YES

77. Have you been **regularly** exposed to tobacco smoke in the last ***12 months***? ['Regularly' means on most days or nights] — NO YES

IF 'NO' GO TO QUESTION 78, IF 'YES':

77.1. Not counting yourself, how many people in your household smoke regularly? — NUMBER

77.2 Do people smoke regularly in the room where you work? — NO YES

77.3 How many hours per day are you exposed to ***other people's*** tobacco smoke? — HOURS

77.4 How many hours per day, are you exposed to other peoples tobacco smoke in the following locations? — HOURS

- at home
- at workplace
- in bars, restaurants, cinemas or similar social settings
- elsewhere

78. Have you used any **inhaled** medicines to help your breathing at any time in the last ***12 months***? — NO YES

IF NO' GO TO QUESTION 79, IF 'YES':

Which of the following have you used in the last ***12 months***?

NO YES

78.1 <u>short acting</u> beta-2-agonist (only) inhalers

(Please include combinations that include beta 2 and steroids in section 78.6)

78.1.1 If used, which one? _____ [ ][ ]
78.1.2 What type of inhaler do you use? [ ]

NUMBER
78.1.3. What is the dose per puff (in micrograms)? [ ][ ][ ][ ]

78.1.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 [ ]
b) in short courses 2 [ ]
c) continuously 3 [ ]
d) not at all 4 [ ]

If answer to 78.1.4 is <u>when needed</u>: NUMBER
78.1.5 Number of puffs per month [ ][ ]
If answer to 78.1.4 is <u>in short courses</u> NUMBER
78.1.6 number of courses [ ][ ]
78.1.7 number of puffs per day [ ][ ]
78.1.8 average number of days per month [ ][ ]
If answer to 78.1.4 <u>is continuously</u> NUMBER
78.1.9 number of puffs per day [ ][ ]

NO YES
78.2 <u>long acting</u> beta-2-agonist inhalers [ ] [ ]
(Please include combinations that include long acting beta 2 and steroids in section 78.6)
78.2.1 If used, which one? _____ [ ]
78.2.2 What type of inhaler do you use? [ ]

NUMBER
78.2.3. What is the dose per puff (in micrograms)? [ ][ ]

78.2.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 [ ]
b) in short courses 2 [ ]
c) continuously 3 [ ]
d) not at all 4 [ ]

If answer to 78.2.4 is <u>when needed</u>: NUMBER
78.2.5 Number of puffs per month [ ][ ]
If answer to 78.2.4 is <u>continuously</u> NUMBER
78.2.6 number of puffs per day [ ][ ]

NO YES
78.3 <u>short acting</u> anti-muscarinic inhalers [ ] [ ]

78.3.1 If used, which one? _____ [ ]
78.3.2 What type of inhaler do you use? [ ]

NUMBER
78.3.3. What is the dose per puff (in micrograms)? [ ][ ][ ]

78.3.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 [ ]
b) in short courses 2 [ ]
c) continuously 3 [ ]
d) not at all 4 [ ]

If answer to 78.3.4 is <u>when needed</u>: NUMBER
78.3.5 Number of puffs per month [ ][ ]

If answer to 78.3.4 is continuously: NUMBER

78.3.6 Number of puffs per day ☐☐

NO YES

78.4 long acting anti-muscarinic inhalers ☐ ☐

78.4.1 If used, which one? _____ ☐☐

78.4.2 What type of inhaler do you use? ☐

NUMBER

78.4.3. What is the dose per puff (in micrograms)? ☐☐☐

78.4.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐

b) in short courses 2 ☐

c) continuously 3 ☐

d) not at all 4 ☐

If answer to 78.4.4 is when needed: NUMBER

78.4.5 Number of puffs per month ☐☐

If answer to 78.4.4 is continuously: NUMBER

78.4.6 Number of puffs per day ☐☐

NO YES

78.5 inhaled steroids (ONLY) ☐ ☐

(Please include combinations that include beta 2 and steroids in section 78.6)

78.5.1 If used, which one? _____ ☐☐

78.5.2 What type of inhaler do you use? ☐

NUMBER

78.5.3. What is the dose per puff (in micrograms)? ☐☐☐☐

78.5.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐

b) in short courses 2 ☐

c) continuously 3 ☐

d) not at all 4 ☐

If answer to 78.5.4 is when needed: NUMBER

78.5.5 Number of puffs per month ☐☐

If answer to 78.5.4 is in short courses NUMBER

78.5.6 number of courses ☐☐

78.5.7 number of puffs per day ☐☐

78.5.8 average number of days per month ☐☐

If answer to 78.5.4 is continuously NUMBER

78.5..9 number of puffs per day ☐☐

NUMBER

78.5.10 How many times over the last 3 months have you temporarily increased this treatment because your symptoms became worse? ☐☐

NO YES

78.6 **inhaled steroids and beta2 agonists (combined therapy)** ☐ ☐

78.6.1 If used, which one? _____ ☐☐

78.6.2 What type of inhaler do you use? ☐

NUMBER

78.6.3. What is the dose per puff (in micrograms)? ☐☐☐☐

(Please insert the dose of the inhaled steroid)

78.6.4. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 78.6.4 is <u>when needed</u>: NUMBER

78.6.5 Number of puffs per month ☐☐

If answer to 78.6.4 is in <u>short courses</u> NUMBER

78.6.6 number of courses ☐☐
78.6.7 number of puffs per day ☐☐
78.6.8 average number of days per month ☐☐

If answer to 78.6.4 is <u>continuously</u> NUMBER

78.6.9 number of puffs per day ☐☐

NUMBER

78.6.10 How many times over the last 3 months have you temporarily increased this treatment because your symptoms became worse? ☐☐

NO YES

78.7 inhaled cromoglycate/nedocromil ☐ ☐

78.7.1 If used, which one? _____ ☐☐

NUMBER

78.7.2. What is the dose per puff (in milligrams)? ☐☐

78.7.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 78.7.3 is <u>continuously</u>: NUMBER

78.7.4 Number of puffs per day ☐☐

NO YES

78.8 inhaled compounds ☐ ☐

78.8.1 If used, which one? _____ ☐☐
78.8.2 What type of inhaler do you use? ☐

NUMBER

78.8.3. What is the dose per puff (in micrograms)? ☐☐☐

79. Have you used any **pills**, **capsules**, **tablets** or **medicines**, other than inhaled medicines, to help your breathing at any time in the last ***12 months***? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 80, IF 'YES':

Which of the following have you used in the last ***12 months***?

NO YES

79.1 **oral beta-2-agonists** ☐ ☐

79.1.1 If used, which one? _____ ☐☐
79.1.2 what dose of tablet ☐☐

79.1.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY

a) when needed 1 ☐

b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 79.1.3 is <u>continuously</u>: NUMBER

79.1.4 Number of tablets per day ☐☐

NO YES

79.2 **oral methylxanthines** ☐ ☐

79.2.1 if used, which one? _____ ☐☐
79.2.2 what dose of tablet ☐☐☐

79.2.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 79.2.3 is <u>continuously</u>: NUMBER

79.2.4 Number of tablets per day ☐☐

NO YES

79.3 **oral steroids** ☐ ☐

79.3.1 If used, which one? _____ ☐☐
79.3.2 what dose of tablet ☐☐.

79.3.3. In the last 12 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐

If answer to 79.3.3 is <u>when needed</u>: NUMBER

79.3.4 number of tablets per month ☐☐

If answer to 79.3 3 is in <u>short courses</u> NUMBER

79.3.5 number of courses ☐☐
79.3.6 tablets per day ☐☐
79.3.7 average number of days per month ☐☐

If answer to 79.3.3 is <u>continuously</u> NUMBER

79.3.8 tablets per day ☐☐

NO YES

79.3.9. Have you used them in the last ***3 months***? ☐ ☐

NO YES

79.4 oral anti-leukotrienes ☐ ☐

79.4.1 If used, which one? _____ ☐☐
79.4.2 what dose of tablet ☐☐☐

79.4.3. In the last 3 months, how have you used them: TICK ONE BOX ONLY
a) when needed 1 ☐
b) in short courses 2 ☐
c) continuously 3 ☐
d) not at all 4 ☐

If answer to 79.4.3 is <u>continuously</u>: NUMBER

79.4.4 Number of tablets per day ☐☐

80. Have you **ever** used inhaled steroids (show list, including combined therapy)? NO YES
IF NO GO TO QUESTION 81;IF YES
80.1 How old were you when you first started to use inhaled steroids? YEARS
80.2 How old were you when you last use inhaled steroids? YEARS
80.3. Have you used inhaled steroids ***every year*** since the last survey? NO YES
IF 'NO' GO TO QUESTION 80.4: IF 'YES'
80.3.1 On average how many months each year have you taken them? MONTHS
NOW GO TO QUESTION 81
80.4 How many of the years since the last survey have you taken inhaled steroids? YEARS
IF 'NONE' ENTER 00 AND GO TO QUESTION 81;IF 'YES'
80.4.1 On average how many months of each of these years have you taken them? MONTHS

81. Have you had a course of antibiotics in the last 12 months to help your breathing? NO YES
IF NO GO TO QUESTION 82;IF YES
81.1 How many courses of antibiotics? NUMBER

82. Have you used antibiotics for nasal/sinus problems in the last 12 months? NO YES

83. Have you **ever** had any vaccinations or injections for the treatment of allergy or had a course of desensitisation? NO YES
IF NO GO TO QUESTION 84;IF YES
83.4.1 What was this treatment? CODE
83.4.2 Have you had this treatment in the last 12 months? NO YES
IF HAS HAD ANOTHER VACCINATION,INJECTION OF DESENSITISATION
83.4.3 What was this treatment? CODE
83.4.4 Have you had this treatment in the last 12 months? NO YES

84. Are you usually vaccinated against flu? NO YES
IF NO GO TO QUESTION 85;IF YES
84.1 Were you vaccinated against flu in the last winter period? NO YES

85. Have you been vaccinated against pneumonia (Pneumovax) in the last 5 years? NO YES DK

86. Have you used any other **remedies** to help your breathing at any time in the last ***12 months***? NO YES
IF 'NO' GO TO QUESTION 87 IF 'YES':
86.1. What remedies? _____
_____
_____

87. Has your doctor ever prescribed medicines, including inhalers, for your breathing? NO YES

IF 'NO' GO TO QUESTION 88, IF 'YES':
87.1 If you are prescribed medicines for your breathing, do you ***normally*** take TICK ONE BOX ONLY
a) all of the medicine? 1
b) most of the medicine? 2

c) some of the medicine? 3 ☐
d) none of the medicine? 4 ☐

87.2 ***When your breathing gets worse***, and you are prescribed medicines for your breathing, do you normally take — TICK ONE BOX ONLY

a) all of the medicine? 1 ☐
b) most of the medicine? 2 ☐
c) some of the medicine? 3 ☐
d) none of the medicine? 4 ☐

87.3 Do you think it is bad for you to take medicines all the time to help your breathing? — NO ☐ YES ☐

87.4 Do you think you should take as much medicine as you need to get rid of ***all*** your breathing problems? — NO ☐ YES ☐

88. What medication, regardless of cause, have you taken regularly for more than 6 of the last 12 months? *(DO NOT include the respiratory medication given in previous questions)*

IF NONE, PROCEED TO Q89, OR COMPLETE THE TABLE

	Medication (name)	A	N	N	A	A	N	N
88.1								
88.2								
88.3								
88.5								
88.6								
88.7								
88.8								
88.9								
88.10								

A=letter N=digit (of seven alphanumeric ATC code)

89. How often do you take paracetamol? — TICK ONE BOX ONLY

a) never 1 ☐
b) less than once a month 2 ☐
c) more than once a month but not every week 3 ☐
d) at least once a week 4 ☐
e) every day 5 ☐

IF LESS THAN WEEKLY GO TO QUESTION 90; IF 'WEEKLY' OR 'DAILY'

89.1 Please give the main reason that you take paracetamol? — TICK ONE BOX ONLY

a) headache 1 ☐
b) backache or arthritis 2 ☐
c) chest problems 3 ☐
d) menstrual pain 4 ☐
e) other – please describe_____ 5 ☐

90. How often do you take pain killers other than paracetomol? — TICK ONE BOX ONLY

a) never 1 ☐
b) less than once a month 2 ☐
c) more than once a month but not every week 3 ☐
d) at least once a week 4 ☐
e) every day 5 ☐

IF LESS THAN WEEKLY GO TO QUESTION 91; IF 'WEEKLY' OR 'DAILY'

90.1 Please give the main reason that you take these other painkillers? TICK ONE BOX ONLY

a) headache	1	☐
b) backache or arthritis	2	☐
c) chest problems	3	☐
d) menstrual pain	4	☐
e) other – please describe_____	5	☐

91. Do you have or have you ever had any of the following illnesses. If yes, please indicate the age you were first diagnosed with the disease?

