Environmental Reduction Potential of Asthma Burden in Finland

Isabell Katharina Rumrich
MSc Thesis
General Toxicology and Environmental Health Risk Assessment (ToxEn) programme
University of Eastern Finland, Department of Environmental Science
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ABSTRACT

UNIVERSITY OF EASTERN FINLAND, Faculty of Science and Forestry
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ABSTRACT

The "Environmental burden of disease of asthma: Impact of mitigation options and protective factors" study was conducted as part of the TEKAISU project. Although the asthma incidence has been stable during the last years, the prevalence has been increasing. However the causes for this trend remain unknown. Currently the research in general is aimed mostly at improving the disease management and the identification of risk factors. This work aimed at quantifying the environmental attributable fraction and the environmentally prevented fraction of asthma. Mitigation options were developed in order to quantify reduction potential of asthma.

A life table model for the years 1986 - 2040 was developed using population data from Statistics Finland and data on asthma from the Finnish Social Security Institution (KELA). The population attributable fraction (PAF) was estimated according to WHO (2014d) and Laaksonen (2010) based on epidemiological studies and exposure data. Due to uncertainties in the asthma duration, prevalence-based Years Lived with Disability (YLD) were calculated according to WHO (2014b).

In 2011 25 % of the asthma burden was attributable to the selected risk factors (tobacco (smoking and second hand smoke), particulate matter ($PM_{2.5}$), indoor dampness and mould, pets (cat and dog) and 2 % was prevented due to protective factors (cat and dog). By banning tobacco products and supplementary small scale wood combustion in urban areas, halving the exposure to dampness and mould and doubling the exposure to cats and dogs in 2015, about 11 % of the total cumulative asthma burden between 2015 and 2040 would be reduced. If tobacco would be annually reduced by 10 % and residential small scale wood combustion in urban areas and dampness and mould is halved, and exposure to cats and dogs in doubled in 2015, the 25 year cumulative asthma burden would be reduced by 8 % of the total asthma burden.

Overall, it was shown that a significant fraction of the total asthma burden is attributable to environmental exposure. Furthermore it was shown that a combination of reduction in exposure to risk factors and an increase in exposure to protective factors seems capable of reducing the burden of asthma. Especially since asthma is still on the rise in Finland, control of exposures to decrease the asthma burden should be considered. However, more studies needed in order to increase the understanding in asthma pathogenesis and the mode of action of risk and protective factors.

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ABBREVIATIONS

BaU	Business as Usual
BoD	Burden of Disease
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability Adjusted Life Years
DW	Disability Weight
EBD	Environmental Burden of Disease
f	exposed fraction of the population
GBD	Global Burden of Disease
IHME	Institute of Health Metrics and Evaluation (University of Washington)
KELA	Finnish Social Security Institution
NO_2	Nitrogen Dioxide
OR	Odds Ratio
PAF	Population Attributable Fraction
PF	Prevented Fraction
$PM_{2.5}$	Particulate Matter with a diameter of 2,5 µm or less
RR	Relative Risk
RR○	Relative Risk per unit exposure
SHS	Second Hand tobacco Smoke
WHO	World Health Organization
YLD_I	incidence-based Years Lived with Disability
YLD_P	prevalence-based Years Lived with Disability
YLL	Years of Life Lost due to premature death

DEFINITIONS

Business as Usual (BaU): mitigation option, in which the exposure is not adjusted, but the currently estimated trend used in the future years

Combined mitigation scenario: a combination of selected mitigation options targeting different exposures

Mitigation option: a hypothetical change in a specific exposure in order to reduce the burden of asthma

Primary exposure: exposure that is included in the risk assessment and the mitigation options

Protective factor: an exposure that is associated with a decrease in the risk for asthma onset or symptoms leading to a prevention of asthma due to this exposure

Risk factor: an exposure that is associated with an increased risk for asthma onset or symptoms leading to increase in asthma attributable to this exposure

Secondary exposure: exposure that is only included in the risk assessment, but not in the mitigation option

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1 INTRODUCTION

Although asthma is a chronic disease, which affects an increasing number of people at any age, there are still many knowledge gaps concerning the etiology and associated risk and protective factors. Asthma is a common diagnosis, which affected 4.5 % of the population in the Helsinki metropolitan area in 2012, and some studies report a prevalence of as high as 10 %. Nevertheless, there is controversy among the scientific community whether asthma is an umbrella term for variety of conditions with similar symptoms or whether it is one disease with different phenotypes. The cellular mechanisms leading to asthma symptoms are roughly understood, but the timeline between the onset of the disease and the occurrence of first symptoms remains unknown. Moreover, the role of risk factors for the onset of asthma is largely still unknown. Hence, the treatment of asthma is purely symptomatic and the onset of asthma cannot be prevented by any measure at present date.

Recent research is focusing on genetic susceptibility as well as environmental stressors, co-morbidities and lifestyle factors as contributors to the onset of asthma or worsening of symptoms. Alone from PubMed 144 481 articles could be retrieved with the query “asthma” (14th July 2014). The current research can be mainly divided into studies aimed at identifying the cellular mechanisms and involved genes, dose-response assessment of risk and protective factors and risk assessment using a burden of disease approach. The burden of disease studies focus mostly either on the global burden or nationwide burden as well as specific exposures or diseases. However, current research does not set a focus on assessing the preventable fraction of a burden of disease.

A substantial fraction of asthma cannot be explained by proposed risk factors. Not only the days and years of healthy life which are lost due to severe asthma conditions and illness, also the limitations in life, such as reduced ability for physical activity and time which can be spent with hobbies and social contacts, as well as the involved costs, due to the need of medication, sick leaves from work and school and emergency room visits, contribute to the burden of disease. Therefore, asthma does not only have a great impact on the personal life of each affected individual, but also on the society as a whole. Furthermore, it is not possible to prevent the onset of asthma so far and the management of symptoms is mostly based on medication and the avoidance of symptoms triggers if they are known. The etiology is too

poorly understood in order to prevent the onset or develop the medication further to achieve more symptom free patients with the help of the medication.

The aims of this work are a quantification of the asthma burden and the components attributable to various risk functions. A literature review is done identifying risk and protective factors and their associated risk and the estimation of the background burden of disease of asthma. Focus is set on quantification of the reducible fraction of asthma burden. The NAS risk assessment paradigm (Figure 1) is followed with the first steps of the risk assessment (Hazard identification, exposure-response assessment and exposure assessment) are based on a literature review. The environmental burden of disease methodology is utilized for the risk characterization. Mitigation options are developed in order to be able to give recommendations for the reduction of the asthma burden (risk management).

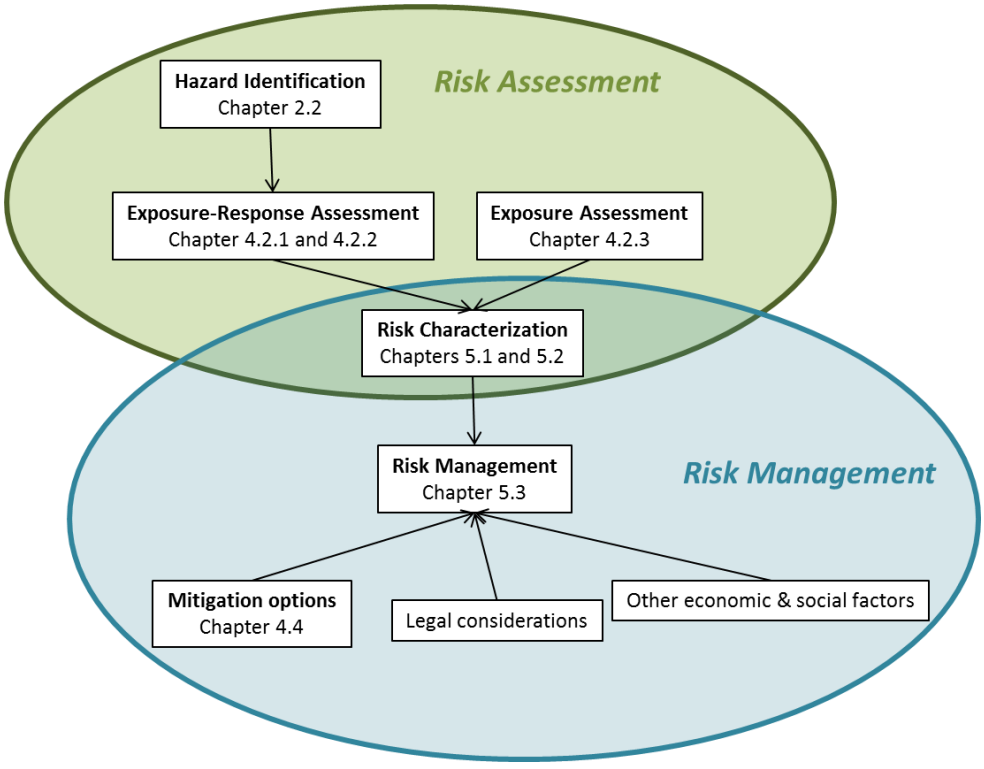


Figure 1: Risk assessment and risk management paradigm (modified from NAS, 1983)

2 LITERATURE REVIEW

2.1 ASTHMA AS A PUBLIC HEALTH PROBLEM

Asthma is a chronic inflammatory disorder of the respiratory tract causing welling and narrowing of the bronchial tubes. The symptoms include wheezing, chest tightness, breathlessness and coughing. The narrowing of the airways is caused by inflammation, bronchospasm and bronchial hyper responsiveness (BHR) (Zeliger, 2011a). Due to its heterogeneity and different disease phenotypes, it is proposed that asthma is not one disease, but more an umbrella for multiple diseases with the same clinical symptoms (Ober and Yao, 2011). The International Statistical Classification of Diseases (ICD) developed by the World Health Organization (WHO) distinguishes different asthma phenotypes, too (Box 1).