		NO	YES				YEARS	
91.1.1	Stroke	☐		☐	91.1.2	Age diagnosed	☐	☐
91.2.1	Angina, heart attack, coronary heart disease	☐		☐	91.2.2	Age diagnosed	☐	☐
91.3.1	Insulin dependent diabetes	☐		☐	91.3.2	Age diagnosed	☐	☐
91.4.1	Non-insulin dependent diabetes	☐		☐	91.4.2	Age diagnosed	☐	☐
91.5.1	Cancer	☐		☐	91.5.2	Age diagnosed	☐	☐
91.6.1	Depression	☐		☐	91.6.2	Age diagnosed	☐	☐
91.7.1	Hypertension	☐		☐	91.7.2	Age diagnosed	☐	☐
91.8.1	Osteoporosis	☐		☐	91.8.2	Age diagnosed	☐	☐
91.9.1	Crohns Disease	☐		☐	91.9.2	Age diagnosed	☐	☐
91.10.1	Migraine	☐		☐	91.10.2	Age diagnosed	☐	☐
91.11.1	Rheumatoid arthritis	☐		☐	91.11.2	Age diagnosed	☐	☐
91.12.1	Ankylosing spondylitis, psoariatic arthritis	☐		☐	91.12.2	Age diagnosed	☐	☐
91.13.1	Gastro-oesophagel reflux hiatus hernia or oesophagitis	☐		☐	91.13.2	Age diagnosed	☐	☐

91.5.3	Type of cancer	☐

Code for 91.5.3
1= breast
2= prostate
3= lung
4= GI tract
5= other

92 Do you have any long term limiting illness not mentioned above and not including asthma, COPD, chronic bronchitis or emphysema?? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 93, IF 'YES':

92.1 Please name this condition_____ CODE ☐☐

93. ***Since the last survey***, have you visited a hospital casualty department or emergency room (for any reason, apart from accidents and injuries)? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 94. IF 'YES':

93.1. Was this due at least once to ***breathing problems***? NO ☐ YES ☐

93.2 Have you visited a hospital casualty department or emergency room (for any reason, apart from accidents and injuries) **in the last 12 months**? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 94, IF 'YES':

93.2.1 How many times in the last ***12 months***? TIMES ☐☐

93.2.2 Among these ones, how many times because of ***breathing problems***? TIMES ☐☐

[Write '0' if s/he had not visited the emergency room for breathing problems]

94. ***Since the last survey***, have you spent a night in hospital (for any reason, apart from accidents and injuries)? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 95, IF 'YES':

94.1 Was this due at least once to ***breathing problems***? NO ☐ YES ☐

94.2 Have you spent a night in hospital (for any reason, apart from accidents and injuries) **in the last 12 months**? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 95, IF 'YES':

94.2.1 How many nights in the last ***12 months***? NIGHTS ☐☐

94.2.2 Was this due at least once to ***breathing problems***? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 95, IF 'YES':

94.3.1-5 In the last ***12 months*** how many nights have you been hospitalized in each of the following types of ward for ***breathing problems***? NIGHTS

94.3.1 general
94.3.2 chest medicine
94.3.3 rehabilitation
94.3.4 intensive care unit
94.3.5 other

95. In the last ***12 months*** have you been seen by a general practitioner (for any reason, apart from accidents and injuries)? NO YES

IF 'NO' GO TO QUESTION 96, IF 'YES':

95.1 How many times **in the last 12 months**? TIMES

95.2 Of these, how many were for ***breathing problems***? TIMES

[Write '0' if not been seen by general practitioner in the last 12 months for breathing problems]

96. In the last ***12 months*** have you seen a specialist (for any reason, apart from accidents and injuries)? NO YES

IF 'NO' GO TO QUESTION 97, IF 'YES':

96.1 How many times in the last ***12 months***? TIMES

96.2 How many times have you seen a specialist (chest physician, allergy specialist, internal medicine specialist, ENT doctor) because of ***breathing problems in the last 12 months***? TIMES

[Write '0' if not been seen by a specialist in the last 12 months for breathing problems]

97. Are you given regular appointments to be seen by a doctor (or nurse) because of ***breathing problems***? NO YES

98. In the last ***12 months*** how many times have you visited the following because of ***breathing problems***? TIMES

98.1 nurse
98.2 physiotherapist
98.3 practitioner of 'alternative' medicine

99. In the last ***12 months*** have you had any clinical or laboratory tests because of health problems (apart from accidents and injuries)? NO YES

IF 'NO' GO TO QUESTION 100, IF 'YES':

99.1 Was this due at least once to ***breathing problems***? NO YES

IF 'NO' GO TO QUESTION 100, IF 'YES':

99.1.1-5 In the last ***12 months*** how many times have you had the following tests for ***breathing problems***? TIMES

99.1.1 breathing test in a laboratory specially for lung function measures
99.1.2 skin test for allergy
99.1.3 blood test for allergy
99.1.4 x-rays
99.1.5 thorax CT

100. In the last ***12 months*** have you lost days of work because of health problems (apart from accidents and injuries)? NO YES HAVE NOT WORKED IN THE LAST 12 months

IF NOT WORKED OR HAS NOT LOST DAYS OF WORK GO TO QUESTION 101; IF 'YES' DAYS

100.1 How many days **in the last 12 months?**

100.2 Among these ones, how many because of breathing problems?

[Write '000' if not lost any days due to breathing problems]

101. **Since the last survey** were you forced to give up working altogether because of health problems (apart from accidents and injuries)? NO YES

IF 'NO' GO TO QUESTION 102, IF 'YES': MONTH YEAR

101.1 When did this occur ?

NO YES

101.2 Were you forced to give working altogether because of **breathing problems**?

102. In the last ***12 months*** have there been any days when you have had to ***give up activities other than work*** (e.g. looking after children, the house, studying) because of health problems (apart from accidents and injuries)? NO YES

IF 'NO' GO TO QUESTION 103, IF 'YES':

DAYS

102.1 How many days **on average** each month?

DAYS

102.2 Among these ones, how many because of ***breathing problems***?

[Write '0' if s/he has not had any days of activity lost due to breathing problems]

103. Interview type TICK ONE BOX ONLY

1 face to face interview at clinic
2 telephone
3 face to face at home
4 other

104. Date of birth check. What is the date of birth of this participant? DAY MONTH YEAR

105. Which of the following best describes you?

TICK ONE BOX ONLY

1 Single
2 Married/cohabiting
3 Separated/Divorced
4 Widowed
5 Other or do not wish to answer

Kompetansesenter for klinisk forskning
HAUKELAND SYKEHUS

Institutt for indremedisin
Seksjon for lungemedisin

Ernst Omenaas

Airways symptoms

1. Have you had wheezing or whistling in your chest at any time **in the last 12 months?** ☐ No ☐ Yes

   If NO go to question 2, if YES:

   1.1 Have you been at all breathless when the wheezing noise was present? ☐ No ☐ Yes

   1.2 Have you had this wheezing or whistling when you did not have a cold? ☐ No ☐ Yes

2. Have you woken up with a feeling of tightness in your chest at any time **in the last 12 months?** ☐ No ☐ Yes

3. Have you been woken by an attack of shortness of breath at any time **in the last 12 months?** ☐ No ☐ Yes

4. Have you been woken by an attack of coughing at any time **in the last 12 months?** ☐ No ☐ Yes

5. Have you had an attack of asthma **in the last 12 months?** ☐ No ☐ Yes

6. Are you currently taking any medicine *(including inhalers, aerosols or tablets)* for asthma? ☐ No ☐ Yes

7. Do you have any nasal allergies including hay fever? ☐ No ☐ Yes

8. What is your date of birth? *(dd/mm/yy)* ...../...../.....

9. What is today's date? *(dd/mm/yy)* ...../...../.....

10. Are you male or female? ☐ Male ☐ Female

11. How tall are you? ..... cm

12. How much do you weigh? ..... kg

    12.1 What is your waist circumference? ..... cm
    (Please use the provided tape measure, and measure your waist at the level of the navel, while standing and under your clothes.)

13. In recent years, have you been troubled by a protracted cough? ☐ No ☐ Yes

14. Do you usually bring up phlegm or do you have phlegm in your lungs which you have difficulty bringing up? ☐ No ☐ Yes

    If NO to question 13 and 14 go to question 15, if YES:

    14.1 Do you cough or bring up phlegm in this way almost every day for **at least three months every year?** ☐ No ☐ Yes

    14.2 Have you had periods of this kind for at least two years in a row? ☐ No ☐ Yes

    14.3 How old were you when these problems began? ..... years

15. Do you have or have you ever had asthma? ☐ No ☐ Yes

If NO go to question 16, if YES:

15.1 Have you ever had asthma diagnosed by a doctor? ☐ No ☐ Yes

15.2 How old were you when you first experienced asthma symptoms? ..... years

15.3 In which year did you last experience asthma symptoms? Year .....

16. Has a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)? ☐ No ☐ Yes

17. Have you ever had wheezing or whistling in your chest? ☐ No ☐ Yes

17.1 If YES, how old were you when you first noticed wheezing or whistling in your chest? ..... years

17.2. If YES, when was the last year you noticed wheezing or whistling in your chest? Year .....

18. Have you ever experienced nasal symptoms such as nasal congestion, rhinorrhoea (runny nose) and/or sneezing attacks without having a cold? ☐ No ☐ Yes

If NO go to question 19, if YES:

18.1 How old were you when you experienced such nasal symptoms for the first time? ..... years

18.2 Have you had such nasal symptoms in the last 12 months? ☐ No ☐ Yes

18.3 At which time of the year are your nasal symptoms worst? *(tick one box only)*

Spring	Summer	Autumn	Winter	Always	Don't know
☐	☐	☐	☐	☐	☐

19. Has your nose been blocked **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

20. Have you had pain or pressure around the forehead, nose or eyes **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

21. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

22. Has your sense of smell been reduced or absent **for more than 12 weeks during the last 12 months?** ☐ No ☐ Yes

Smoking habits

23. Do you smoke? *(this applies even if you only smoke the odd cigarette/cigar or pipe every week)* ☐ No ☐ Yes

24. Did you smoke previously? ☐ No ☐ Yes

If NO to question 23 and 24 go to question 25, if YES:

24.1 How much do you smoke / did you smoke? *(give an average)*

..... cigarettes/day

..... cigars/week

..... pkts pipe tobacco/week

24.2 How old were you when you started smoking? ..... years

24.3 For how long have you smoked? *(applies to both smokers and ex-smokers)* .....years

24.4 If you are an ex-smoker, when did you stop smoking? Year .....

Marital status

25. What is your current marital status? *(tick one box only)*

Single	Married	Cohabitating	Separated or divorced	Widowed	Do not wish to answer
☐	☐	☐	☐	☐	☐

Education

26. Please mark the educational level which best describes your level. *(tick one box only)*

Primary school	Lower or upper secondary school, or technical school	College or university
☐	☐	☐

Occupation and work

27. Are you currently working? ☐ No ☐ Yes

28. Which is your current or most recent work or occupation? *(please use capital letters)*

……

28.1 How many years have you worked or did you work in this occupation? ……years

29. We assume that your work ability, when it was as best, was 100 percent. How would you rate your current work ability, expressed in percent? ..... %

30. Have you ever changed job because the job affected your breathing? ☐ No ☐ Yes

31. Have you ever changed job because of hayfever or nasal symptom ☐ No ☐ Yes

32. Have you ever changed job because of other health problems/diseases? ☐ No ☐ Yes

33. Have you ever worked as a painter? ☐ No ☐ Yes

If YES, for how many years? ..... years

34. Have you ever worked as a cleaner? ☐ No ☐ Yes

If YES, for how many years? ..... years

35. Have you been reporting any days of sick leave in **the last 12 months?** ☐ No ☐ Yes

35.1 *If YES,* how many days have you been on sick leave? *(tick one box only)*

1–7 days	8-30 days	31 days–90 days	More than three months
☐	☐	☐	☐

36. Have you been reporting any days of sick leave because of breathing problems in **the last 12 months?** ☐ No ☐ Yes

36.1 *If YES,* how many days have you been on sick leave for breathing problems? *(tick one box only)*

1–7 days	8–30 days	31 days–90 days	More than three months
☐	☐	☐	☐

In-door and out-door environment

37. In which type of accommodation do you live? *(tick one box only)*

Detached house	Semidetached or terraced house	Apartment	Other
☐	☐	☐	☐

38. When did you move to your current home? Year .....

39. How many hours per day do you spend in your home most days? Approx. ..... hours/day

40. Does tobacco smoking take place in your present home? *(tick one box only)*

Yes, every day	Yes, frequently 1-4 times/week	Yes, sometimes 1-3 times/month	No, never
☐	☐	☐	☐

41. Have any of the following been identified in your home in **the last 12 months:**

41.1 Water leakage or water damage indoors in walls, floor or ceilings ☐ No ☐ Yes

41.2 Bubbles or yellow discoloration on plastic floor covering, or black discoloration of parquet floor ☐ No ☐ Yes

41.3 Visible mould growth indoors on walls, floor or ceilings. ☐ No ☐ Yes

42. Have you seen any signs of damp, water leakage or mould in your home at any time in **the past 10 years?** ☐ No ☐ Yes

43. Have you seen any signs of damp, water leakage or mould in your workplace at any time in **the past 10 years?** ☐ No ☐ Yes

44. Is your bedroom window towards a nearby street (less than 20 m)? *(tick one box only)*

No	Yes a street with little traffic	Yes a street with moderate traffic	Yes a street with much traffic
☐	☐	☐	☐

45. Can you in your bedroom hear traffic noise? *(tick one box only)*

Not at all	A little	Much	Very much
☐	☐	☐	☐

46. How much time do you usually spend walking or travelling along streets with busy traffic a typical weekday? Approx ..... minutes/day

Childhood and family

47. What term best describes the place you lived most of the time when you were under the age of five years? *(tick one box only)*

☐ Farm with livestock
☐ Farm without livestock
☐ Village in rural area
☐ Small town
☐ Suburb of city
☐ Inner city

48. When you were a child, which of the following were mainly used for heating? *(more than one box may apply)*

Open wood	Stove with coke, coal or wood	Paraffin	Electricity	Gas or oil fired boiler
☐	☐	☐	☐	☐

49. Did you have a serious respiratory infection before the age of five years? ☐ No ☐ Yes ☐ Don't know

50.1 Did your father ever smoke regularly during your childhood? ☐ No ☐ Yes ☐ Don't know

50.2 Did your mother ever smoke regularly during your childhood? ☐ No ☐ Yes ☐ Don't know

50.3 Did other people (other than parents) smoke regularly at home during your childhood? ☐ No ☐ Yes ☐ Don't know

51. When you were a child, how often did you eat fresh fruits and berries? *(more than one box may apply)*

Never	Rarely	Every week	Almost daily	Almost daily in the autumn season
☐	☐	☐	☐	☐

52. Did your biological parents ever suffer from any of the following: *(more than one box may apply)*

	Mother *(tick box if Yes)*	Father *(tick box if Yes)*
Asthma	☐	☐
Chronich bronchitis, emphysema and/or COPD	☐	☐
Heart disease	☐	☐
Hypertension	☐	☐
Stroke	☐	☐
Diabetes	☐	☐
Cancer	☐	☐

53. Do you have children (including grown-up children)? ☐ No ☐ Yes

If N0 go to question 54, *If YES:*

53.1 how many children do you have? ..... children

53.2 Please write the years when your children were born, and tick *"YES"* if they have had any of the following:

	Asthma before 10 year Yes	Asthma after 10 years Yes	Hayfever/ rhinitis Yes	Atopic eczema/Skin allergies Yes
Child 1 born year	☐	☐	☐	☐
Child 2 born year	☐	☐	☐	☐
Child 3 born year	☐	☐	☐	☐
Child 4 born year	☐	☐	☐	☐
Child 5 born year	☐	☐	☐	☐
Child 6 born year	☐	☐	☐	☐
Child 7 born year	☐	☐	☐	☐

General health

54. Does your gum bleed when you brush your teeth? *(tick one box only)*

Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

55. How often do you usually brush your teeth? *(tick one box only)*

2 times/day or more ☐ Once daily ☐ Less than daily ☐

56. How frequently do you exercise? *(give an average, tick one box only)*

Never ☐ Less than once a week ☐ Once a week ☐ 2-3 times a week ☐ Almost every day ☐

If you do such exercise as frequently as once or more times a week:

56.1 How hard do you push yourself? *(tick one box only)*

☐ I take it easy without breaking into a sweat or losing my breath /
☐ I push myself so hard that I lose my breath and break into a sweat /
☐ I push myself to near-exhaustion

56.2 How long does each session last? *(give an average, tick one box only)*

Less than 15 minutes ☐ 16-30 minutes ☐ 30 minutes to 1 hour ☐ More than 1 hour ☐

Sleep and daytime symptoms

The numbers mean:

1: Never or almost never
2: Less than once a week
3: Once or twice a week
4: 3- 5 nights/days a week
5: Almost every day or night

How often has it occurred in the last months *(circle one number for each question):*

57.	...that you snore loudly and disturbingly?	1	2	3	4	5
58.	...that you have heartburn or belching when you have gone to bed?	1	2	3	4	5
59.	...that you have difficulty in getting to sleep at night?	1	2	3	4	5
60.	...that you wake up repeatedly during the night?	1	2	3	4	5
61.	...that you perspire heavily during the night?	1	2	3	4	5
62.	...that you feel drowsy in the daytime?	1	2	3	4	5
63.	...that you wake up too early and have difficulty in getting to sleep again?	1	2	3	4	5

64. Have you ever had sleep apnoea diagnosed by a doctor? ☐ No ☐ Yes

If NO go to question 65, if YES:

64.1 When did you get the diagnosis of sleep apnoea? Year .....

64.2 If you are currently treated for sleep apnoea, what treatment do you have? *(more than one box may apply)*

- ☐ CPAP
- ☐ Oral appliance (bite splint)
- ☐ Previous surgery in the throat or nose
- ☐ Others

65. How long time do you usually sleep per night? .....hours and .....minutes

Other diseases

66. Have you ever had hypertension (high blood pressure) diagnosed by a doctor? ☐ No ☐ Yes

If YES:

66.1 When did you get the diagnosis hypertension (high blood pressure)? Year .....

66.2 Are you currently taking any medication for hypertension (high blood pressure)? ☐ No ☐ Yes

67. Have you ever had stroke? ☐ No ☐ Yes

67.1 *If YES,* when did you have stroke (for the first time)? Year .....

68. Have you ever been treated in hospital because of heart infarction or angina pectoris? ☐ No ☐ Yes

68.1 *If YES,* when were you treated (for the first time) at a hospital because of heart infarction or angina pectoris? Year .....

69. Have you ever had diabetes diagnosed by a doctor? ☐ No ☐ Yes

If YES:

69.1 When did you get the diagnosis diabetes? Year: .....

69.2 What treatment are you currently using for diabetes? *(tick one box only)*

Insulin	Tablets	Both insulin and tablets	Only diet
☐	☐	☐	☐

70. Have you ever had ulcerative collitis? ☐ No ☐ Yes

70.1 *If YES:* how old were you when the disease started? ..... years

71. Have you ever had Crohn's disease? ☐ No ☐ Yes

71.1 *If YES:* how old were you when the disease started? .....years

Body shape

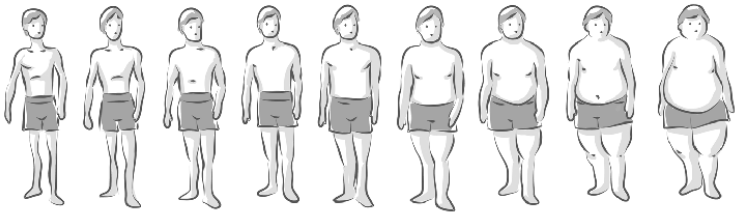
72. What picture best describes your body shape at each age
(tick one box only for each age / period you have reached)

WOMEN

Current	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 8 years	☐	☐	☐	☐	☐	☐	☐	☐	☐
At first menstruation	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 30	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 45	☐	☐	☐	☐	☐	☐	☐	☐	☐
At menopause	☐	☐	☐	☐	☐	☐	☐	☐	☐

(periods stopped 12 months or more)

MEN



Current	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 8 years	☐	☐	☐	☐	☐	☐	☐	☐	☐
At age voice broke	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 30	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 45	☐	☐	☐	☐	☐	☐	☐	☐	☐
Age 55	☐	☐	☐	☐	☐	☐	☐	☐	☐

73. What picture best describes the body shape of each of your biological parents at age 50 years?

Mother	☐	☐	☐	☐	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐	☐	☐	☐	☐

Don't know ☐ Mother
☐ Father

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Papers

Respiratory Health in Cleaners in Northern Europe: Is Susceptibility Established in Early Life?

Øistein Svanes , Trude Duelien Skorge, Ane Johannessen, Randi Jacobsen Bertelsen, Magne Bråtveit, Bertil Forsberg, Thorarin Gislason, Mathias Holm, Christer Janson, Rain Jögi, Ferenc Macsali, Dan Norbäck, Ernst Reidar Omenaas, Francisco Gómez Real, Vivi Schlünssen, Torben Sigsgaard, Gunilla Wieslander, Jan-Paul Zock, Tor Aasen, Julia Dratva, Cecilie Svanes

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Abstract

Rationale

There is some evidence that maternal smoking increases susceptibility to personal smoking's detrimental effects. One might question whether early life disadvantage might influence susceptibility to occupational exposure.

Objectives

In this cross-sectional study we investigated respiratory symptoms, asthma and self-reported chronic obstructive pulmonary disease (COPD) as related to working as a cleaner in Northern European populations, and whether early life factors influenced susceptibility to occupational cleaning's unhealthy effects.

Methods

The RHINE III questionnaire study assessed occupational cleaning in 13,499 participants. Associations with respiratory symptoms, asthma and self-reported COPD were analysed with multiple logistic regressions, adjusting for sex, age, smoking, educational level, parent´s educational level, BMI and participating centre. Interaction of occupational cleaning with early life disadvantage (maternal smoking, severe respiratory infection <5 years, born during winter months, maternal age at birth >35 years) was investigated.

Main Results

Among 2138 ever-cleaners the risks of wheeze (OR 1.4, 95% CI 1.3–1.6), adult-onset asthma (1.5 [1.2–1.8]) and self-reported COPD (1.7 [1.3–2.2]) were increased. The risk increased with years in occupational cleaning (adult-onset asthma: ≤1 year 0.9 [0.7–1.3]; 1–4 years 1.5 [1.1–2.0]; ≥4 years 1.6 [1.2–2.1]). The association of wheeze with cleaning activity ≥4 years was significantly stronger for those with early life disadvantage than in those without (1.8 [1.5–2.3] vs. 1.3 [0.96–1.8]; $p_{interaction}$ 0.035).

Conclusions

Occupational cleaners had increased risk of asthma and self-reported COPD. Respiratory symptom risk was particularly increased in persons with factors suggestive of early life disadvantage. We hypothesize that early life disadvantage may increase airway vulnerability to harmful exposure from cleaning agents later in life.

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Data Availability: Due to Norwegian ethical and legal restrictions, not all the data underlying the findings in our study can be made available in manuscript, in supplemental files or in a public repository. Requests for data access can be directed to Haukeland University Hospital, 5021 Bergen, Norway, Att. Med. Director Alf H. Andreassen; e-mail: postmottak@helse-bergen.no; telephone +47 55 97 50 00. Org. nr: 983 974 724.

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Introduction

Several studies have shown that cleaners have more airway symptoms and asthma than a general population [1, 2], but even though exposure to cleaning agents is a risk factor for asthma, not all cleaners develop such problems. Likewise, only a limited proportion of smokers develop COPD. An analysis of the European Community Respiratory Health Survey showed that early life disadvantage was associated not only with adult lung function level, but also with accelerated lung function decline [3]. Why early life development may influence lung ageing decades later is not well understood. Two recent analyses revealed that persons with characteristics reflecting early life disadvantage were more susceptible to the harmful effects of adult smoking: Guerra *et al* [4] found stronger effects on airflow limitation of personal smoking in those exposed to parental smoking. Stronger detrimental effects of smoking on lung function decline was found in persons exposed to maternal smoking, born during the winter season, with maternal age at birth above 35 years and/or severe childhood respiratory infections (Dratva et al., 2014, manuscript in preparation). In these analyses, early life disadvantage factors appeared to increase the vulnerability to adult active smoking. Smoking involves a complex mix of harmful chemical exposures and it would be reasonable to suspect a similar interaction for other harmful chemical exposures. We hypothesise that early life disadvantage factors may modify adult responses to occupational exposures, such as cleaning agents.

There is little knowledge on the risk of COPD in cleaners. Smoking is still the single most important cause of COPD, but as the prevalence of smoking declines, non-smoking factors such as working conditions may become increasingly more important [5]. It seems plausible that exposure to different types of airways irritants (gases and aerosols) from cleaning agents over time might lead to COPD development among cleaners, but as of today this is not well investigated [6, 7].

The Respiratory Health In Northern Europe (RHINE) study provided an opportunity to investigate cleaners in a large population-based sample that included information on early life exposures. In addition, the study has sufficiently large numbers to address effect modification. In this article we investigated associations between working as a cleaner and respiratory symptoms, asthma and self-reported COPD, taking the duration of exposure into account, and we investigated whether early life factors modified the adverse effects of occupational cleaning on respiratory health.

Methods

Design and subjects

From 1990 to 1994, randomly selected population-based samples of men and women aged 20 to 44 years were invited to a postal screening questionnaire as part of the European Community Respiratory Health Survey (ECRHS) I stage I. The RHINE study is a postal questionnaire follow-up study of the 21,659 persons who participated from the seven Nordic and Baltic centres (Bergen in Norway; Umeaa, Gothenburg and Uppsala in Sweden; Aarhus in Denmark; Reykjavik in Iceland and Tartu in Estonia). From 1999 to 2001, a comprehensive postal questionnaire was answered by 16,106 responders (75%). The timing corresponded with the second follow-up of ECRHS II and, thus, is referred to as the RHINE II study. The third stage of the RHINE study, RHINE III, took place from 2010 to 2012, and included 13,499 responders (62% of the original sample) [8]. The questionnaires in RHINE II and RHINE III included questions on respiratory symptoms, asthma, rhinitis, bronchitis, smoking, indoor environment, occupation, early life exposures and sleep disorders. This article presents data from 13,283 persons who responded to a question on having worked as a cleaner (included only in the RHINE III questionnaire).

Written consent was obtained from all the participants at each stage of the study. The Regional Committees for Medical and Health Research Ethics West in Norway, the National Bioethics Committee in Iceland, the Research Ethics Committee of the University of Tartu in Estonia, The Regional Ethical Review Board in Uppsala, Sweden and the Scientific Committees for Central Jutland in Denmark approved each stage of the study.

Outcomes

The standard ECRHS questions were used to assess respiratory symptoms and diseases (for wording see www.ecrhs.org). Wheezing and other respiratory symptoms were reported as 12 months prevalence, while the respiratory diseases adult asthma and COPD were reported as lifetime prevalence. Asthma was defined on participants' report of having or ever having had asthma; adult asthma was defined as onset of asthma after the age of 16 years. Self-reported COPD was defined by the question "Has a doctor ever told you that you have chronic obstructive pulmonary disease (COPD)?" Chronic bronchitis was defined as participants reporting bringing up phlegm almost every day for at least three months in two consecutive years [9, 10]. "Three or more asthma symptoms" was defined as having answered yes to three or more of the following symptoms in the last 12 months: Wheezing or whistling from the chest; breathless when wheezing; wheezing or whistling when not having a cold; woken with feeling of tightness in chest; been woken by attack of shortness of breath; been woken by attack of cough; attack of asthma; currently taking any asthma medicine [11].

Exposure

"Occupational cleaner" and "years worked as an occupational cleaner" were defined from the questions "*Have you ever worked as a cleaner / cleaning assistant?"* and "*If yes, for how many years?".* Participants who had ever worked as a cleaner were treated as exposed, whereas all other participants were treated as unexposed, thus, persons with other occupational exposures are included in the reference category. Based on the exposure duration in tertiles we built a categorical variable: never exposed, exposed for ≤1 year, >1 to <4 years, ≥4 years.

Covariates

Body mass index was calculated from self-reported weight and height, as weight in kilos per square height in meters. Smoking history was assessed by the questions *"Are you a smoker?"* and *"Are you an ex-smoker?"*; defining never smokers, current smokers and ex-smokers. Participants' and their parents' educational level (primary school, lower/upper/technical school or college/university) was used as proxy variables for adult and early life socioeconomic status [12, 13].

Early life disadvantage

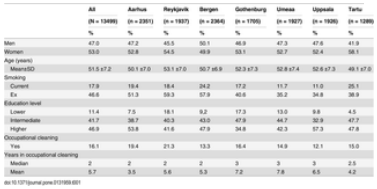
Early life disadvantage was defined as reporting maternal smoking in childhood, having had severe respiratory infection before 5 years of age, being born during winter months (December, January, February), and/or reporting maternal age at delivery above 35 years. These factors have been associated with accelerated lung function decline in a previous analysis (Dratva et al., 2014, manuscript in preparation). Participants reporting any of these factors were defined as having early life disadvantage.