Box 1: Asthma classification according to ICD-10 (WHO, 2014a)

Chronic lower respiratory disease
- Other chronic obstructive pulmonary disease (J44)
  - Chronic obstructive bronchitis and chronic obstructive asthma, asthma (J45)
    - Predominantly allergic asthma (J45.0)
    - Non-allergic asthma (J45.1)
    - Mixed asthma (45.8)
    - Unspecific asthma (J45.9)
    - Status Asthmaticus (J46)

Other respiratory disease principally affecting the interstitium
- Eosinophilic asthma (J82)

The pathogenesis is not fully understood yet and therefore there is no special test or biomarker for the diagnosis of asthma established. The clinical diagnosis is based reversible expiratory airflow obstruction. This method has high sensitivity but low specificity, which means that it is able to find nearly all asthma cases, but it cannot differ between different lung diseases with similar symptoms, for example chronic obstructive pulmonary disease (COPD) (Ober and Yao, 2011). Overall, the children's developing respiratory system appears to be particularly sensitive for asthma (Zeliger, 2011b). Furthermore, the severity of the symptoms predicts the likelihood of the persistence of the condition (Yeatts et al, 2006). Currently, there is no treatment to prevent the onset of asthma, which is why the treatment aims at the decrease of impairment and risk (Lemanske and Busse, 2010). Impairment is defined as the frequency and intensity of symptoms and functional limitations at current or recent time, whereas risk refers to the risk of future adverse events like asthma symptoms (Schatz, 2012).

In Finland asthma has been identified as an important public health concern in the 1990s due to the heavy increase in incidence and prevalence. The Ministry of Social Affairs and Health set up the National Asthma Programme in 1994 to 2004, which aimed at improving the standards of asthma care and the limitation of the expected increase in the costs due to the disease. Sub programmes considered asthma medication (1997 -) and childhood asthma (2002 -) (Haahtela et al, 2006). During the asthma programme the number of annual hospital days of asthmatics was reduced by 69 % from prior the programme in 1993 to 2003. Nevertheless, the entitlements for anti-asthmatic drug reimbursement rose from 49 300 in 1981 to 212 000 in 2004. Compared to that, the total hospital days due to all causes rose only slightly by 10 % (Haahtela et al, 2006). In 2010 big differences in the number of hospital days per age group have been observed. 39 % of all hospital days were attributable to asthmatics older than 65 years, whereas patients being 15 years or younger and 5 years or younger only consumed 15 % and 12 % respectively. The subpopulation with highest risk for hospital admission due to asthma has been women older than 65 years. It is hypothesized, that this is due to a difficult treatment because of co-morbidities and memory impairment (Kauppi et al, 2012). The overall decrease in hospital days can be attributed to an earlier detection of asthma, more effective treatment and actively implemented guided self-management to prevent exacerbations (Kauppi et al, 2012). The number of deaths caused by asthma fell from 123 in 1993 to 85 in 2003, with only 10 deaths in asthmatics younger than 20 years. The costs per asthma patient have been reduced, too. In 1993 one patient cost on average 1611 €/a, whereas in 2003 the costs per patient were only 1031 €/a, which is a reduction of 36 % (Haahtela et al, 2006).

The underlying mechanism of asthma is characterized by a complex interaction of cells of the immune system and epithelial cells (Cohn et al, 2004). Research suggests that asthmatic symptoms, such as wheezing, occur when a critical degree of airway remodelling took place (Cohn et al, 2004). This assumption is based on the observation of inflammation and structural changes in the airways already long before first symptoms are noticed (Cohn et al, 2004). At present, it is not possible to determine, which cell or mediator is the initiator of the development. (Cohn et al, 2004). Some studies suggest that overall there are two main cellular pathways: an atopic one, which is mediated by the adaptive immune system, and a non-atopic one, which is mediated by the innate immune system. It is very controversial in what extent these pathways are similar (Pillai et al, 2011 and Douwes et al, 2002).

The described immune response is controlled by genes, which code for the involved proteins. Therefore, the individual genetic background and hence, the genetic susceptibility is a major risk factor for the development of asthma (Stanwell Smith, et al, 2012). The susceptibility can be inherited from the parents. 80 % of children, who's both parents have asthma, develop asthma themselves. If only one parent has asthma, 40 % of the children develop the conditions. The incidence of asthma of children without asthmatic parents is substantially lower (Yeatts et al, 2006).

2.2 IDENTIFICATION OF ASTHMA ASSOCIATED EXPOSURES

This work follows the NAS (1983) risk assessment and risk management paradigm (Figure 1). A systematic literature search was conducted in order to identify environmental exposures associated with asthma. In this sub-chapter the search history will be described as well as the selection process and literature background of the exposures, which have been selected to be included in the risk assessment.

2.2.1 Systematic Literature Search

A literature search was conducted in order to identify environmental exposures associated with asthma between February 2012 and May 2013, with a search update in June 2014 using seven (7) international search engines on scientific literature. The search engines and bibliographic databases are listed together with search terms in Box 2.

Box 2: Literature search – used databases and queries
Databases: PubMed, Scopus, Web of Science – WoS (ISI), SpringerLink, Science Direct (Elsevier), Google Scholar and Wiley Online Library (The Cochrane Library)

Search queries: asthma; asthma AND environment; asthma AND risk; asthma AND environment NOT atopy; asthma AND risk NOT atopy; asthma AND mechanism; asthma AND risk NOT occupation*; asthma AND environment NOT occupation*; asthma AND protecti*

After screening the title, publication year and abstract, a total of 235 articles published between 1982 and 2014 were retrieved for further assessment. Papers were evaluated for the content and due to missing information (such as quantitative dose-response data), poor study

quality, focus on non-environmental and occupational exposures and atopy instead of asthma and multiple papers on same studies, 22 articles were selected for a detailed consideration. The studies, which were excluded due to non-environmental exposures or unlikelihood of exposure in Finland, are summarized in Appendix I. In a third selection step further exposures have been excluded based on the likelihood of exposure in Finland (i.e. cockroaches), a rough estimation for the population attributable fraction and whether reliable exposure data are available. This exclusion step resulted in the selection of 12 papers covering 13 exposures for the estimation of the environmental burden of asthma in this work (Figure 2).

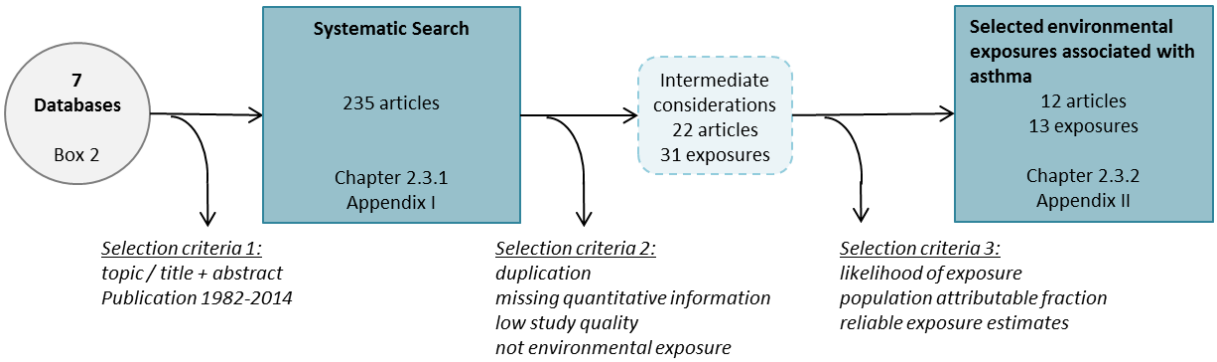


Figure 2: Selection process of articles and exposures from literature search to inclusion in the environmental asthma burden assessment

2.2.2 Review of Environmental Exposures Associated with Asthma

An overview of the associations between the thirteen environmental exposures identified in the literature search (Figure 2) and asthma is given here. Since the studies did not clarify if they investigate the relationship with onset or aggravation of asthma and no scientific justification was given, all reviewed factors are applied on asthma prevalence in this work.

Second Hand Tobacco Smoke (SHS) affects the onset of asthma, as well as the response to asthma treatment with Corticosteroids (Stapleton et al, 2011). Prenatal smoking, as well as SHS, is associated with asthma symptoms (Yeatts et al, 2006 and Subbarao et al, 2009). The effects of prenatal and postnatal exposure to SHS on asthma were assessed in a meta-analysis by Burke and colleagues (2012). Exposure to SHS prenatal maternal, postnatal maternal, paternal and in the household were all associated with an increased risk of asthma onset in the childhood. The association between SHS and asthma was assessed in the OLIN paediatric study, which is a longitudinal study conducted in Northern Sweden. The results of this study

suggest a positive association between SHS exposure and asthma in teenagers (Hedman et al, 2011). According to Jaakkola et al (2003) the risk for asthma onset caused by SHS is increased, too. Additionally, the evidence of the effects of SHS on children's asthma has been concluded to be sufficient by the Environmental Protection Agency of California, United States (Cal-EPA, 2005).

The relationship for active tobacco smoking and asthma is not as clear as SHS, but new insights are gained daily (Annesi-Maesano et al, 2004). Active tobacco smoking is associated with uncontrolled asthma (Schatz, 2012). Additionally, it is associated with asthma onset (Yeatts et al, 2006). A gender-difference in the risk of asthma onset due to active smoking may exist (McLeish and Zvolensky, 2010). The risk for asthma symptoms is increased in smoking adolescents in France, according to Annesi-Maesano et al (2004). The occurrence of symptoms seems to be more likely in smoking adults, too (Langhammer et al, 2000).