Statistical analyses

Descriptive analyses of the study population and by cleaner-status were performed calculating prevalence of outcomes, exposure and covariates, using Pearson´s chi-squared test. Multiple logistic regression analysis was used to evaluate possible associations between occupational cleaning and respiratory health. Never having worked as a cleaner was used as a reference group. Associations are reported as odd ratios [OR] with 95% confidence intervals [CI]. Due to varying numbers of missing for each variable, numbers at risk differ slightly between different outcomes. Based on prior knowledge and literature, adjustments were made for age, sex, smoking habits, educational level, parents' educational level, BMI (continuous) and participating centre. Sensitivity analyses in men, women, never smokers, current smokers, normal weight and overweight were performed. Potential heterogeneity between centres was analysed using meta-analysis according to derSimonian and Laird [14]. Analyses of associations between occupational cleaning ≥4 years and respiratory health outcomes were stratified by the dichotomous variable early life disadvantage. Potential interaction between early life disadvantages and cleaning status was analysed by including an interaction term of occupational cleaning ≥4 years and early life disadvantage in effects on respiratory outcomes. STATA (StataCorp, College Station, TX, USA), version IC 13.1, was used in all the statistical analyses.

Results

Overall, 2138 persons (16%) reported ever having worked as a cleaner, the median duration was 2.0 years and the mean duration was 5.7 years. The highest prevalence of participants having worked as a cleaner was found in Reykjavik (21%) and Aarhus (19%); whereas reporting work as a cleaner was least common in Bergen (13%) and Uppsala (12%) (p <0.05) (Table 1).



	All (N = 13499)	Aarhus (n = 2351)	Reykjavik (n = 1937)	Bergen (n = 2364)	Gothenburg (n = 1705)	Umeaa (n = 1927)	Uppsala (n = 1926)	Tartu (n = 1289)
	%	%	%	%	%	%	%	%
Men	47.0	47.2	45.5	50.1	46.9	47.3	47.6	41.9
Women	53.0	52.8	54.5	49.9	53.1	52.7	52.4	58.1
Age (years)								
Mean±SD	51.5 ±7.2	50.1 ±7.0	53.1 ±7.0	50.7 ±6.9	52.3 ±7.3	52.8 ±7.4	52.6 ±7.3	49.1 ±7.0
Smoking								
Current	17.9	19.4	18.4	24.2	17.2	11.7	11.0	25.1
Ex	46.6	51.3	59.3	57.9	40.6	35.2	34.8	36.9
Education level								
Lower	11.4	7.5	18.1	9.2	17.3	13.0	9.8	4.5
Intermediate	41.7	39.7	40.3	43.0	47.9	44.7	30.9	47.7
Higher	46.9	53.8	41.6	47.9	34.8	42.3	57.3	47.8
Occupational cleaning								
Yes	16.1	19.4	21.3	13.3	16.4	14.9	12.1	15.0
Years in occupational cleaning								
Median	2	2	2	2	3	3	3	2.5
Mean	5.7	3.5	5.6	5.3	7.2	7.8	6.5	4.2

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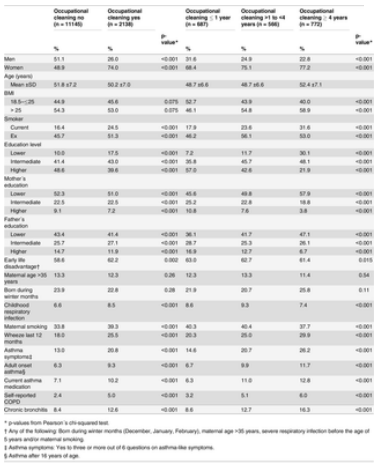
Table 1. Characteristics of the study population by study centre.
https://doi.org/10.1371/journal.pone.0131959.t001

The majority of the cleaners was female (74%), the current mean age among ever cleaners was 50.2 ±7.0 years and mean duration of work as a cleaner was 5.7 ±7.8 years. More cleaners reported current (25%) or previous smoking (51%) than those never having worked as a cleaner (16.4% and 46% respectively) (p<0.05) (Table 2). The prevalence of smoking increased with increasing duration of years having worked as a cleaner (Table 2).



	Occupational cleaning no (n = 11146)	Occupational cleaning yes (n = 2138)	p-value*	Occupational cleaning ≤ 1 year (n = 687)	Occupational cleaning >1 to <4 years (n = 566)	Occupational cleaning ≥ 4 years (n = 772)	p-value*
	%	%		%	%	%	
Men	51.1	26.0	<0.001	31.6	24.9	22.8	<0.001
Women	48.9	74.0	<0.001	68.4	75.1	77.2	<0.001
Age (years)							
Mean ±SD	51.8 ±7.2	50.2 ±7.0		48.7 ±6.6	48.7 ±6.6	52.4 ±7.1	
BMI							
18.5–<25	44.9	45.6	0.075	52.7	43.9	40.0	<0.001
>25	54.3	53.0	0.075	46.1	54.8	58.9	<0.001
Smoker							
Current	16.4	24.5	<0.001	17.9	23.6	31.6	<0.001
Ex	45.7	51.3	<0.001	46.2	56.1	53.0	<0.001
Education level							
Lower	10.0	17.5	<0.001	7.2	11.7	30.1	<0.001
Intermediate	41.4	43.0	<0.001	35.8	45.7	48.1	<0.001
Higher	48.6	39.6	<0.001	57.0	42.6	21.9	<0.001
Mother's education							
Lower	52.3	51.0	<0.001	45.6	49.8	57.9	<0.001
Intermediate	22.5	22.5	<0.001	25.2	22.8	18.8	<0.001
Higher	9.1	7.2	<0.001	10.8	7.6	3.8	<0.001
Father's education							
Lower	43.4	41.4	<0.001	36.1	41.7	47.1	<0.001
Intermediate	25.7	27.1	<0.001	28.7	25.3	26.1	<0.001
Higher	14.7	11.9	<0.001	16.9	12.7	6.7	<0.001
Early life disadvantage†	58.6	62.2	0.002	63.0	62.7	61.4	0.015
Maternal age >35 years	13.3	12.3	0.26	12.3	13.3	11.4	0.54
Born during winter months	23.9	22.8	0.28	21.9	20.7	25.8	0.11
Childhood respiratory infection	6.6	8.5	<0.001	8.6	9.3	7.4	<0.001
Maternal smoking	33.8	39.3	<0.001	40.3	40.4	37.7	<0.001
Wheeze last 12 months	18.0	25.5	<0.001	20.3	25.0	29.9	<0.001
Asthma symptoms‡	13.0	20.8	<0.001	14.6	20.7	26.2	<0.001
Adult onset asthma§	6.3	9.3	<0.001	6.7	9.9	11.7	<0.001
Current asthma medication	7.1	10.2	<0.001	6.3	11.0	12.8	<0.001
Self-reported COPD	2.4	5.0	<0.001	3.2	5.1	6.0	<0.001
Chronic bronchitis	8.4	12.6	<0.001	8.6	12.7	16.3	<0.001

* p-values from Pearson's chi-squared test.
† Any of the following: Born during winter months (December, January, February), maternal age >35 years, severe respiratory infection before the age of 5 years and/or maternal smoking.
‡ Asthma symptoms: Yes to three or more out of 6 questions on asthma-like symptoms.
§ Asthma after 16 years of age.

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Table 2. Characteristics of occupational cleaners in 13283 persons from Northern European population samples.
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Respiratory symptoms, asthma, self-reported COPD and chronic bronchitis were significantly more prevalent among ever cleaners ($p<0.001$) (Table 2). The occurrences of wheeze in the last 12 months, asthma symptoms, adult onset asthma, current use of asthma medication, self-reported COPD, and chronic bronchitis were all significantly increased with time worked as a cleaner ($p<0.001$) (Table 2).

There was a significantly increased risk for self-reported COPD among cleaners (OR 1.69 [95% CI 1.29–2.20]), as well as for respiratory symptoms (1.44 [1.27–1.62]; 1.66 [1.46–1.90]) and asthma (1.47 [1.22–1.77]), after adjusting for potential confounding factors (Table 3). Those having worked with cleaning for more than one year had a significantly increased risk of wheeze last 12 months (1.46 [1.18–1.83]; 1.62 [1.34–1.96]), asthma symptoms (1.68 [1.33–2.31]; 2.04 [1.67–2.49]), current use of asthma medication (1.65 [1.23–2.21]; 1.67 [1.30–2.15]), self-reported COPD (1.80 [1.14–2.85]; 1.65 [1.14–2.42]) and chronic bronchitis (1.77 [1.34–2.32]; 1.84 [1.46–2.32]) compared to those never having worked as a cleaner. The risk for asthma, bronchitis and respiratory symptoms increased with increasing time having worked as a cleaner (Table 3). There was no significant heterogeneity between the participating centres with respect to respiratory symptoms and disease; the results for three or more asthma symptoms are presented in Fig 1.

Fig 1. Adjusted odd ratios for the association of occupational cleaning with asthma symptoms (≥3 symptoms) in each study centre, as estimated from meta-analysis.
For each centre the square gives the OR and the horizontal lines indicate 95% CI; the area of the square is proportional to the size of the study sample in each centre. Adjustment within each centre made for sex, smoking habits, age, education level, parent´s education level, BMI and participating centre. For combined odds ratios, the diamond indicates 95% CI from a model with centre as random effect. p-value for heterogeneity = 0.8.
https://doi.org/10.1371/journal.pone.0131959.g001

Table 3. Respiratory health outcomes as associated with occupational cleaning in 13283 persons from Northern Europe population samples.
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Increased risk of wheeze, three or more asthma symptoms and chronic bronchitis among occupational cleaners was consistently found in sensitivity analysis of various subgroups (Table 4).

Table 4. Sensitivity analysis: The association of occupational cleaning with respiratory symptoms in various subgroups.
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Respiratory symptoms and diseases were more common in cleaners, both among persons with early life disadvantage and among those without such disadvantage. However, the asthma risk associated with occupational cleaning generally appeared to be higher among those with early life disadvantage (Table 5) (Fig 2). Interaction between early life disadvantage and occupational cleaning was statistically significant for the most prevalent outcome, wheeze ($p_{interaction}$ 0.035), and $p_{interaction}$ was 0.053 for ≥3 asthma symptoms (Table 5). A similar tendency was not indicated for chronic bronchitis and self-reported COPD. S1 Table shows analysis of the association of occupational cleaning with wheeze stratified by each of the components of the “early life disadvantage” factor.

Fig 2. Associations of occupational cleaning ≥4 years with respiratory symptoms in persons with and without early life disadvantage.
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Table 5. Association of occupational cleaning with respiratory outcomes in persons with and without early life disadvantage.
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Discussion

This analysis observed that persons who had worked as cleaners had increased risk of respiratory symptoms, asthma and self-reported COPD. The suggested association with self-reported COPD was supported by increased risk also for symptoms of chronic bronchitis. For most outcomes, there was a trend toward a dose-response relationship with higher risks for those having worked as cleaners for longer duration. The findings were consistent across study centres from different countries in Northern Europe. To our knowledge, this analysis shows the first evidence of early life influence on susceptibility to an occupational hazard: Associations between occupational cleaning and respiratory symptoms were stronger among persons with early life disadvantage; thus, early life disadvantage appeared to constitute an important effect modifier by increasing the vulnerability to the harmful effects of occupational cleaning exposures. Our analyses suggest that early life disadvantage may increase susceptibility to chemical exposures later in life, a concept that may have considerable impact on public health policies.

An important novel finding of this paper regards the observed effect modification of exposure to cleaning agents by early life disadvantage factors. The “early life disadvantage” factor in this analysis was based on biological plausibility and previous knowledge [15, 16]; thus, this factor conveys a general concept beyond the individual components. An interaction between working as a cleaner and early life disadvantage was significant for wheeze and borderline significant for asthma symptoms. The findings are supported by two other analyses showing how factors reflecting early life disadvantage increased the susceptibility to the harmful effects from personal smoking with regard to airflow limitation [4] and lung function decline (Dratva et al., manuscript in preparation). A previous study showed that individuals with early life disadvantage were at risk of accelerated lung function decline and had substantially increased risk for COPD [3]. One may speculate that early life disadvantage might impair molecular maintenance mechanisms, and thereby reduce the ability to later in life deal with subsequent insults from harmful exposures such as cleaning chemicals.

This analysis confirmed the increased health hazard from work as a cleaner seen in several previous studies with similar increased risk of airway symptoms and asthma [17, 18, 19, 20, 21]. Proposed mechanisms include irritant effects as well as potential specific immunological effects. Although occupational exposures and COPD is described for other vocations [22, 23], there is little literature concerning COPD in occupational cleaners. An association seems biological plausible, given emerging understanding of inflammatory effects from cleaning chemicals [21] as well as potential for chronification of asthma on exposure after symptom debut. Repeated inhalation of irritants from cleaning chemicals, either from daily low-dose exposure or multiple single high-dose exposures, can cause damage to the bronchial epithelium through a pro-inflammatory response, neurogenic inflammation due to exposed nerve endings and increased lung permeability, and remodelling of the airway epithelium [24, 25, 26].

The strengths of this study include its population-based design, the extensive data from the participants, the large number of participants and the multicentre structure. That the participants were randomly selected from a general population makes the results applicable to a general population rather than to select groups. Furthermore, the data from the participants are reasonably extensive, ensuring that each individual is well characterised. Because of the large number of participants, the study had enough power to investigate possible interactions between work as a cleaner and early life disadvantage.

There was no apparent heterogeneity between the different centres, supporting an interpretation of the results in terms of biological mechanisms rather than confounding by sociocultural factors that are likely to differ between centres.

This analysis has some methodological challenges. Asthma and COPD were defined by self-report and could be subject to misclassification bias. Differential misclassification bias with regard to occupational cleaning is possible and could cause positive or negative confounding. However, the findings were generally consistent with results for symptoms of asthma or chronic bronchitis, for which non-differential misclassification is more likely than differential misclassification. Further, the findings were robust for various adjustments and consistent between subgroups and study centres. Reporting error in cleaning exposure assessment is likewise more likely to give non-differential bias. An analysis of adult reporting of childhood factors found high repeatability and that the reporting error was non-differential with regard to asthma and asthma symptoms [27]. It seems unlikely that error in reporting early life factors could have created the effect modification observed in the present study. We believe the overall result of misclassification in the present analysis may have led to underestimation of true effects.

The definition of COPD was based on self-reported doctor’s diagnosed COPD, a definition that gives the lowest estimates of prevalence [28, 29], as COPD is substantially under diagnosed [30]. The numbers with self-reported diagnosed COPD in the study population where small, also due to the relatively young age group studied. Low numbers might explain less consistent findings on analyses of self-reported COPD in subgroups. Residual confounding by smoking is likely, thus, sensitivity analyses of never-smokers were conducted. This gave similar results as in the whole population, suggesting that the observed results were not related to rest confounding by smoking. As data on occupational cleaning was only collected in the last RHINE survey and with limited detail, it was not possible to confirm a temporal relationship between starting work as a professional cleaner and the development of asthma and COPD. Further, our data did not allow for more detailed exploration of susceptibility windows in adulthood.

The exposure assessment in the present paper (“having worked as a cleaner”) is very crude. It is likely that occupational groups exposed to cleaning agents such as industrial cleaners and homecare takers [31] may be included in the reference category. The reference group further included occupational groups with known asthma risk [32, 33], thereby leading to an underestimation of the respiratory health risk related to occupational cleaning. It is possible that symptomatic subjects more often would quit work as cleaner. This potential “healthy worker effect” may further contribute to an underestimation of the negative impact from cleaning work [34] and might explain why there was not a stronger trend with increasing years in cleaning occupation. Overall, while the analysis have several methodological challenges; these are likely to have attenuated the associations and cannot easily explain an interaction between early life disadvantage and occupational exposure on asthma symptoms.

In conclusion, this analysis found increased asthma, respiratory symptoms and self-reported COPD in persons who have worked as occupational cleaners, particularly among persons with early life disadvantage. The findings suggest that early life disadvantage might increase individual susceptibility to an adult occupational exposure. This seems biologically plausible, and agrees with findings of increased susceptibility to smoking in persons with factors included in early life disadvantage, such as maternal smoking. This finding needs further confirmation in other studies, as there may be widespread implications. Firstly, this may lead to focused mechanistic research as to how early life disadvantage may influence adult respiratory health, and how responses to a chemical hazard may be modified. Secondly, work-place interventions might focus in particular on persons with early life disadvantage, although optimal work-place air quality and adequate protective measures are important for all. Finally, long-term

respiratory health effects of exposures in cleaning occupations need further investigation, as this study indicated increased risk of self-reported COPD in cleaners. Given the large scale use of cleaning agents and disinfectants in occupational setting as well as in private homes, it is essential to understand modifying factors, as well as long-term and short-term respiratory health consequences of such exposures.

Supporting Information

S1 Table. Association of occupational cleaning with respiratory symptoms in subgroups according to each of the components of the "early life disadvantage" factor.
* Adjusted for age, smoking, education level and participating centre.
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(DOCX)

Author Contributions

Analyzed the data: ØS CS. Wrote the paper: ØS CS. Participated with study design and revision of the manuscript: JD. Participated in coordination and collection of data and revised the manuscript: TDS AJ RJB MB BF TG MH CJ RJ FM DN ERO FGR VS TS GW JPZ TA.

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Maternal preconception occupational exposure to cleaning products and disinfectants and offspring asthma

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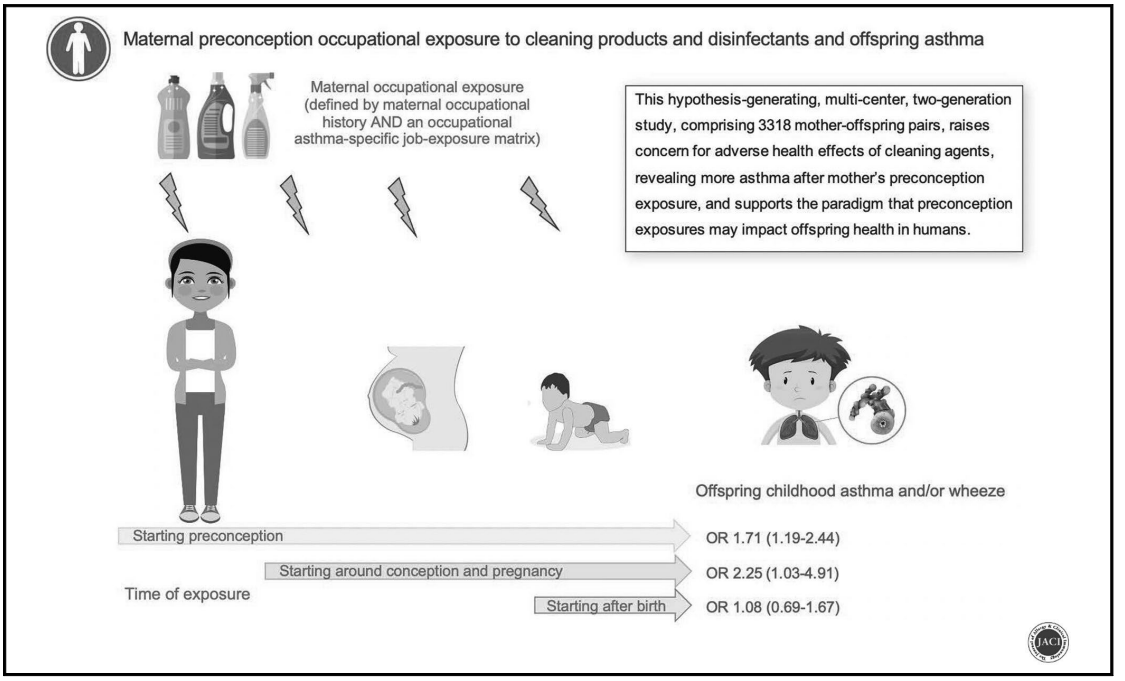
GRAPHICAL ABSTRACT



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Background: Emerging research suggests health effects in offspring after parental chemical exposures before conception. Many future mothers are exposed to potent chemicals at work, but potential offspring health effects are hardly investigated.
Objective: We sought to investigate childhood asthma in relation to mother's occupational exposure to cleaning products and disinfectants before conception.
Methods: The multicenter Respiratory Health In Northern Europe/Respiratory Health In Northern Europe, Spain and Australia generation study investigated asthma and wheeze starting at age less than 10 years in 3318 mother-offspring pairs. From an asthma-specific Job-Exposure Matrix and mothers' occupational history, we defined maternal occupational exposure to indoor cleaning agents (cleaning products/detergents and disinfectants) starting before conception, in the 2-year period around conception and pregnancy, or after birth. Never-employed mothers were excluded. Exposed groups include cleaners, health care workers, cooks, and so forth. Associations were analyzed using mixed-effects logistic regression and ordinary logistic regression with clustered robust SEs and adjustment for maternal education.
Results: Maternal occupational exposure to indoor cleaning starting preconception and continuing (n = 610) was associated with offspring's childhood asthma: odds ratio 1.56 (95% CI, 1.05-2.31), childhood asthma with nasal allergies: 1.77 (1.13-2.77), and childhood wheeze and/or asthma: 1.71 (95% CI, 1.19-2.44). Exposure starting around conception and pregnancy (n = 77) was associated with increased childhood wheeze and/or asthma: 2.25 (95% CI, 1.03-4.91). Exposure starting after birth was not associated with asthma outcomes (1.13 [95% CI, 0.71-1.80], 1.15 [95% CI, 0.67-1.97], 1.08 [95% CI, 0.69-1.67]).
Conclusions: Mother's occupational exposure to indoor cleaning agents starting before conception, or around conception and pregnancy, was associated with more childhood asthma and wheeze in offspring. Considering potential implications for vast numbers of women in childbearing age using cleaning agents, and their children, further research is imperative. (J Allergy Clin Immunol 2022;149:422-31.)

Key words: *Occupational exposures, preconception exposures, Job-Exposure Matrix (JEM), disinfectants, cleaning products, mother, childhood asthma, generation study, RHINESSA*

In many countries, the prevalence of childhood asthma has increased substantially since the 1980s.[1] The reason remains largely unknown; however, numerous mechanisms have been proposed, including events occurring early in life, both before and after birth.[1,2]

Abbreviations used

ISCO:	The International Standard Classification of Occupations
JEM:	Job-Exposure Matrix
OAsJEM:	Occupational Asthma-specific Job-Exposure Matrix
RHINE:	Respiratory Health In Northern Europe
RHINESSA:	Respiratory Health In Northern Europe, Spain and Australia

It is well established that workers who are directly exposed to cleaning products and disinfectants are at risk for respiratory symptoms and asthma.[3-9] In addition, it has been suggested that exposures related to cleaning activities may constitute a risk to long-term respiratory health.[10] A dose-response pattern with increased risk of respiratory symptoms and diseases by increased dose and duration of exposure has been reported.[5,6,9]

Cleaning products and disinfectants comprise a wide range of ingredients that are irritants and/or potential sensitizers.[5,7,9] Furthermore, the use of spray devices results in a substantial airborne exposure to nonvolatile aerosolized agents in the lower airways.

The biological mechanisms by which these products affect respiratory health are not fully understood but include both irritant and allergic mechanisms.[5,7,9,11] Moreover, recent evidence suggests that predisposition to adult-onset asthma may be related to the interaction between genes and occupational exposure to low-molecular-weight agents/irritants.[5] Genes potentially involved in adult asthma by interaction with occupational exposure play a role in the nuclear factor kappa B pathway, which is involved in inflammation.[12]

When future parents are exposed to chemicals, both their somatic and germ cells may be affected.[13] Emerging evidence from human and animal models suggests that preconception parental exposures may influence the health of future generations.[14-24] Previous studies on maternal occupational exposure and respiratory health in offspring are scarce.[25-27] However, a registry study found that several parental occupations were associated with increased hospitalization for childhood asthma among offspring.[26]

We hypothesize that preconception occupational exposures might impact offspring's health through germline cell exposure. Furthermore, occupational exposure in a pregnant woman might directly affect the fetus at critical time windows during the fetal growth and development.[28] Finally, a shared home environment influenced by maternal occupational habits might influence the health of the child after birth.[29] A theoretical model is summarized in Fig 1.

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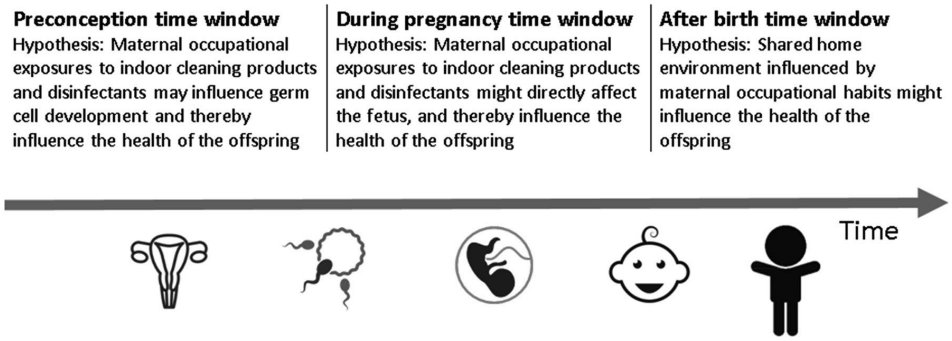

FIG 1. Theoretical model of time windows in which maternal occupational exposure to indoor cleaning products and disinfectants could have an impact on their offspring's health outcomes. When a future mother is exposed to chemicals before conception, even her germ cells will be exposed. Hence, the exposure might influence the health of her future offspring. In a pregnant woman, the exposure might directly affect the fetus, whereas shared home environment influenced by maternal occupational habits might influence the health of the child after birth.

The aim of our study was to investigate asthma risk in children whose mother had been occupationally exposed to indoor cleaning products and disinfectants before conception or around the time of conception and pregnancy.

METHODS

Study population

Two linked cohorts were used: the population-based RHINE (Respiratory Health In Northern Europe) study and the RHINESSA (Respiratory Health In Northern Europe, Spain and Australia) study of their offspring (www.rhinessa.net).[18,30] The present analysis includes data from 3318 RHINESSA study participants (offspring born 1962-1998) and their mothers who participated in the RHINE study (Fig 2). RHINE II included questionnaire-based data on persons born 1945 to 1973 from 7 centers in Northern Europe (Bergen in Norway, Umeå, Gothenburg, and Uppsala in Sweden, Aarhus in Denmark, Reykjavik in Iceland, and Tartu in Estonia). The survey was conducted from 1999 to 2001, and comprised a full occupational history for individual mothers within the time span 1963 to 1998.

The studies were approved by regional ethics committees, and all participants signed written informed consents.

Mother's exposure

Maternal occupational history, including job titles with start-year and stop-year for each job, was coded by an expert group according to the International Standard Classification of Occupations-1988 (ISCO-88).[31] Subsequently, each mother's ISCO job codes were combined with an Occupational Asthma-specific Job-Exposure Matrix (OAsJEM). The OAsJEM considers exposure to 30 specific sensitizers/irritant agents for all job codes in ISCO-88. The Job-Exposure Matrix (JEM) category "indoor cleaning" defines occupational exposure to indoor cleaning agents (=cleaning products/detergents and low/intermediate-level disinfectants).[32] Such exposures were present in 21 ISCO-88 job codes (see Table E1 in this article's Online Repository at www.jacionline.org).

In the present study, maternal occupational exposure to indoor cleaning agents was defined according to the OAsJEM as having had at least 1 ISCO job code with high (high probability and moderate to high intensity) or medium (low to moderate probability or low intensity) exposure to indoor cleaning agents for 6 months or longer. The reference category included mothers who had held at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to ISCO job code in combination with the OAsJEM.