Particulate Matter (PM), as well as Nitrogen dioxide (NO_2), are acting direct or indirect as oxidant leading to oxidative stress and cell damage. As a result the lung tissue is constantly damages and repaired (WHO, 2005). PM are included in this work, but only fine particles with a diameter of less than 2.5 µm are considered, because this fraction is dislocating deep into the alveoli of the lungs and therefore are believed to be more prone to cause chronic respiratory symptoms. According to the WHO the evidence of the causality between air pollution and aggravation of asthma in children is sufficient (WHO, 2000). In line with that, an increase in in the antioxidant metabolism can be observed after exposure to NO_2. Moreover, NO_2 exposure is associated with changes in lung lipids, cell injury and an increase in its associated enzymes, as well as the induction of oedema (WHO, 2010a). However, it is thought to be mostly an indicator for other traffic-related air pollutants rather than the causing agent itself (Guarnieri and Balmes, 2014).

The exposure to dampness and/or mould in buildings means the exposure to a variety of different fungi, bacteria, viruses, as well as their toxins and microbial volatile organic compounds. The relation between the exposure to a single compound out of this mixture and the onset of respiratory symptoms is not fully understood yet (WHO, 2009a). The role of dampness in association to asthmatic conditions is unclear. The evidence for a causal relationship between exposure to indoor dampness and exacerbation of asthma was concluded

to be sufficient (WHO, 2009a). But there is controversy about an association between exposure to moulds and onset of asthma. An increase in exposure to fungi seems to be the causal factor of this exposure (Richardson et al, 2005). Richardson and colleagues (2005) concluded that there is no evidence for a causal relationship between exposure to moulds and the onset of asthma. Karvala and her colleagues (2011) assessed the association of exposure to dampness and mould at the workplace and risk of asthma onset, in a population, which already suffered from asthma-like symptoms, but lacked the decrease in lung function for an asthma diagnosis. Their study suggests, that dampness and mould exposure can cause asthma onset, if asthma-like symptoms already persist. The ENRIECO initiative, a meta-analysis of eight European birth cohorts, reported an increased risk of asthma onset in school aged children for early-childhood exposure to dampness and mould (Tischer et al, 2011). A meta-analysis showed an association between both, the exposure to dampness and mould and asthma onset as well was asthma symptoms (Fisk et al, 2007).

There is controversy about the evidence for a causal relationship between allergy and asthma. The risk of asthma exacerbation is increased in sensitized individuals in relation to the exposure to the allergen. The positive association of exposure to pollen and asthma symptoms in sensitized populations was reported in different studies (DellaValle et al, 2012). Although there is controversy about the causality between asthma and allergy, allergies might contribute significantly to the asthma burden in Finland.

Although the impact of living in a farm environment and exposure to livestock is repeatedly investigated in terms of its association to asthma to determine the consistency of the ‘Hygiene Hypothesis’, the evidence of exposure to cat or dog as a risk or protective factor is not sufficient. Chen and colleagues (2010) concluded in their meta-analysis that exposure to cat or dog in early childhood as an effect on development of asthma symptoms up to school age. Mostly, these exposures are proposed as protection factors, but which exposure in detail might lead to the protection is controversial. Exposure to fungi and bacteria and the diversity of exposures, as well as the consumption of raw cow milk have been suggested to be the specific exposure causing the protection (Antó, 2012). According to Ege et al (2011), exposure to *Eurotium* species or *Penicillium* species, which are both characteristic for farm environment, can prevent the occurrence of asthma symptoms. However, the evidence for a causal relationship between exposure to fungi and bacteria and asthma is not sufficient. Different modes of action have been proposed so far, for example the activation of the innate

immune system. The activation acts partly via pattern-recognition receptors, such as toll-like receptors, which in turn activate induce regulatory T helper cells. Th1 cells might be activated and counterbalance Th2 cells, whose activity is increased in asthmatic individuals. These proposals are not sufficient though, because small numbers of microbes and a small exposure should be enough to see the beneficial effect, because the number of pattern-recognition receptors is very limited. A second proposed mode of action is the effect of a broad variety of microbes on the colonization of the airways. The exposure of many different microbes might prevent the colonization by harmful bacteria. There is controversy about the exact species presenting protective properties (Ege et al, 2011).

The impact of formaldehyde on asthma onset and symptoms is controversial (Jie et al, 2011). According to the WHO evidence for causality between exposure and asthma onset is not sufficient (WHO, 2010b). However, McGwin Jr. and colleagues. (2010) conducted a systematic review of formaldehyde exposure and asthma in childhood. They included 10 studies from the United States, Australia, Sweden, United Kingdom, China, Japan and India. Their analysis suggests a slightly increased risk of asthma symptoms in children. Rumchev and colleagues (2002) study, which is used as source for the risk estimate of formaldehyde exposure and asthma, is included in that meta-analysis.

Recent research proposes mechanism of actions for the causality between childhood weight and asthma focusing on the development of the immune system and low level chronic inflammation. But the impact of underweight and obesity remains controversial. Nevertheless, research suggests, that a too low weight in early childhood is associated with an increased risk in asthma in later childhood. It is proposed, that obesity, which is only present in early childhood, is beneficial for the postnatal lung development and alveolarization and therefore prevents asthma. Many times obese children keep being obese in later life, too. Obesity is the cause of many metabolic diseases and is a risk factor for asthma, if individuals are obese in later life (Zhang et al, 2010). Fetal and infant growth and weight gain pattern are proposed to be associated with childhood asthma, too. Studies reported that smaller and lighter children are more prone to develop asthma than children with an average size and body weight (Duijts, 2012 and Zhang et al, 2010). On the other hand, other studies reported, that an increased weight gain during infancy is positively associated with an increase in risk of asthma (Flexeder et al, 2012).

The effect of breast feeding on asthma is controversial. Exclusive breast feeding for a longer period of time was reported to be a protective factor for asthma onset in later childhood (Brew et al, 2012), whereas in other studies the associated risk of asthma was increased (Subbarao et al, 2009). Breast feeding is attributed to a better functioning immune system and by that with a protection of overreaction of the immune system, which might trigger asthma (Brew et al, 2012). The proposed reason for an increase in asthma prevalence is the exposure to fat-soluble chemicals via breast milk, which might induce asthma symptoms. (Takemura et al, 2001). Nevertheless, more studies suggest a negative association between breast feedings and asthma.

2.2.3 Information Sources for Asthma Status Used in Considered Studies

Epidemiological studies use different sources of information for the disease status. One study used information obtained from health care facilities (Jaakkola et al, 2003), but commonly participant questionnaires were used. The questionnaires differ in the wording for asking about disease history and asthma. Three times it was asked for physician diagnosed asthma or wheezing (Rumchev et al, 2002, Zhang et al, 2010, Ege et al, 2011), whereas in two other studies it was only ask generally whether the subject has ever had asthma (‘Have you ever had asthma?’) (Annesi-Maesano et al, 2004, Langhammer et al, 2000) indicating a self-reported status that does not necessarily include any doctor diagnosis.

Wheezing was included as asthma phenotype in some studies, if it occurred more than once and was more or less persistent. Two studies defined that more than one diagnosis of wheezing within a year is enough for a positive asthma definition (‘Have you ever had any attack of wheezing or breathlessness during the past 12 months?’) (Annesi-Maesano et al, 2004, Langhammer et al, 2000). One study demanded four or more diagnosis of asthma within a year for a positive asthma occurrence (Olmedo et al, 2011). Questions about the use of asthma medication were included in some questionnaires, too. The questions varied greatly from a general question such as ‘Do you use or have you used asthma medication?’ (Langhammer et al, 2000, Olmedo et al, 2011) to detailed questions about prescription of short- or long-acting β-agonist, long-term controller medications or both (Zhang et al, 2010). If results were available on for asthma excluding wheezing, these results were used in this work due to the different definitions when wheezing is counted as asthma.

In publications about meta-analysis, the used sources for information on the asthma status of the included studies, were not specified (Cal-EPA, 2005, Anderson et al, 2013, Brew et al, 2012).

2.3 CHARACTERISATION OF PUBLIC HEALTH PROBLEMS USING BURDEN OF DISEASE METHODOLOGY

Burden of Disease (BoD) is a concept used to characterize the overall annual loss of health in a population, often on a national level. Environmental Burden of Disease (EBD) refers to the fraction of BoD that can be attributed to environmental risk factors. An overview of these two concepts is given in this section.

2.3.1 Burden of Disease (BoD)

Burden of Disease (BoD) is a concept that quantifies the years of healthy life lost due to diseases and death.

The BoD concept was developed in the WHO Global BoD programme launched in 1990 (WHO, 2004a). The programme accounted for more than 100 diseases and injuries for eight regions in the world. It was the first global study aiming at quantifying the contribution of single diseases on the total burden of disease. Mortality and morbidity by age, sex and region were estimated and they are thought to be comprehensive and internationally consistent. The national input datasets were provided by the member states of the WHO. The study has been updated for the years 2000 – 2002 and 2004 with an update on 26 global risk factors (WHO, 2004a).

The burden of disease (BoD) consists of two components: morbidity measured as Years Lived with Disability (YLD) (Equation 1) and mortality measured as Years of Life Lost due to premature death (YLL) (Equation 2). YLD is the sum of all years spent with illness or disability for all individuals in the studied population. YLL sums all years, which are lost compared to the life expectancy of the studied population due to a death before the life expectancy. The sum of YLD and YLL measure the general gap in health of the studied

population compared to a population at perfect health (Equation 3) (Hänninen and Knol, 2011). YLD consists of incidence data of the disease (n_i), the duration of the disease (L) and the disability weight (DW) of the disease (Equation 1). The duration is the time a person suffers on average from a disease, measured in years. The DW is the severity of a disease, with 0 meaning perfect health and 1 being equal to death (WHO, 2003). The unit of BoD is Disability Adjusted Life Year (DALY).

$$YLD_I = n_i \times L \times DW \qquad \text{Equation 1}$$

YLL is based on the number of deaths (N) and the remaining years to standard life expectancy at age of death (LE) (Equation 2).

$$YLL = N \times LE \qquad \text{Equation 2}$$

$$BoD = YLD + YLL \qquad \text{Equation 3}$$

A large update of the 1990's project was done with the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD, 2010), which is conducted by the Institute of Health Metrics and Evaluation (IHME) of the University of Washington, which first results have been published in 2012. The scope of this study is with an inclusion of 291 diseases and injuries, 67 risk factors and 21 regions significantly broader (IHME, 2014). Furthermore, the methods and databases developed within the project enable an easier update of the data by using the provided platforms (Lim et al, 2012). The Lancet dedicated Issue 9859, which has been published in December 2012, to the project including 17 publications. In contrast to the WHO global BoD project, IHME did not use incidence data as input for the YLD calculation, but prevalence data (Equation 4). Due to this change, it is not necessary anymore to include the disease duration estimation, but only the number of prevalent cases (n_P) and the disability weight (DW).

$$YLD_P = n_p \times DW \qquad \text{Equation 4}$$

2.3.2 Environmental Burden of Disease (EBD)

Various studies aimed at connecting the burden of disease to known environmental risk factors and the quantification of the attributable fraction in order to utilize the information in risk management. World Health Organization launched the Quantifying environmental health impacts -programme in early 2000's (WHO, 2003) and has since then performed more than ten global evaluations.

One of the latest large studies on environmental burden of disease is the GBD (2010) study. With the included 67 risk factors, this IHME study assessed the BoD attributable to selected few environmental factors such as household air pollution, ambient PM, sanitation, ozone, lead, and radon (Lim et al., 2012).

Attributing health risks to risk factors was developed by epidemiologists in the 20th century. Levin first proposed the concept of the population attributable fraction (PAF; Levin, 1953). Since then, the phrases "population attributable risk," "population attributable risk proportion," "excess fraction," and "etiologic fraction" have been used interchangeably to refer to the proportion of disease risk in a population that can be attributed to the causal effects of a risk factor or set of factors (Rockhill et al. 1998; Hänninen, 2015)

PAF is the proportion of outcome, which is thought not to occur in the population under study without exposure to the risk factor (WHO, 2014d). Thus, the PAF as defined in Equation 5, gives the proportion of the disease, which can be attributed to the stressor, which is studied (Laaksonen, 2010). The methodology is directly applicable also to protective associations, where relative risks are smaller than 1. In these cases PAF becomes negative, and the concept of Prevented Fraction (PF) (Equation 6) has been introduced. The PF gives the proportion of outcome which has been prevented by exposing the population to a protective factor (Laaksonen, 2010).

$$PAF = \frac{f \times (RR - 1)}{f \times (RR - 1) + 1} \qquad \text{Equation 5}$$

$$PF = 1 - \frac{1}{1 - PAF} \qquad \text{Equation 6}$$

The relative risks, which are used in this work, are either relative risk (RR) or odds ratio (OR). According to Hänninen and Knol (2011) OR can be used as an estimate of the RR, if the prevalence of the disease is relatively low in the non-exposed population. The asthma prevalence used in this work is about 5 % and therefore, if studies only report an OR, the OR has been used as the RR. RR gives the probability to develop the disease at a specific exposure compared to the risk in a non-exposed group therefore it gives a risk probability (Hänninen and Knol, 2011).

For ambient exposures, such as air pollutants, the whole population is exposed and the attributable fraction does not depend on the exposed population, but the concentration of exposure. Therefore, the used RR has to be derived from the relative risk per unit exposure (RR○) with the RR being the RR○ to the power of exposure (E) (Equation 7) (Hänninen and Knol, 2011).

$$RR = e^{E \ln RR^{\circ}} = RR^{\circ E} \qquad \text{Equation 7}$$

The environmental burden of disease (EBD) is the product of PAF (or PF) and BoD (Hänninen and Knol, 2011).

First asthma EBD estimates for Finland have been published in the European Perspectives on Environmental Burden of Disease – Estimates for Nine Stressors in Six European Countries (EBoDE) project. It is a project, which has been launched by the European Office of the WHO. The six participating countries have been Belgium, Finland, France, Germany, Italy and the Netherlands. It was aimed at guiding environmental health policy making by harmonizing estimates of EBD for selected stressors (benzene, dioxins (including furans and dioxin-like PCBs), second hand tobacco smoke, formaldehyde, lead, noise, PM and radon). The focus of this study was therefore not to quantify the contribution of diseases to the total burden of disease, but to identify and quantify the attributable fraction of the burden to specific stressors (Hänninen and Knol, 2011).

The SETURI project is a national project implemented in Finland in 2010. It is a collaboration project between four Finnish research institutions. The aim of the project has been to rank the most relevant chemical, physical, occupational and environmental exposures in Finland. The included stressors, which have been more than 40, were chosen according to the public health

relevance, having possibly high individual risk or due to public concern. Again the focus of the work was laid on the exposure to specific stressors and the attributable risk and not the attributable burden of a disease to the total burden of disease (Asikainen et al, 2013).

The HealthVent study aimed at investigating the contribution of poor indoor air quality on the total Burden of Disease in 26 countries of the European Union and the identification of possibilities to increase the indoor air quality and with that decrease the BoD of associated diseases. This work focusses only on a specific set of exposures and outcomes, which are associated with poor indoor air quality and assesses how the BoD changes if the indoor air quality is improved (Hänninen and Asikainen, 2013).

As one of the first Finnish project, the TEKAISU project aims at the development and assessment of control options capable of reducing the EBD. As part of it, control options for active smoking, particulate matter ($PM_{2.5}$) and Radon have been developed (Kutvonen, 2014).

3 THE AIMS OF THE WORK

The overall aim of this work is the development and evaluation of a set of mitigation options for asthma in Finland in order to quantify the environmentally reducible fraction. The outcomes of this work contribute to the assessment of environmental burden of disease and the prioritization of mitigation options in Finland, currently done in the "Ympäristöstä aiheutuvien terveyshaittojen arviointi kaikkeen suunnitteluun ja päätöksentekoon" (TEKAISU) project.

The methodological aims of this work are the development of a life table model to quantify the trends in population age structure and exposures and the evaluation of the suitability of different measures of asthma burden, including comparison of incidence and prevalence based estimates.

The specific objectives are to

i. To characterize the population and age-specific trends of asthma in Finland from 1986 to 2040.
ii. To identify adjustable environmental risk and protective exposures associated with asthma using a systematic literature review.
iii. To quantify the asthma burden associated with the selected exposures in Finland.
iv. To identify mitigation options related to the selected risk and protective exposures from the literature.
v. To estimate the reduction potential of asthma in Finland.
vi. To prioritize mitigation options according to the reduction potential.

4 MATERIAL AND METHODS

A life table model for 1-year age groups from 0 - 99 years and the years 1986 to 2040 was developed. The life table was used to estimate the Finnish population, as well as the asthma burden (Chapters 4.1.1and 4.1.2).

In order to be able to estimate the environmental attributable fraction of the asthma BoD, the Population attributable fraction (PAF) was calculated (Equation 5 and Equation 6). Since the model was a life table, it was tried to extrapolate all needed data to the age groups and the years included in the model. The RRs were identified in a literature review and extrapolated for the age (Chapters 4.2.1 and 4.2.2) and the exposure estimates were extrapolated for the years 1986 to 2040 where it was possible (Chapter 4.2.3).

The environmental attributable and environmental prevented fractions of the total asthma burden, as well as the plausibility and feasibility of adjusting the exposure, were used to select those exposures, which were used to estimate the asthma burden reduction potential (Chapters 4.3 and 4.4 and Figure 3). By adjusting the exposure mitigation options were developed and tested for their reduction potential. Methodological, the same calculation with the unchanged exposures and the adjusted exposures were done and the difference between these two asthma burden estimates were considered to be the reduction potential of the mitigation option.

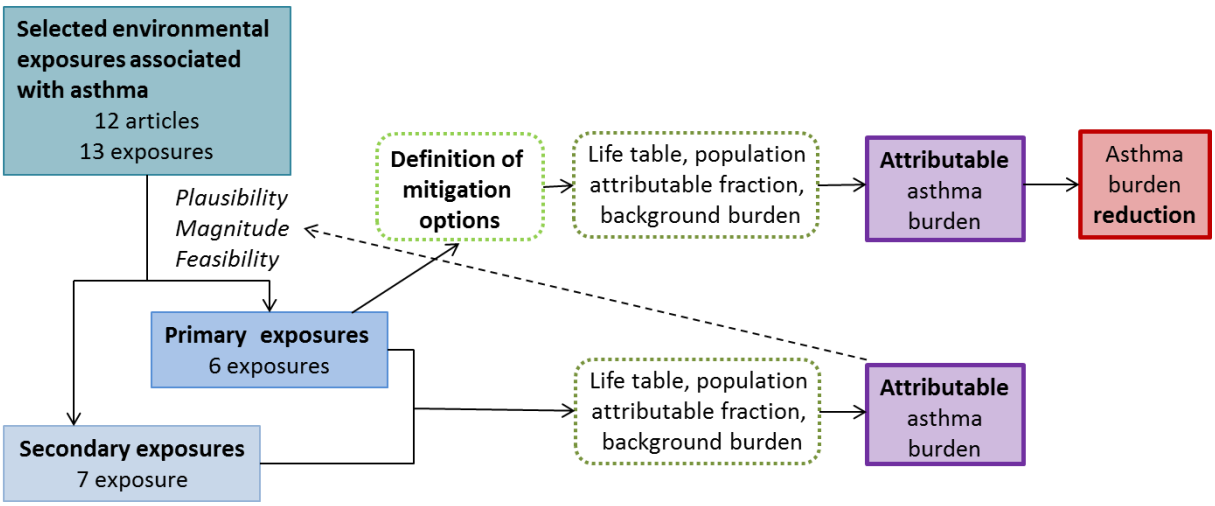


Figure 3: Steps from the selected environmental exposures associated with asthma to the definition of mitigation options

4.1 LIFE TABLE MODEL

A life table model was developed to quantitatively describe Finnish population from 1986 to 2040 (a period of 55 years). The life table contains the population size for each year of age from 0 (new births) to 99 years and the corresponding age specific prevalence of asthma. The main components of the model were implemented in Microsoft Excel (v. 2010) (Figure 4).