Time windows of exposure were defined on the basis of when the first exposed job *started* (Fig 3); (1) Exposure only before conception (2 years or more before the child's birth year), (2) Exposure starting before conception and continuing around conception and pregnancy and/or after birth, (3) Exposure starting around conception and pregnancy, and (4) Exposure only after birth (starting the year after the child's birth year, or later). Because of the 1-year time resolution, the time window around conception and pregnancy covers 2 years, including approximately 3 to 15 months preconception, 9 months pregnancy, and 0 to 12 months infancy. In sensitivity analyses with smaller numbers, categories 1 to 3 were merged.

Offspring health outcomes

Three asthma outcomes, all starting before age 10 years, were defined on the basis of questionnaire data from RHINESSA adult offspring (wording given in this article's Online Repository at www.jacionline.org): childhood asthma, childhood asthma with nasal allergies, and childhood wheezing and/or asthma. Age 10 years was set as cutoff to distinguish childhood asthma and wheeze from asthma with onset in puberty or in adulthood.

Covariates

Potential confounders were identified on the basis of previous studies[2,17,33-36] and directed acyclic graphs.[33,37] Variables that had the potential to be associated with maternal occupational exposure and to cause childhood asthma/wheeze, and were not on the causal pathway between the exposure and outcome, were considered for inclusion in the model.[33] The minimal sufficient adjustment set included maternal education only[33,37] (see Fig E1 in this article's Online Repository at www.jacionline.org). Sensitivity analyses included adjustment for additional variables (offspring sex, nonsmoking mother, birth cohort).

Statistical methods

For the main analysis, associations between maternal exposure to indoor cleaning agents and offspring outcomes were analyzed using mixed-effects logistic regression with random intercept for study center and mother. In analyses stratified on offspring's birth cohort (1962-1979 and 1980-1998), offspring's sex, and mother's smoking habits, such models did not converge because of few exposed in some categories, and we used ordinary logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers. Association between the 5-category variable with level and timing of exposure and risk of asthma before age 10 years in the offspring was analyzed using mixed-effects logistic regression with random intercept for study center and mother.

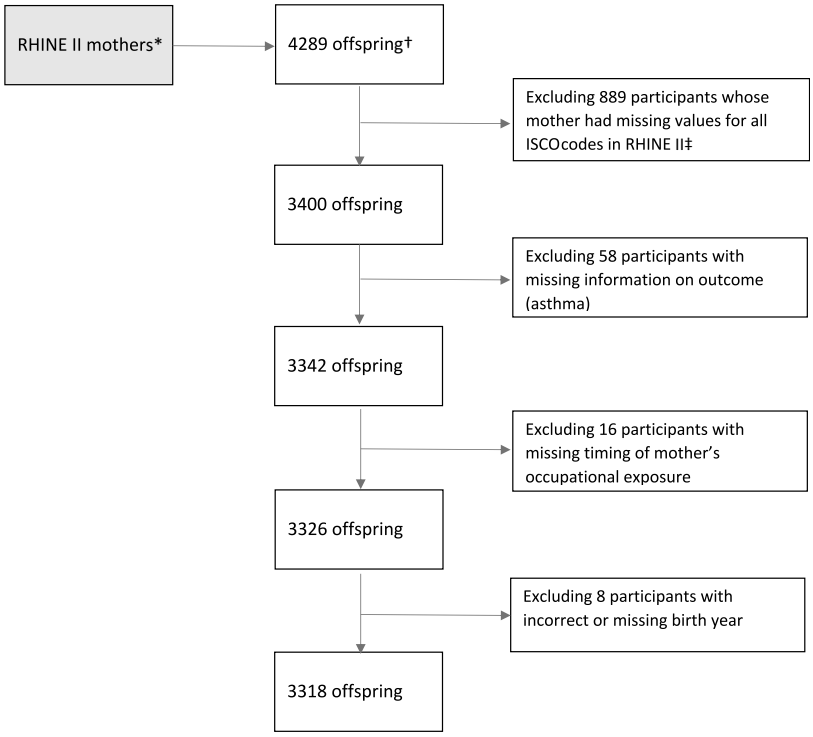

FIG 2. Definition of study population. *Female participants in the RHINE II study. †RHINE II offspring 18 years or older who had participated in the RHINESSA study. ‡Mothers who had missing values for all ISCO job codes included mothers who did not report any jobs, that is, those who never were employed, and those who failed to respond to this question in the questionnaire.

Two-sided tests and significance level of 5% were used. Analyses were performed in STATA15 (StataCorp LLC, College Station, Tex).

RESULTS

Of 3318 offspring, 1307 had a mother who had been employed for at least 6 months in a job that involved exposure to indoor cleaning agents, whereas 2011 had a mother who had held at least 1 job for 6 months or more, but no occupational exposure to such agents. Exposed mothers were slightly younger, had lower education, and smoked slightly more (Table I).

For 150 offspring (11.5% of the exposed), the mother had been exposed to indoor cleaning agents only before conception (scenario 1 in Fig 3); on average, this exposure stopped 7 years before the offspring was born (mean, 7.8 years; median, 7 years). In 610 persons (46.7%), maternal exposure had started before conception and continued (scenario 2), whereas maternal exposure started around the time of conception and pregnancy for 77 persons (5.9%) (scenario 3). Finally, in 470 persons (36%), the maternal exposure started after the offspring were born (scenario 4).

Offspring asthma outcomes appeared to be higher if the mother had been occupationally exposed to indoor cleaning agents only before conception. Maternal exposure starting before conception and continuing was associated with offspring's childhood asthma: odds ratio 1.56 (95% CI, 1.05-2.31), childhood asthma with nasal allergies: 1.77 (95% CI, 1.13-2.77), and childhood wheeze and/or asthma: 1.71 (95% CI, 1.19-2.44). Exposure starting around conception and pregnancy was associated with increased childhood wheeze and/or asthma: 2.25 (95% CI, 1.03-4.91). Exposure only after birth of the child was not associated with offspring asthma outcomes (Table II). Sensitivity analyses with adjustment for maternal smoking during pregnancy or offspring's childhood, and maternal asthma, slightly weakened the associations, but did not substantially alter the estimates (Table II).

Maternal exposure before conception or around conception and pregnancy appeared to be more strongly associated with offspring asthma if the exposure level had been high than if the exposure level had been medium (Table III). The magnitude of the associations of maternal exposure to indoor cleaning agents during preconception/pregnancy and childhood asthma appeared to be similar in male and female offspring (Table IV). The association was also consistent among offspring with a mother who did not smoke when she was pregnant or during their childhood (Table IV). Few cases in some exposure groups prevented detailed categorization in these sensitivity analyses. Sensitivity analyses stratified by birth cohort (1962-1979 and 1980-1998) suggested stronger associations for exposure back in time even though the CIs were overlapping (see Table E2 in this article's Online Repository at www.jacionline.org).

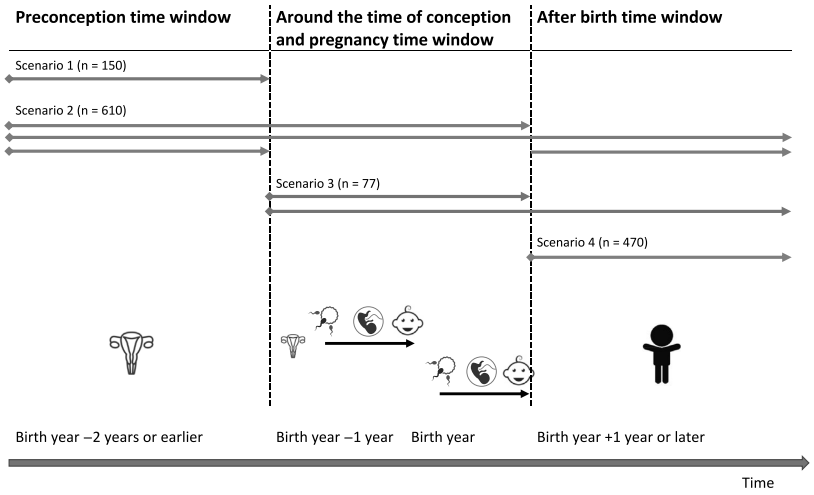

FIG 3. Real-life scenarios of time windows in which maternal occupational exposure to indoor cleaning products and disinfectants could have an impact on offspring health outcomes. Within each time window, the mother could have several consecutive jobs. Four exposure scenarios were defined on the basis of when mother's exposure started: (1) Exposure only before conception; (2) Exposure starting before conception and continuing into different time windows, around the time of conception and pregnancy, and/or after birth; (3) Exposure starting around the time of conception and pregnancy; and (4) Exposure only after birth. The time window around conception and pregnancy covers 2 years, including approximately 3 to 15 months preconception, 9 months pregnancy, and 0 to 12 months infancy.

TABLE I. Characteristics of the study population, according to mother's occupational exposure status

Characteristic	Total study sample	No jobs with exposure to indoor cleaning agents*	At least 1 job with exposure to indoor cleaning agents†	*P* value‡
n	3318	2011	1307	
Sex: female, n (%)	1900 (57.3)	1157 (57.5)	743 (56.9)	.69
Birth year, n (%)				
1962-1969	161 (4.9)	108 (5.4)	53 (4.1)	.21
1970-1979	907 (27.3)	534 (26.6)	373 (28.5)	
1980-1989	1318 (39.7)	789 (39.2)	529 (40.5)	
1990-1998	932 (28.1)	580 (28.8)	352 (26.9)	
Asthma before age 10 y, n (%)	234 (7.1)	127 (6.3)	107 (8.2)	.045
Mother's age at birth, mean ± SD	27.3 ± 4.9	27.5 ± 4.9	27.0 ± 5.0	.007
Mother's educational level, n (%)				
Primary	514 (15.5)	257 (12.8)	257 (19.7)	<.001
Secondary	1158 (34.9)	656 (32.6)	502 (38.4)	
College/university	1629 (49.1)	1090 (54.2)	539 (41.2)	
Missing	17 (0.5)	8 (0.4)	9 (0.7)	
Mother's smoking, n (%)				
No smoking during childhood	2143 (64.6)	1355 (67.4)	788 (60.3)	.01
Smoking during childhood	837 (25.2)	574 (23.7)	361 (27.6)	
Smoking during pregnancy	289 (8.7)	189 (7.7)	134 (10.3)	
Missing	49 (1.5)	25 (1.2)	24 (1.8)	
Asthma in mother, n (%)				
Yes	363 (10.9)	198 (9.9)	165 (12.6)	.07
Missing	149 (4.5)	99 (4.9)	50 (3.8)	

Information on mother's education and smoking during pregnancy and/or childhood was reported by the offspring in the RHINESSA study. Information on mother's asthma and occupational history was reported by the mother in the RHINE II study.

*Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.

†According to the ISCO-88 job code and the OAsJEM.

‡Differences in characteristics between offspring of exposed and nonexposed mothers were tested using bivariate linear regression for continuous outcomes, bivariate logistic regression for binary outcomes, and bivariate multinomial logistic regression for categorical outcomes. Clustered robust SEs were used to account for clustering of siblings within the same mother.

TABLE II. Associations between timing of mother's occupational exposure to indoor cleaning agents* and asthma, asthma with nasal allergies, and wheezing and/or asthma before age 10 years in the offspring†

Exposure time categories for offspring outcomes	n outcome/ n total (%)	OR (95% CI) Crude model‡	Model 2§	Model 3‖	Model 4¶
Asthma before age 10 y in the offspring					
n	234/3318 (7.0)	3318	3301	3254	2906
Timing of mother's occupational exposure					
No jobs with exposure to indoor cleaning agents#	127/2011 (6.3)	1	1	1	1
Exposure only before conception	12/150 (8.0)	1.29 (0.64-2.61)	1.26 (0.63-2.54)	1.29 (0.64-2.62)	1.31 (0.63-2.74)
Exposure started before conception and continued	55/610 (9.0)	**1.55 (1.05-2.29)**	**1.56 (1.05-2.31)**	**1.50 (1.00-2.24)**	1.46 (0.97-2.21)
Exposure started around the time of conception or pregnancy	9/77 (11.7)	2.26 (0.98-5.21)	2.30 (1.00-5.28)	2.27 (0.98-5.26)	2.32 (1.00-5.39)
Exposure only after year of birth	31/470 (6.6)	1.04 (0.66-1.64)	1.13 (0.71-1.80)	1.10 (0.68-1.76)	1.13 (0.69-1.87)
Asthma before age 10 y in the offspring, with nasal allergies**					
n	169/3253 (5.2)	3253	3236	3190	2852
Timing of mother's occupational exposure					
No jobs with exposure to indoor cleaning agents#	86/1970 (4.4)	1	1	1	1
Exposure only before conception	11/149 (7.4)	1.75 (0.84-3.65)	1.72 (0.82-3.60)	1.78 (0.85-3.71)	1.71 (0.77-3.78)
Exposure started before conception and continued	43/598 (7.2)	**1.77 (1.14-2.75)**	**1.77 (1.13-2.77)**	**1.72 (1.09-2.69)**	**1.62 (1.00-2.61)**
Exposure started around the time of conception or pregnancy	7/75 (9.3)	2.49 (0.99-6.27)	2.52 (1.00-6.36)	2.48 (0.98-6.26)	2.44 (0.94-6.37)
Exposure only after year of birth	22/461 (4.8)	1.07 (0.63-1.81)	1.15 (0.67-1.97)	1.09 (0.63-1.88)	1.08 (0.60-1.95)
Wheezing and/or asthma before age 10 y in the offspring					
n	267/3311 (8.1)	3311	3294	3247	2900
Timing of mother's occupational exposure					
No jobs with exposure to indoor cleaning agents#	143/2006 (7.1)	1	1	1	1
Exposure only before conception	15/150 (10.0)	1.50 (0.80-2.81)	1.46 (0.78-2.74)	1.49 (0.79-2.81)	1.52 (0.77-2.59)
Exposure started before conception and continued	66/610 (10.8)	**1.69 (1.18-2.40)**	**1.71 (1.19-2.44)**	**1.64 (1.14-2.37)**	**1.59 (1.08-2.34)**
Exposure started around the time of conception or pregnancy	10/77 (13.0)	**2.22 (1.02-4.83)**	**2.25 (1.03-4.91)**	**2.23 (1.02-4.89)**	2.01 (0.87-4.63)
Exposure only after year of birth	33/468 (7.1)	0.99 (0.64-1.53)	1.08 (0.69-1.67)	1.00 (0.64-1.58)	1.03 (0.63-1.68)

Boldface indicates statistical significant associations at significance level 0.05.
OR, Odds ratio.
*According to the ISCO-88 job code and the OAsJEM.
†Analyzed using mixed-effects logistic regression with random intercept for study center and mother.
‡Crude estimates with random intercept for study center and clustering by family in case of multiple offspring from the same mother.
§Adjusted for mother's level of education (primary, secondary, and college/university). Fully adjusted model identified by directed acyclic graphs.
‖Adjusted for mother's level of education and maternal smoking in 3 categories (no smoking, during pregnancy and/or childhood, during childhood).
¶Adjusted for mother's level of education, maternal smoking in 3 categories (no smoking, during pregnancy and/or childhood, during childhood) and maternal ever asthma.
#Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.
**Excluding 65 offspring with asthma without nasal allergies.