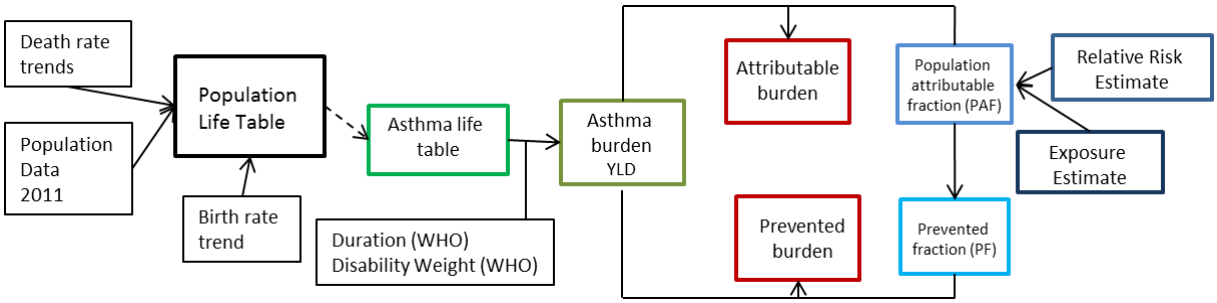


Figure 4: Structure of the Life Table Model indicating the flow from input data to the attributable and prevented Years Lived with Disability (YLD).

The life table was constructed by entering the Finnish population data for year 2011 (Statistics Finland, 2014a) and using age specific mortality rates (Statistics Finland, 2014b) and annual births for 1986-2011 (Statistics Finland, 2014c) to calculate the age specific population backwards to 1986 and forward to 2040 (Chapter 4.1.1). Nine aggregated age groups were defined for the presentation of the results (Table 1).

Table 1: Age group definitions

Age group	**Infant**	**Toddler**	**Preschool Child**	**Child**	**Teen**	**Young Adult**	**Working Age**	**Pensioner**	**Elderly**
Age (years)	0	1-3	4-6	7-12	13-19	20-25	26-65	66-80	81-99

4.1.1 Population Data and Projections

A life table was developed to describe the whole population by each year of age and included changes due to births and deaths. Migration and immigration were not included.

The life table was developed to gain estimates for the population from 1986 - 2040. The observed numbers of individuals living in Finland were obtained from the Statistics Finland database for the years 1986 - 2011 (Statistics Finland, 2014a). The number of deaths per year and age (Statistics Finland, 2014b) and the number of birth per year (Statistics Finland, 2014c) were collected from the same database for 1987 - 2011. These three input data sets were used to estimate a trend with 2011 as the baseline year. Trends for birth- and death rates were estimated based on observed data and applied to estimate the population prior and after baseline, so that only for the baseline year observed data were used and for all other years the estimate was used (Figure 5). The trend calculation for the death rate was done using the LOGEST function of Excel. The death rate trend was calculated for each year of age separately, because the death rate increases greatly with higher age. The trend calculation smoothed the variability of the observed data. The birth rate trend was calculated using the same function as the death rate trend. Since the birth rate changed a lot, one trend from 1986 to 2001 and one from 2002 to 2011 was calculated. The later was used for calculating the future estimation. Again, the trend estimates showed less variability than the observed data (Figure 6).

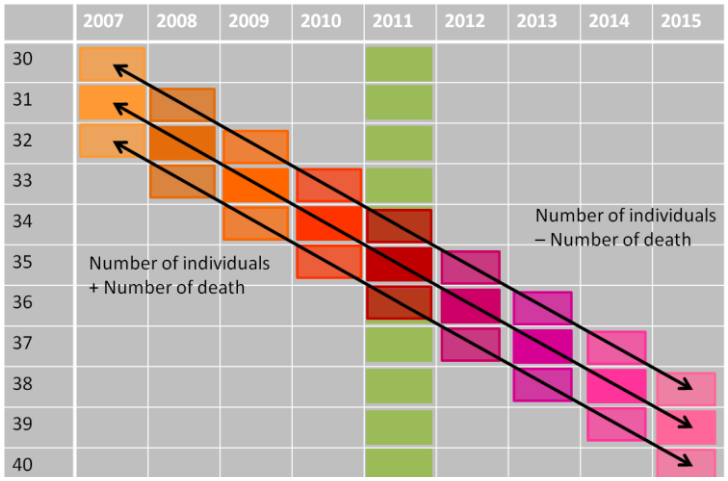


Figure 5: Example of population life table calculation with using 2011 as baseline year for the years 2007 to 2015 and the starting ages of 34 to 36 in 2011.

The birth rate and the age rate in the new-borns were used to estimate the number of individuals in the 0 years olds. For the other groups it was assumed that any change in the number of individuals per age group and year is solely due to individuals dying and leaving the age group that way. Obviously, the number of death had to be added to the age group for estimating the past years, whereas the number of deaths had to be subtracted for the future years (Figure 5). The detailed equations that have been used for the development of the population life table are described in Appendix II.

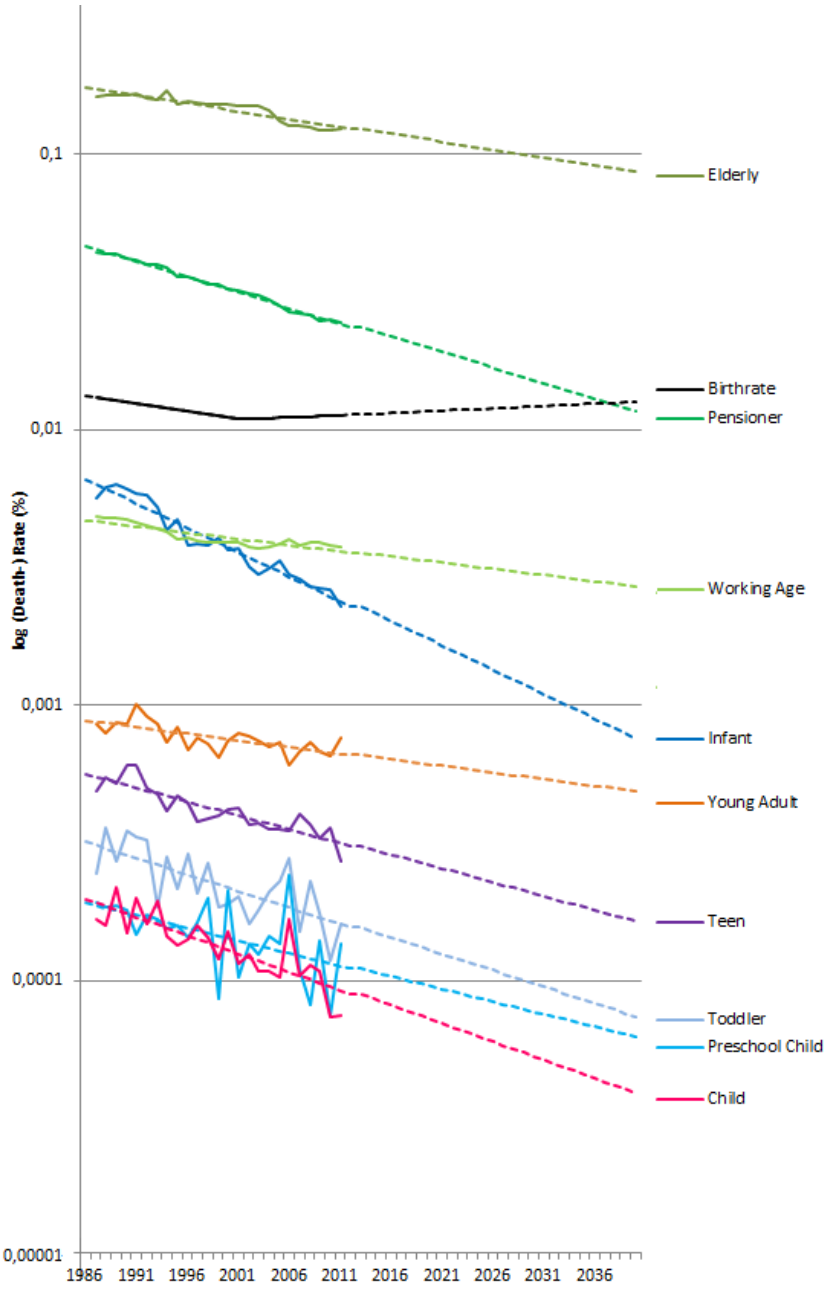


Figure 6: Death rates per aggregated age group and birth rate with observed data shown with a solid line and trend estimates with a dashed line in logarithmic scale.

In order to review the validity of the population life table estimation, it was compared to the observed data and a population projections provided by Statistics Finland (Figure 7) (Statistics Finland, 2014d). The comparison shows, that the estimate fitted rather well, but overestimated the population in the past. A population projection, obtained from Statistics Finland, was also included. It contained estimates for the same time period as the life table, in which the data for the past years are the same as the observed ones. The population estimate for 1986 was about 130 000 higher than the observed population, which is a less than 3 %.

The trend estimate for 2040 was about 285 000 smaller than the projection data, which is less than 5 % difference.

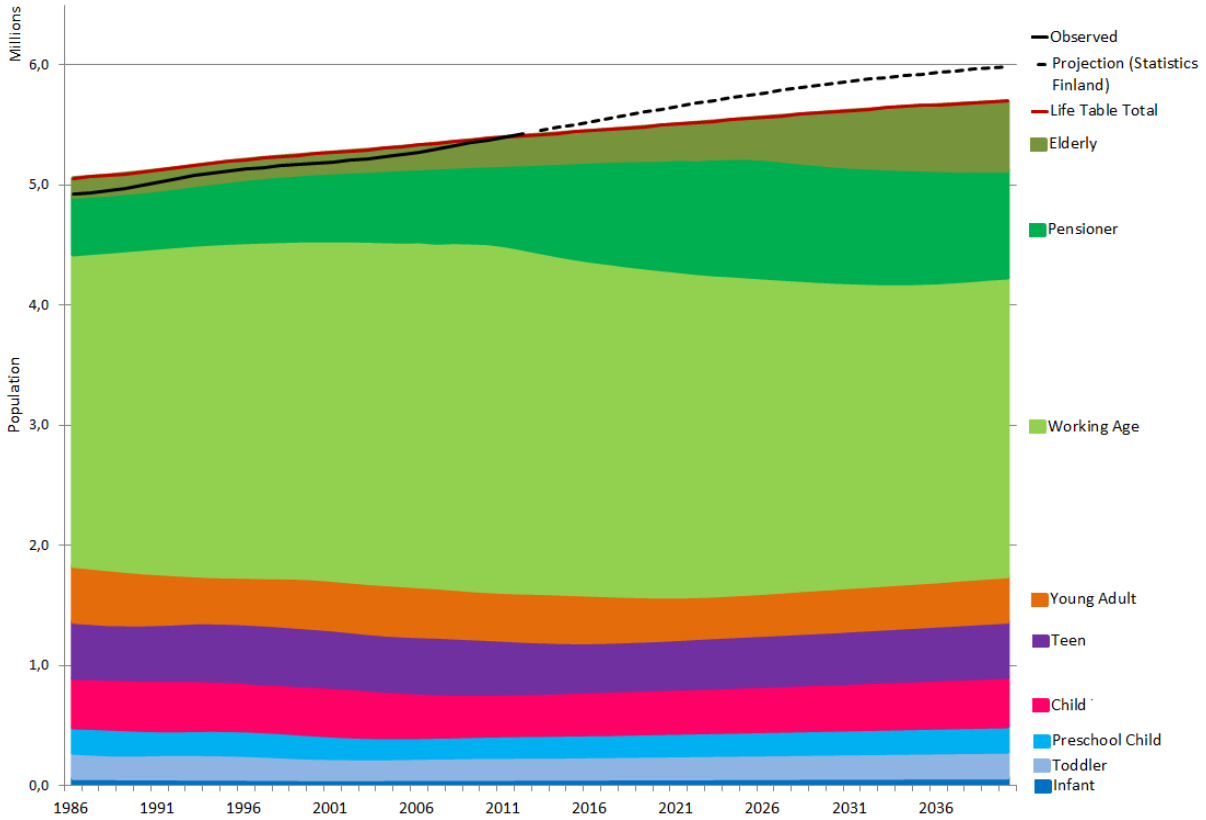


Figure 7: Overview of population development in the life table model from 1986 to 2040 and comparison with Statistics Finland observation and projection (solid and dashed lines).

4.1.2 Data and Projections on Asthma Burden

The incidence and prevalence were described as patients entitled to medication cost reimbursement due to asthma and data were obtained from the Social Insurance Institution of Finland (KELA), statistics department. The data, which are published in the official database, include ‘Asthma and similar chronic respiratory diseases’ under the disease code 203 (KELA, 2014b). KELA provided a dataset from which the CPD entitlements were left out. KELA sets up guidelines for the entitlement for reimbursement of medical expenses and only those, who are entitled for reimbursement, are counted as asthma case. The asthma diagnosis has to be physician-made and proven with lung function tests.. Children from the age of 5 years on are believed to be able to undergo a lung function test. Children younger than 3 years do not need to undergo lung function tests, but they have to experience forced expiratory wheezing and

recurrent respiratory distress, as well as improvement under bronchodilator therapy. Infants have to have physician-diagnosed respiratory distress seizures at least 2 – 3 times per year to be diagnosed with asthma. Children under the age of 16 years are granted an allowance for up to 5 years, whereas children less than 3 years of age are granted an allowance for a maximum of 2 years No information about the period of validity of the entitlements for adults (≥16 years) are available. (KELA, 2014c).

The incidence and prevalence data were allocated in one-year age groups for every year from 1986 to 2012. The incidence and prevalence rates of asthma differ in their target ages: the highest incidence rate is in toddlers, whereas the highest prevalence rate was in elderly (Figure 8).

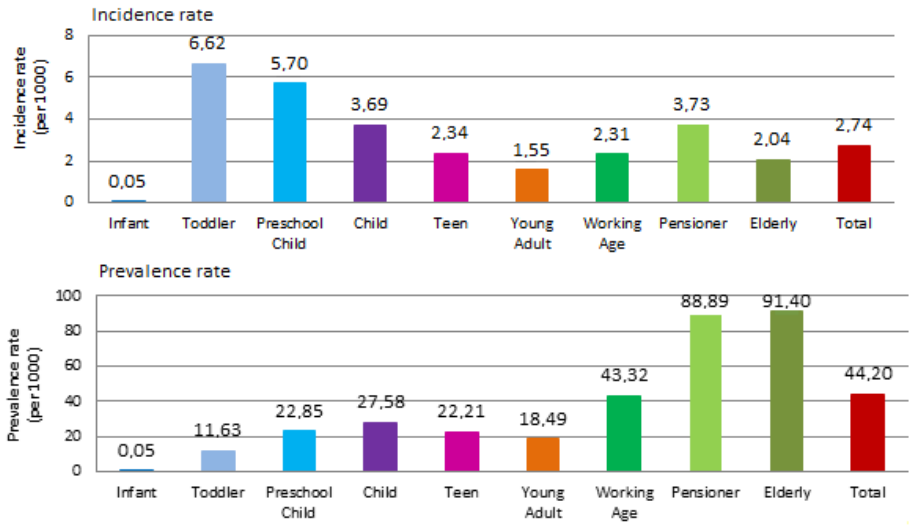


Figure 8: Incidence and prevalence rates in Finland at baseline (2011).

The incidence rate was relatively constant in the last ten years, whereas the prevalence rate was increasing during the whole time period 1986 - 2011. For the future years, the trends were derived differently for incidence and prevalence (Figure 9). Since the number of new cases (incidence) was rather constant since the beginning of the new century, it was assumed that this trend continues in the future. Therefore the same number of new cases as in 2012 by age was used for all years up to 2040. In contrast, the prevalence was constantly increasing from 1986 to 2012. Therefore a POWER function of Microsoft Excel based on the observed data from 2008 to 2012 was used to derive the estimates for the future prevalence. Furthermore, the trend was calculated for every year of age separately. A non-explainable drop in the number of new cases was observable in the year 1994.

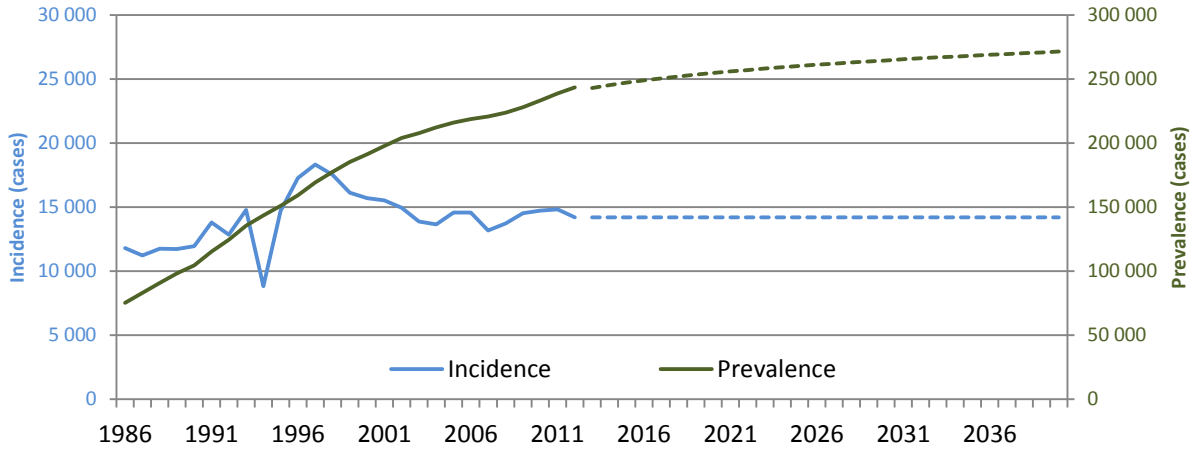


Figure 9: Incident cases (left y-axis) and prevalent cases (right y-axis) of asthma in Finland from 1986 to 2040 with observed data being shown as a solid line and the future estimations as a dashed line.

4.2 QUANTIFYING ENVIRONMENTAL ASTHMA BURDEN USING PAF

The environmental burden of asthma was calculated from the population attributable fraction (PAF) and the background burden of disease (BoD). In order to gain estimates for each year of age and each year of the life table model, the PAF and the asthma burden had to be available for each year of age during the 55 year period.

For the estimation of the asthma attributable burden only the morbidity (YLD) were considered and not mortality. YLD estimates were based on observed data obtained from the Finnish Social Security Institution (KELA) (Chapter 4.1.2). The asthma burden was derived using the prevalence-based approach (Equation 4). The Disability Weight (DW) of 0.04 was obtained from the WHO (WHO, 2004b**)**.

In order to be able to estimate the environmental attributable fraction of the asthma burden, the Population attributable fraction (PAF) was calculated (Equation 5 and Equation 6). The RRs were identified from literature and extrapolated for the age (Chapters 4.2.1 and 4.2.2) and the exposure estimates were extrapolated for the years 1986 to 2040 where it was possible

(Chapter 4.2.3) in order to gain a specific PAF for each year of age in each year of the life table (1986-2040).