TABLE III. Level of maternal occupational exposure to indoor cleaning agents* and risk of asthma before age 10 years in offspring†

Exposure time categories for levels of exposure	n asthma/n total	Adjusted model,‡ OR (95 % CI)
Maternal occupational exposure		
n	234/3318	3301
Medium exposure§		
Timing of exposure‖		
No jobs with exposure to indoor cleaning agents¶	127/2011	1
Exposure started the year of offspring's birth or before	34/415	1.32 (0.84-2.08)
Exposure only after offspring's year of birth	12/239	0.81 (0.42-1.58)
High exposure#		
Timing of exposure‖		
No jobs with exposure to indoor cleaning agents¶	127/2011	1
Exposure started the year of offspring's birth or before	42/422	**1.83 (1.18-2.83)**
Exposure only after year of offspring's birth	19/231	1.52 (0.85-2.71)

Boldface indicates statistical significant associations at significance level 0.05.
OR, Odds ratio.
*According to the ISCO-88 job code and the OAsJEM.
†Analyzed using logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers.
‡Adjusted for mother's level of education (primary, secondary, and college/university).
§Low to moderate probability or low-intensity exposure to indoor cleaning for each ISCO-88 job code according to the OAsJEM.
‖Few cases in some exposure groups prevented a more detailed timing of exposure categorization than the year of offspring's birth or before vs after offspring's year of birth.
¶Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.
#High probability of exposure and moderate- to high-intensity exposure to indoor cleaning for each ISCO-88 job code according to the OAsJEM; with or without medium exposure.

TABLE IV. Mother's occupational exposure to indoor cleaning agents* and risk of asthma before age 10 years in subgroups of offspring—male offspring, female offspring, and offspring with nonsmoking mother†

Exposure time categories for offspring subgroups	n asthma/ n total	Adjusted model,‡ OR (95 % CI)
Male offspring		
n	121/1418	1411
Timing of exposure§		
No jobs with exposure to indoor cleaning agents	67/854	1
Exposure started the year of offspring's birth or before	39/366	1.38 (0.89-2.13)
Exposure only after year of offspring's birth	15/198	1.05 (0.57-1.92)
Female offspring		
n	113/1900	1890
Timing of exposure§		
No jobs with exposure to indoor cleaning agents‖	60/1157	1
Exposure started the year of offspring's birth or before	37/471	1.49 (0.95-2.36)
Exposure only after year of offspring's birth	16/272	1.14 (0.62-2.08)
Offspring with nonsmoking mother¶		
n	150/2143	2137
Timing of exposure§		
No jobs with exposure to indoor cleaning agents‖	83/1355	1
Exposure started the year of offspring's birth or before	51/538	**1.60 (1.09-2.36)**
Exposure after year of offspring's birth	16/250	1.15 (0.64-2.06)

Boldface indicates statistical associations at significance level 0.05.
OR, Odds ratio.
*According to the ISCO-88 job code and the OAsJEM.
†Analyzed in separate models using logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers.
‡Adjusted for mother's level of education (primary, secondary, and college/university).
§Few cases in some exposure groups prevented a more detailed timing of exposure categorization than the year of offspring's birth or before vs after offspring's year of birth.
‖Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.
¶Mother did not smoke when pregnant with them or during their childhood.

DISCUSSION

This 2-generation study finds that maternal occupation that involved exposure to indoor cleaning agents (cleaning products/detergents and disinfectants), when starting before conception, was associated with increased risk for childhood asthma in the offspring. This was found consistently for asthma, asthma with nasal allergies, and wheezing and/or asthma, and for offspring of nonsmoking mothers. There was modest evidence of an association with exposure that started around conception and pregnancy. Preconception exposure (suggesting germ cell impact) could not be definitely separated from exposure *in utero* (suggesting a direct effect on the fetus). Our hypothesis-generating results suggest potential impact of preconception exposure, because the estimates for exposure only before conception (small sample) were of crudely similar magnitude as estimates for preconception exposure continuing after conception (large sample). The associations appeared to be stronger with higher *versus* medium maternal exposure. Estimates were similar in male and female offspring, and fairly consistent with adjustment for maternal educational level, maternal smoking, and maternal asthma. Maternal exposure starting after birth of the offspring showed no clear associations with offspring outcomes, giving additional support to a specific role of preconception exposure rather than confounding.

To our knowledge, this is the first study that addresses potential offspring health impact of mother's preconception occupational exposure to cleaning products and disinfectants. Our findings are to some extent supported by a recent article suggesting increased risk for early-onset asthma if the mother had been occupationally exposed to allergens and reactive chemicals both before and after the offspring's year of birth.[38] This analysis of the RHINESSA/RHINE/ European Community Respiratory Health Survey cohorts studied 4 groups of occupational exposures, including 20 of the 30 asthmagens defined by the OAsJEM,[32] but *not* the JEM category "indoor cleaning," which is the focus of the present analysis. Furthermore, a recent analysis found higher asthma risk in offspring if mothers had been exposed to air pollution before age 18 years.[20] A role of preconception occupational exposure through the paternal line was suggested in an analysis of fathers' exposure to welding and metal fumes, showing increased asthma related to preconception exposure but no effect of postnatal exposure.[18] Indirect support to a role of preconception occupational exposure in childhood asthma is provided by a Swedish registry study that found that several occupations, in which the employees most likely would have been exposed to cleaning agents, were associated with an increased risk of hospitalization for childhood asthma in offspring.[26]

Emerging evidence from animal and human studies supports that environmental and occupational exposures might cause epigenetic changes that might be transmissible to offspring.[14-22,39] Such environmentally induced epigenetic alterations must be present in the germline to be transmissible to the next generation.[13,24] Alterations passed through the germline might result in inherited changes in gene expression in offspring in any kind of tissue and hence induce alteration in various tissues and cell types with impact on offspring phenotype.[13,16,40] With regard to cleaning agents, many have lipophilic properties and may accumulate in the future mother's fat tissue; thereby, such agents may constitute a continuous internal source of exposure because the accumulated chemicals subsequently are slowly released into the mother's bloodstream.[41]

Another potential mechanism for our findings could involve the microbiome. We speculate that maternal exposure to cleaning chemicals and disinfectants could influence the maternal microbiome, which in turn could influence her germline cells and thereby future offspring. Alternatively, the exposure could possibly contribute to persistent changes in the mother's microbiome, which may impact gestational biology directly. To our knowledge, there is no relevant literature exploring effects mediated by the microbiome across generations, but it is an interesting question for future research.

The increased risk for offspring asthma related to maternal exposure *during pregnancy* is biologically plausible, and supported by a rich literature showing that an unfavorable intrauterine environment may increase the risk of developing diseases later in life.[42,43] A Danish birth cohort study found that prenatal and postnatal maternal occupational exposure to low-molecular-

weight agents and irritants was associated with asthma in 7-year-old offspring.[25] A British birth cohort study found that maternal exposure to biocides/fungicides during and following pregnancy was associated with higher asthma risk in 7-year-old children.[27] Mother's domestic use of cleaning sprays during pregnancy was associated with increased risk of wheezing and lower respiratory tract infections during offspring's early life in an analysis of 4 Spanish birth cohorts.[44] Because most cleaning agents comprise low-molecular-weight chemicals and are lipophilic, they readily diffuse across the placenta,[28] and it seems plausible that they may affect the prenatal development of the airways.[28,42]

In the present study, the participants were born during the period 1962 to 1998. During this time interval, the chemical content, application devices, and cleaning methods changed considerably. Several studies have identified the use of cleaning sprays as an important risk factor for asthma and wheezing.[7,9,44,45] Unfortunately, our study could not investigate specific chemicals, cleaning methods, or time trends.

A major strength of the present study was the multicenter generational study design, with data from mothers and offspring from 2 separate but linked studies.[30] The mother provided information about her own occupational history in the RHINE II study, more than 15 years before the offspring provided information about their asthma and wheeze in the RHINESSA study. The multicenter design increases the external validity of the findings but may also introduce random error due to random differences between study centers, which would reduce observed associations toward the null.

The exposure assessment in relation to the birth year of the offspring represents another important strength of the study. Data included full parental occupational history comprising up to 10 ISCO job codes[31] for each mother with start- and stop-years, and OAsJEM classification of all these job codes with respect to exposure to indoor cleaning products and disinfectants.[32] These 2 measures, together with the birth year of the offspring, enabled us to model maternal occupational exposure into 4 time windows of interest. This is quite unique in a human study.

An inherent limitation in a human study is the lack of ability to disentangle the immediate preconception from the intrauterine time window. Women starting in a job before conception will often continue into other time windows, and probably few would quit an exposure immediately after conception. The modeling of time windows was also limited by the 1-year time resolution in employment period and offspring year of birth; thus, the category "Exposure started around the time of conception and pregnancy" included 3 to 15 months before conception. However, by defining "Exposure only before conception" as mother's occupational exposure that had ended 2 years or more before year of birth for each child (median, 7 years), this subcategory was well separated from the exposure category *in utero*. Because the association estimates were of similar magnitude for this subcategory and the subcategory in which the exposure started preconception and continued, a preconception effect seems likely.

Defining asthma in epidemiological studies implies some degree of misclassification. We analyzed 3 outcome variables capturing different aspects of asthma: asthma, asthma with nasal allergies, and wheezing and/or asthma. Reassuringly, these outcomes gave consistent results. The retrospective questionnaire data imply an inherited risk of recall bias when reporting childhood asthma back in time. However, both types of misclassification in definition of the outcomes, reported by the offspring themselves, are unlikely to be related to start- and stop-years of a range of different jobs reported by their mother in another survey. Thus, such misclassification is likely to have attenuated observed results but not to have produced spurious results.

The mothers' occupational exposure was based on job title and a JEM, and not self-reported exposure or personal measurements of exposure. This implies both limitations and strengths. Exposure measurements would be impossible in this setting because the exposure is back in time; furthermore, cleaning products and disinfectants constitute a mixed exposure with multiple constituents. We used an asthma-specific JEM[32] specifically designed for this kind of studies, based on an expert evaluation step to define the category "indoor cleaning." The JEM thus defines group averages of exposures, rather than exposure in each individual. Studies using a JEM are prone to a Berkson-type error, which in theory causes nearly unbiased effect estimates, but at the expense of loss of statistical power.[11] Thus, misclassification in exposure is likely to cause less precise results, but it is unlikely that our results are caused by information bias, while they might be underestimated because of nondifferential misclassification bias. Confounding by other occupational exposures that are correlated to exposure to indoor cleaning agents seems unlikely because exposure to cleaning and disinfectants was found in many different occupations (see Table E1). Rest confounding by socioeconomic status is possible. However, the variety in occupations with exposures to cleaning products and disinfectants reduces the chance for such confounding. Together with the adjustment for maternal education, we consider the risk of rest confounding by socioeconomic status to be relatively low. Rest confounding by smoking is unlikely because the results were consistent in offspring of never-smoking mothers.

Defining a reference group is critical in epidemiological studies involving occupational exposure. In this study, we compared offspring whose mother had been occupationally exposed to cleaning products and disinfectants with all other working mothers. Thus, the control group included offspring whose mother might have been occupationally exposed to any other of the 30 asthmagens in the OAsJEM[32] as well as persons with no such exposure. We considered the group of persons exposed to none of the 30 asthmagens more subject to selection bias, for instance, with regard to socioeconomic conditions, and therefore less appropriate as reference category. The group that was exposed only after the offspring's year of birth constitutes a different comparison group, which would have similar characteristics except the onset of exposure in relation to the birth year of a particular offspring. This group showed a null effect, strengthening the interpretation of a preconception/prenatal effect rather than shared environment.

Even though causality cannot be inferred from a single study, we speculate that the associations we observed in this study might possibly be causal.[46] Maternal occupational exposure preceded the onset of offspring disease, and a biological gradient is suggested. In addition, our results are consistent with the emerging understanding of intergenerational inheritance[16,39] and of how an unfavorable intrauterine environment might cause diseases later in life,[42,43] supporting the biological plausibility of our findings. Misclassification error is likely to be nondifferential, but unknown/unmeasured confounding cannot be ruled out.

Conclusions

We find a consistent association between mother's use of cleaning products and disinfectants at work that started before conception, and offspring asthma, in this 2-generation study. This is the first human study addressing offspring respiratory health effects of maternal preconception occupational exposure to cleaning products and disinfectants. Our hypothesis-generating study adds substantially to the emerging understanding of intergenerational effects. The use of cleaning products and disinfectants is widespread, not least in women of childbearing age. Our findings on adverse health effects of preconception exposure to such products adds a new dimension to the growing concern about health effects of cleaning agents. Because of potentially vast implications of this, there is an urgent need for focused mechanistic research and replication in human studies.

Data availability statement

The data set is held and managed by the RHINESSA study coordinating center at the Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway. Data cannot be made freely available because they are subject to Norwegian Data Protection regulations, but deidentified data can be made available to researchers on request. Requests for data can be sent to the principal investigator of the RHINESSA study: Cecilie Svanes, cecilie.svanes@helse-bergen.no.