The environmental attributable and environmental prevented fractions of the total asthma burden were derived by multiplying the YLD with the PAF or PF respectively.

4.2.1 Selection of Epidemiological Relative Risk Values

A quantitative description of the exposure-response relationship is needed for the PAF estimation. Relative Risks (RR) were identified as part of the literature review. A short summary of each of the studies, in which the RR was estimated, is given (Table 2 and Table 3).

Second Hand Smoke effects on asthma in Children

Cal-EPA 2005. The Environmental Protection Agency of California, USA, conducted a research of the health effects of second hand tobacco smoke on humans. Included in this research they published the results of an update of the OEHHA study from 1997. This study was a meta-analysis of 85 studies representing 29 countries worldwide. This analysis, which controlled for child's history of atopy and personal smoking, gave a pooled OR for new-onset of asthma of 1.32.

Second Hand Smoke effects on asthma in Adults

Jaakkola et al, 2003. A population-based case-control study was used to determine the association between second hand tobacco smoke and the adult-onset of asthma. Case patients were systematically recruited from the Pirkanmaa Hospital District, Finland. All patients who were diagnosed with asthma in any kind of health care facility were recruited. Additionally, all individuals receiving reimbursement for asthma medication for the first time from the Social Insurance Institute of Finland (KELA) were recruited during the study period. The control subjects were recruited via the national population registry. Questionnaires were used to collect personal data, as well as exposure data for tobacco smoke and possible confounding factors. All cases underwent a lung function measurement. The statistical analysis was adjusted for age, gender, parental atopy or asthma, education, mould and/or dampness at home/work, history of pets in the home as well as self-reported occupational exposure to

sensitizers, dusts or fumes. The reported OR for asthma onset due to exposure to SHS at home and at the workplace combined is 1.97.

Smoking (Teens)

Annesi-Maesano et al, 2004. A population-based study was used to study the connection between asthma prevalence and active smoking in adolescents. For the analysis a questionnaire-based survey on asthma and likewise diseases from 1993 – 1994 was used. As health outcomes wheeze (a history of 'chest wheezing or whistling in the chest over the previous 12 months'), asthma (chest wheezing or whistling over the previous 12 months with a history of asthma at some point in life or a history of asthma at some point in life ('Have you ever had asthma?')), hay fever and eczema were included and smoking habits were defined as non-smoker, active cigarette smoker and passive tobacco smoker. Information about history of asthma has been obtained using the question 'Have you ever had asthma?'. The relationship between current asthma and active smoking without exposure to second hand tobacco smoke was reported to be positively associated. The OR was 1.2.

Smoking (Adults)

Langhammer et al, 2000. This study is based on questionnaires filled by participants of the Nord-Trøndelag Health Study (HUNT). This study was conducted between 1995 and 1997 and it recruited all residents 20 years of age and older in Nord-Trøndelag, Norway. Questions about asthma included coughing ('Do you cough daily during periods of the year?'), wheezing, breathlessness ('Have you ever had any attack of wheezing or breathlessness during the past 12 months?'), chronic bronchitis ('Have you ever had cough with phlegm for periods of at least three months during each of the past two years?'), asthma history ('Do you have or have had asthma?') and use of asthma medication ('Do you use or have you used asthma medication?'). The analysis gave an OR for current asthma of 1.03.

Particulate Matter

Anderson et al, 2013. A meta-analysis of cohort studies was done to quantify the association between chronic exposure to different air pollutants and the asthma incidence. The inclusion criteria were English language, population-based sample and a numerical exposure-response description, which was adjusted for confounders and complemented by an estimate for precision. All results were standardized to 10 µg m^{-3} increase of air pollutant. All included studies had a definition of asthma as physician-diagnosed, but wheeze was also included as a

health outcome. The analysis of NO_2 was based on 13 studies and gave a random effect estimate of 1.07 per 10 µg m^{-3}. The main analysis of $PM_{2.5}$ was based on 5 estimates and gave a random effect estimate of 1.16 per 10 µg m^{-3}.

Dampness and Mould

Fisk, Lei-Gomez and Mendell, 2007. This meta-analysis of health effects of dampness and mold is based on a study identification using PubMed. Including criteria were a publication in a refereed journal, based on original data, statistical analysis producing OR or RR with confidence interval, dampness and/or mold as risk factor in developed country, relevant health outcome, controlling for potential confounding, subject age of 3 years or older, study size of more than 3 cases. As health outcome upper respiratory tract symptoms, cough, wheeze, ever diagnosed asthma, current asthma and asthma development were investigated. All asthma diagnoses have been physician-made. The analysis for asthma aggravation ('ever-diagnosed asthma') was based on 8 studies and gave an OR central estimate of 1.37, whereas the analysis of asthma onset ("asthma development") was based on 4 studies and gave an OR central estimate of 1.34.

Cat and Dog (Protective Factor)

Hugg et al, 2008. The association between the risk of allergic asthma and exposure to animals was studied using a population-based cross-sectional study with Finnish and Russian children. Only the outcomes of the Finnish subpopulation are used in this work, therefore only the Finnish part of the study will be presented in the following paragraph. The study was conducted in the town of Imatra in October and November 2003. Questionnaires, based on previous studies, were distributed by schoolteachers to 1 400 children with an age between 7 and 16 years. The questionnaire was filled by the parents and included questions about the allergy and asthma status of the child ('Does your child have any allergies?' (no/yes); 'If yes, does your child have asthma?' (no/yes)), as well as the timing and frequency of children's contact with pets. The current exposure to cats living indoors was associated with a decrease in risk to develop asthma. The OR was 0. 47. The OR for current exposure to dogs was 0.37.

Cat and Dog (Risk Factor)

Olmedo et al, 2011. This study investigated the association between the level of exposure and sensitization to different allergens and asthma prevalence in New York City, USA. The study included cockroach, mouse, dust mite, cat and dog exposure. The children were recruited via

their parents, who were identified using the Health Insurance Plan of New York (HIP). Questionnaires were done to gain information about asthma and use of asthma medication. During visits of the homes information about other environmental exposures, health history of the child, socioeconomics and demographics were collected. Asthma was defined as reporting at least one of the following in the 12 months before administration of the questionnaire: (1) wheeze; (2) being woken at night by cough without having a cold; (3) wheeze with exercise; (4) medication use for asthma. Allergens were collected from the child's pillow as dust samples. The allergens Fel d 1 for cat exposure and Can f 1 for dog exposure were analysed. Additionally, serum IgE levels for allergens, for cat and dog dander, were measured to determine the atopic status of the child. The association between sensitization an asthma, expressed as adjusted OR, were 1.67 for cat sensitization and 2.78 for dog sensitization.

Allergens

Olmedo et al, 2011. This study investigated the association between the level of exposure and sensitization to different allergens and asthma prevalence in New York City, USA. The study included cockroach, mouse, dust mite, cat and dog exposure. The children were recruited via their parents, who were identified using the Health Insurance Plan of New York (HIP). Questionnaires were done to gain information about asthma and use of asthma medication. During visits of the homes information about other environmental exposures, health history of the child, socioeconomics and demographics were collected. Asthma was defined as reporting at least one of the following in the 12 months before administration of the questionnaire: (1) wheeze; (2) being woken at night by cough without having a cold; (3) wheeze with exercise; (4) medication use for asthma. Allergens were collected from the child's pillow as dust samples. The allergens Fel d 1 for cat exposure and Can f 1 for dog exposure were analysed. Additionally, serum IgE levels for allergens, for cat and dog dander, were measured to determine the atopic status of the child. The association between sensitization and asthma, expressed as adjusted OR, were 1.67 for cat sensitization and 2.78 for dog sensitization and 3.14 for sensitization to any allergen.

Formaldehyde

Rumchev et al, 2002. A population based case-control study was used to investigate the association between home exposure to Formaldehyde and asthma symptoms in children. As cases children between 6 months and 3 years, who were discharged from the Princess Margaret Hospital for Children in Perth, Australia, with a primary diagnosis of asthma, were

recruited. As controls children without any asthma diagnosis were recruited through the Health Department of Western Australia. A questionnaire was used to collect data about personal information, social factors, personal susceptibility factors and environmental exposures. Formaldehyde was measured during summer and during winter for 8 hours by passive sampling. The analysis gave an OR of 1.003 per 10 µg m^{-3} increase in formaldehyde. This resembles an OR of about 1.017 above a threshold of 40 µg m^{-3}.

NO_2

Anderson et al, 2013. A meta-analysis of cohort studies was done to quantify the association between chronic exposure to different air pollutants and the asthma incidence. The inclusion criteria were English language, population-based sample and a numerical exposure-response description, which was adjusted for confounders and complemented by an estimate for precision. All results were standardized to 10 µg m^{-3} increase of air pollutant. All included studies had a definition of asthma as physician-diagnosed, but wheeze was also included as a health outcome. The analysis of NO_2 was based on 13 studies and gave a random effect estimate of 1.07 per 10 µg m^{-3}. The main analysis of $PM_{2.5}$ was based on 5 estimates and gave a random effect estimate of 1.16 per 10 µg m^{-3}.

Underweight

Zhang et al, 2010. The relation between childhood weight and length ratio and asthma was examined in high-risk children. This analysis is part of the COAST study which recruited 289 newborns with birth weights greater than 2 000 g and one parent with respiratory allergies. Asthma was defined as physician-diagnosed wheezing, medication use for asthma or wheezing and other likewise diagnosis. Furthermore a pulmonary function test was done at the age of 5 years. The weight status was obtained from physician's records collected at routine visits. A weight-per-length at 1 year below the 85th Percentile was associated with an OR for asthma at 6 years of 3.14 and for asthma at 8 years of 2.85.