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Key messages

- **This study finds more childhood asthma outcomes if the mother had held a job that included exposure to cleaning products/detergents and disinfectants before conception.**
- **The findings appeared to be stronger with higher *versus* medium exposure to indoor cleaning agents, and were consistent for 3 asthma outcomes, in offspring of never-smoking mothers, and on adjustment for potential confounding variables from 2 generations.**
- **The study raises concern for adverse health effects of cleaning products and disinfectants, even in the next generation, and supports the paradigm that exposures before conception may have an impact on offspring phenotype in humans.**

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METHODS

Study population

In this study, we used data from 2 linked surveys: (1) RHINE II (www.rhine.nu), a postal questionnaire follow-up of stage I of the European Community Respiratory Health Survey, which included randomly selected population-based samples of participants in more than 30 centers in Europe; and (2) RHINESSA (www.rhinessa.net), a questionnaire survey on offspring of the RHINE participants.[E1]

RHINE II included data on persons born from 1945 to 1973 from 7 centers in Northern Europe (Bergen in Norway, Umeå, Gothenburg, and Uppsala in Sweden, Aarhus in Denmark, Reykjavik in Iceland, and Tartu in Estonia). This survey, which took place from 1999 to 2001, comprised a full occupational history.

Our study population consisted of adult offspring who had participated in the RHINESSA study, but restricted to those who had a mother with at least 1 job lasting for at least 6 months and who had participated in the RHINE II study. The RHINESSA study was conducted in the period 2013 to 2016. In total, there were 4289 adult offspring of female participants in RHINE II, born before 1999. After excluding participants due to missing information on critical variables (Fig 2 in the main article), the final study population comprised 3318 adult offspring, of which 1307 had a mother with at least 1 job that involved exposure to indoor cleaning agents. The control group (n = 2011) included adult offspring whose mother had held at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents.

Exposure in mother

Characterization of exposure. RHINE II comprised a full maternal occupational history, including start- and stop-year for each job, based on the question "List your jobs including branch, your work tasks and the period of employment. Periods shorter than six months need not to be specified. Employment also includes work done by people with their own company." All jobs were coded according to ISCO-88.[E2]

An OAsJEM that considers exposure to 30 specific sensitizers/irritant agents was used to characterize the mothers' occupational exposure to indoor cleaning agents.[E3] In the OAsJEM, an expert group previously assessed the exposure to each of the 30 agents for all job codes in ISCO-88.[E2] The JEM category "indoor cleaning" was defined as exposure to cleaning products/detergents or low/intermediate-level disinfectants.[E3] A total of 21 different job codes in ISCO-88 included exposure to indoor cleaning agents; from cleaners in offices, hotels, and other establishments, building caretakers, domestic helpers and cleaners, health care personnel, institutional-based and home-based personal care workers, and hairdressers, to food handlers such as butchers, cooks, and waiters (Table E1). In the OAsJEM, the job codes were classified into 3 exposure-level categories: (1) "High" (high probability of exposure and moderate to high intensity); (2) "Medium" (low to moderate probability or low intensity); and (3) "Unexposed" (Table E1). For the main analyses, maternal exposure was defined as having held at least 1 job with high or medium exposure to indoor cleaning agents, lasting for 6 months or more.

The control group included offspring whose mother had held at least 1 job for at least 6 months, but not been occupationally exposed to indoor cleaning agents, according to ISCO job code and OAsJEM. However, the mother might have been occupationally exposed to any other of the 30 agents in the OAsJEM.[E3]

Time windows. In this observational study, it was impossible to establish mutually exclusive groups for maternal occupational exposure to indoor cleaning agents because most occupationally exposed women had been exposed during more than 1 single time window. Even if the first exposed job ended before conception, there were often later exposed jobs for the same woman. Based on the theoretical model (Fig 1 in the main article) and modeling of different real-life scenarios for maternal lifetime occupational exposure (Fig 3 in the main article), we decided to categorize maternal occupational exposure according to when her first exposed job started. Preconception exposure was defined as mother's occupational exposure to indoor cleaning agents that had started 2 years or more before year of birth for each child. Because we suspected that the mothers whose exposure also stopped within this time window differed from the mothers whose exposure continued, we decided to split the preconception category into 2 subcategories: Exposure only before conception and Exposure starting before conception and continued. This resulted in a total of 5 exposure categories: (a) No occupational exposure to indoor cleaning agents; (b) Exposure only before conception (= scenario 1 in Fig 3 in the main article); (c) Exposure started before conception and continued (= scenario 2); (d) Exposure started around the time of conception and pregnancy (scenario 3); (e) Exposure only after year of birth (= scenario 4). Occupational exposure around the time of conception and pregnancy was crudely assessed as exposure starting during the offspring's birth year or the year before birth for each child, because we only had start- and stop-year and not exact start- and stop-dates for each job. For different women, exposure in this time window included 3 to 15 months preconception exposure and up to 12 months exposure during offspring's infancy. For the Exposure only after birth year category, the mother's exposure to indoor cleaning agents started the year after the child's birth year, or later. In all the exposure groups, the mother could have several consecutive jobs (up to 10) with different exposure levels to indoor cleaning agents, or only 1 single job with such exposure.

To investigate whether level of exposure influenced the outcome, we also made a categorical variable in which we incorporated the level of exposure, according to the OAsJEM, for each woman.[E3] A mother with a combination of jobs with high and medium exposure was categorized as having high exposure, and start of exposure was defined as the start-year for the first exposed job regardless of the level of exposure in this job. Because of few cases, we combined the time windows before conception and time around conception and pregnancy in this variable, giving the following 5 exposure-level categories: (1) No occupational exposure to indoor cleaning agents; (2) Medium exposure starting the year of birth or before; (3) High exposure starting the year of birth or before; (4) Medium exposure, only after year of birth; (5) High exposure, only after year of birth.

Health outcomes in offspring

The RHINESSA study provided information given by offspring about their own asthma, allergies, and wheeze (www.rhinessa.net).

Childhood asthma was defined as an affirmative answer to the question "Do you have, or have you ever had asthma?" and a self-reported age less than 10 years on the question "How old were you when you first experienced asthma symptoms?" Children with nasal allergies were defined as the above, plus a confirmation to the question "Have you ever experienced nasal symptoms such as nasal congestion, rhinorrhea (runny nose), and/or sneezing attacks without having a cold?"

Childhood wheeze was defined as an affirmative answer to the question "Have you ever had wheezing or whistling in your chest?" and a self-reported age less than 10 years on the question "How old were you when you first noticed wheezing or whistling in your chest?" The outcome "Wheezing and/or asthma before age 10" was defined as an affirmative answer to either childhood asthma, or childhood wheeze, or both.

Age 10 years was set as cutoff to distinguish childhood asthma and wheeze from asthma with onset in puberty or adulthood because the latter 2 may be related to other causes and/or biased by other exposures, such as offspring's own smoking and occupational exposure.

Statistics

Descriptive statistics for the study population were calculated as mean and SDs for continuous variables, and counts and percentages for categorical variables. Differences in characteristics between offspring of exposed and nonexposed mothers were tested using linear regression for continuous outcomes, logistic regression for binary outcomes, and multinomial logistic regression for categorical outcomes. Clustered robust SEs were used to account for clustering of siblings within mothers.

Association between timing of exposure to indoor cleaning agents and risk of asthma before age 10 years in the offspring was analyzed using mixed-effects logistic regression with random intercept for study center and mother and reported as odds ratios with 95% CIs. The same method was applied for asthma before age 10 years with nasal allergies, and wheezing and/or asthma before age 10 years.

For models with stratification on offspring's birth cohort, offspring's sex, and mother's smoking, the mixed-effect logistic regression failed to converge because of the low number of outcomes within each exposure category, and we therefore applied ordinary logistic regression with adjustment for study center as a covariate and clustered robust SEs to account for clustering of siblings within mothers. In models with stratification on sex and mother's smoking, we also collapsed the 3 exposure categories for exposure before and during pregnancy into 1 category.

Association between the 5-category variable with level and timing of exposure and risk of asthma before age 10 years in the offspring was analyzed using mixed-effects logistic regression with random intercept for study center and mother.

Two-sided tests with a significance level of 5% were used in all analyses. All analyses were performed in STATA version 15 (StataCorp LLC, College Station, Tex).

Confounders/adjustment

Potential confounders in the association between mother's occupational exposure to indoor cleaning agents and offspring asthma and wheeze were identified a priori on the basis of previous studies,[E4-E10] and by using directed acyclic graphs[E4,E11] in the online tool http://www.dagitty.net/dags.html. Variables that had the potential to be associated with the exposure of interest and to cause childhood asthma/wheeze, such as parental educational level, asthma, and smoking, were considered for inclusion in the model (Fig E1). According to the online tool, which specifies minimal sufficient adjustment sets, the fully adjusted model indicated adjustment for maternal education only.[E4,E11]

Information on mother's educational level was reported by the offspring in the RHINESSA study.

Ethics

This study was approved by regional committees of medical research ethics in each study center according to national legislations. A written informed consent was obtained from each participant before participation.

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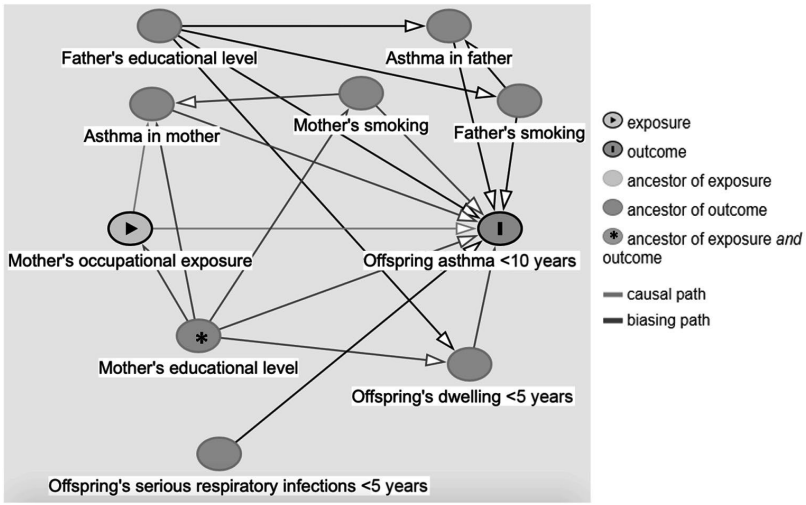

FIG E1. Directed acyclic graph (DAG) identifying potential confounders in the association between mother's occupational exposure to indoor cleaning agents and offspring asthma, based on previous studies. The DAG is created by the online DAGitty software, which is available at www.dagitty.net.

TABLE E1. ISCO-88 job codes* including exposure to indoor cleaning agents,† and corresponding exposure-level categories†

3-digit ISCO code (minor group)*	4-digit ISCO code (unit group)*	ISCO minor group or unit group description	Exposure level‡	N
	2230	Nursing and midwifery professionals	Medium	172
	3231	Nursing associate professionals	Medium	148
512		Housekeeping and restaurant services workers	Medium	2
	5121	Housekeepers and related workers	Medium	13
	5122	Cooks	Medium	94
	5123	Waiters, waitresses, and bartenders	Medium	56
513		Personal care and related workers	Medium	21
	5131	Child-care workers	Medium	267
	5132	Institution-based personal care workers	High	429
	5133	Home-based personal care workers	Medium	170
	5139	Personal care and related workers not elsewhere classified	Medium	17
	5141	Hairdressers, barbers, beauticians, and related workers	Medium	53
	5143	Undertakers and embalmers	Medium	3
	7411	Butchers, fishmongers, and related food preparers	Medium	17
913		Domestic and related helpers, cleaners, and launderers	Medium	1
	9131	Domestic helpers and cleaners	High	17
	9132	Helpers and cleaners in offices, hotels, and other establishments	High	295
	9133	Hand-launderers and pressers	Medium	7
914		Building caretakers, window and related cleaners	Medium	0
	9141	Building caretakers	Medium	45
	9142	Vehicle, window, and related cleaners	Medium	5

*ISCO-88's hierarchical structure consists of 10 major groups at the top level of aggregation, subdivided into 28 submajor groups, 116 minor groups, and 390 unit groups.
†According to the OAsJEM.
‡High: high probability of exposure and moderate to high intensity. Medium: low to moderate probability or low intensity, both according to the OAsJEM.

TABLE E2. Analyses stratified by year of birth for the child: Association* between timing of exposure† and asthma before age 10 years in the offspring (N = 3318)

Exposure time categories for birth cohorts	n asthma/N total	Crude model,‡ OR (95 % CI)	Model 2,§ OR (95 % CI)
Year of birth 1963-1979			
n		1013	1004
Timing of mother's occupational exposure			
No jobs with exposure to indoor cleaning agents‖	24/642	1	1
Exposure only before conception	0/12	—	—
Exposure started before conception and continued	7/125	1.48 (0.61-3.58)	1.53 (0.62-3.76)
Exposure started around the time of conception or pregnancy	3/36	2.34 (0.67-8.22)	2.34 (0.67-8.22)
Exposure only after year of birth	11/253	1.17 (0.56-2.44)	1.21 (0.56-2.59)
Year of birth 1980-1998			
n		2250	2242
Timing of mother's occupational exposure			
No jobs with exposure to indoor cleaning agents‖	103/1369	1	1
Exposure only before conception	12/138	1.10 (0.56-2.13)	1.10 (0.57-2.14)
Exposure started before conception and continued	48/485	1.27 (0.88-1.85)	1.28 (0.87-1.87)
Exposure started around the time of conception or pregnancy	6/41	1.95 (0.80-4.77)	1.97 (0.81-4.81)
Exposure only after year of birth	20/217	1.21 (0.72-2.04)	1.27 (0.75-2.14)

OR, Odds ratio.

*ORs are estimated using logistic regression with clustered robust SEs to take into account clustering of siblings. Study center is included as an adjustment variable in all models.

†According to the ISCO-88 job code and the OAsJEM.

‡Adjusted for study center.

§Adjusted for mother's level of education (primary, secondary, and college/university). Fully adjusted model identified by directed acyclic graphs.

‖Mothers with at least 1 job for 6 months or more, but with no occupational exposure to indoor cleaning agents according to the ISCO-88 job code and the OAsJEM.

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