Breast feeding

Brew et al, 2012. Brew and colleagues conducted a meta-analysis of two studies, the Childhood Asthma Prevention Study (CAPS) from Australia and the Barn Allergi Mijo Stockholm (BAMSE) cohort from Sweden to assess the association between breastfeeding and asthma. CAPS is a randomized, parallel-group controlled trial with the aim to investigate the effectiveness of interventions to reduce exposure to house dust mite. The study was

enrolled between 1997 and 1999. To assess the health status of the child, questionnaires were distributed and research nurses recorded the breastfeeding status every three month during the first year of the children's life. The BAMSE cohort was enrolled between 1994 and 1996. Both, information about the breastfeeding status and the asthma status of the children were collected by questionnaires at different time points. The definition of asthma at the age of 4 years was wheeze in the last 12 months and ever having a doctor or hospital's diagnosis for asthma or wheeze ≥ 4 times in the last 12 months / wheeze for longer than a week ≥ 3 times in the last 12 months. Asthma at the age of 8 years was defined as wheeze in the last 12 months and ever having a doctor or hospital's diagnosis for asthma or wheeze ≥ 4 times in the last 12 months. Breastfeeding was defined as exclusive breastfeeding for more than three month or less than three month. The BAMSE study suggests an association between breastfeeding for three month or longer and a decrease in the risk to develop asthma at the age of 4 – 5 years. The RR was 0.48. The RR for asthma at the age of 8 years and breastfeeding for three month or more was 0.69, if both studies, BAMSE and CAPS were combined.

Eurotium and Penicllium

Ege et al, 2011. Ege and colleagues present a review about two big studies, which examine the relationship between living in farm environment and allergies and asthma. The cross-sectional GABRIELA (Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community Advanced Study) study compared the prevalence of asthma of children living on a farm with a reference group. 9668 subjects, who were between 6 and 12 years old and lived in southern Germany, Switzerland or Austria, participated in the study and 444 dust samples for analysis were collected in the children's bedroom in southern Germany. The dust samples were plated on five different growth mediums for seven days. After incubation the colonies were counted and identified using light microscopy. Information about the health history was collected by questionnaires. Asthma was defined as a physician diagnosis at one point or repeated diagnosis of wheezing. The mutually adjusted OR for exposure to *Eurotium* species was 0.37 and for *Penicillium* species was 0.57, indicating a decreased risk for asthma symptoms due to the exposure to this fungi.

Table 2: Summary of the epidemiological studies on primary exposures selected as asthma mitigation targets.

Stressor	Association	Response	Definition of Asthma	Age (years)	Exposure Unit	ERF parameter	ERF [CI]	Country	Study Design and Size	Author, year
Second Hand Tobacco Smoke	Risk	Onset	self-reported and physician diagnosed	< 14	yes/no	OR	1.32 [1.24 – 1.41]	worldwide	Meta-Analysis of 29 studies	Cal-EPA, 2005
Second Hand Tobacco Smoke	Risk	Onset	physician diagnosed and/or KELA reimbursement	≥ 21	yes/no	RR	1.97 [1.19 – 3.25]	Finland	Case-Control study [521 cases, 932 controls]	Jaakkola et al, 2003
Active Smoking	Risk	Exacerbation	self-reported asthma	13 – 14	yes/no	OR	1.2 [0.7 – 2.1]	France	Cohort study [15171 subjects]	Annesi-Maesano et al, 2004
Active Smoking	Risk	Exacerbation	self-reported asthma	≥ 20	yes/no	OR	1.03 [1.03 – 1.04]	Norway	Cohort study [65717 subjects]	Langhammer et al, 2000
Particulate Matter ($PM_{2.5}$)	Risk	Onset and wheezing	physician-diagnosed	all ages	$\mu g\ m^{-3}$	RR	1.16 [0.98 – 1.37]	worldwide	Meta-Analysis of 5 studies	Anderson et al, 2013
Dampness and Mould	Risk	Onset	physician diagnosed and first-time diagnosis	all ages	yes/no	OR	1.34 [0.86 – 2.10]	worldwide	Meta-Analysis of 4 studies	Fisk, Lei-Gomez and Mendell, 2007
Cat	Protection	Onset	self-reported by parents	7 – 16	yes/no	OR	0.47 [0.14 – 1.58]	Finland	population-based cross sectional study [1 400 subjects]	Hugg et al, 2008
Dog	Protection	Onset	self-reported by parents	7 – 16	yes/no	OR	0.37 [0.13 – 1.1]	Finland	population-based cross sectional study [1 400 subjects]	Hugg et al, 2008
Cat Allergy	Risk	Exacerbation	self-reported symptoms	7 -8	yes/no	OR	1.67 [0.83 – 3.37]	USA	Case-Control study [128 cases, 111 controls]	Olmedo et al, 2011
Dog Allergy	Risk	Exacerbation	self-reported symptoms	7 – 8	yes/no	OR	2.78 [1.29 – 5.99]	USA	Case-Control study [128 cases, 111 controls]	Olmedo et al, 2011

Table 3: Summary of epidemiological studies on secondary exposures that were excluded from the mitigation options modelled.

Stressor	Association	Response	Definition of Asthma	Age (years)	Exposure Unit	ERF parameter	ERF [CI]	Country	Study Design and Size	Author, year
Allergens	Risk	Exacerbation	self-reported symptoms	7 -8	yes/no	OR	3.14 [1.76 – 5.62]	USA	Case-Control study [128 cases, 111 controls]	Olmedo et al, 2011
Formaldehyde	Risk	Exacerbation	physician-diagnosed	< 3	µg m^{-3}	RR	1.017 [1.004 – 1.025]	Australia	Case-Control study [88 cases, 104 controls]	Rumchev et al, 2002
Nitrogen dioxide	Risk	Onset and wheezing	physician-diagnosed	all ages	µg m^{-3}	RR	1.07 [1.02 – 1,13]	worldwide	Meta-Analysis of 13 studies	Anderson et al, 2013
Underweight	Risk	Onset	self-reported physician-diagnosed asthma and/or medication	6	yes/no	OR	3.14 [1.117 – 8.44]	USA	Cohort study [289 subjects]	Zhang et al, 2010
Underweight	Risk	Onset	self-reported physician-diagnosed asthma and/or medication	8	yes/no	OR	2.85 [1.07 – 7.57]	USA	Cohort study [289 subjects]	Zhang et al, 2010
Breastfeeding	Protection	Exacerbation	self-reported	4	yes/no	RR	0.48 [0.31 – 0-76]	Sweden	Cohort study [4089 subjects]	Brew et al, 2012
Breastfeeding	Protection	Exacerbation	self-reported	8	yes/no	RR	0.69 [0.52 – 0-93]	Sweden and Australia	Meta-analysis of 2 studies [4705 subjects]	Brew et al, 2012
***Eurotium* species**	Protection	Exacerbation	physician-diagnosed	6 – 12	yes/no	OR	0.37 [0.18 – 0.76]	Germany, Switzerland and Austria	cross-sectional study [9 668 subjects]	Ege et al, 2011
***Penicillium* species**	Protection	Exacerbation	physician-diagnosed	6 – 12	yes/no	OR	0.57 [0.31 – 1.05]	Germany, Switzerland and Austria	cross-sectional study [9 668 subjects]	Ege et al, 2011

4.2.2 Extrapolation of the Relative Risks Across Ages

The relative risks were estimated in most original studies for variable ages (Table 2 and Table 3). In some cases (such as Olmedo et al., 2011), very narrow age window was used; in others the target population was divided to children and adults (e.g. SHS and smoking, see Table 4). Since it seems to be unlikely, that a stressor produces a certain risk or protection in a very narrow time window of life, without a smooth transition between the maximal risk or protection and no effect, the available risk data were partly extrapolated for a longer period of time based on author judgement (Table 4).

Table 4: Target age and Relative Risks (RR) of considered Factors

Target		Factor	Age [years]	RR	Ages [years] that have been extrapolated	Reference
I	Tobacco	SHS	0-13	1.32	14-20	Cal-EPA, 2005
			21-99	1.97		Jaakkola et al, 2003
		Smoking	13-14	1.2	15-20	Amnesi-Maesano et al, 2004
			21-99	1.03		Langhammer et al, 2000
II	$PM_{2.5}$	$PM_{2.5}$	0-99	(RR○ =) 1.16	No extrapolation	Anderson et al, 2013
III	Dampness	Dampness and Mould	0-99	1.34	No extrapolation	Fisk et al, 2007
IV	Pet	Cat (Protection)	7-16	0.47	0-6 and 17-21	Hugg et al, 2007
		Dog (Protection)	7-16	0.37	0-6 and 17-21	
		Cat (Risk)	7-8	1.67	0-6 and 9-21	Olmedo et al, 2011
		Dog (Risk)	7-8	2.78	0-6 and 9-21	
V		Allergens	7-8	314	0-6 and 9-21	Olmedo et al, 2011
VI		Formaldehyde	0-2	1.017	3	Rumchev et al, 2002
VII		NO_2	0-99	(RR○ =) 1.07	No extrapolation	Anderson et al, 2013
VIII		Infant underweight	6	3.14	0-5 and 7 and 9-21	Zhang et al, 2010
			8	2.85		
IX		Breast feeding	4	0.48	0-3 and 5-7 and 9-21	Brew et al, 2012
			8	0.69		
X	Microbial	*Eurotium*	6-12	0.37	0-5 and 13-21	Ege et al, 2011
		Penicillium	6-12	0.57	0-5 and 13-21	

For those exposure for which only RR for the childhood were available (Pets, allergens, underweight, breast feeding, microbial exposures), it was assumed that these exposures have an effect from birth (age 0) up to age 21. The risks were defined as 1 at age 0 and 21 and from these points the risk was extrapolated to the available data points. If there was a gap between the RR for certain ages (tobacco, underweight, breast feeding), the gap was closed using the same linear extrapolation (

Figure 10). For the extrapolation a Visual Basics Macro, which calculated a linear regression between the data points, was used.

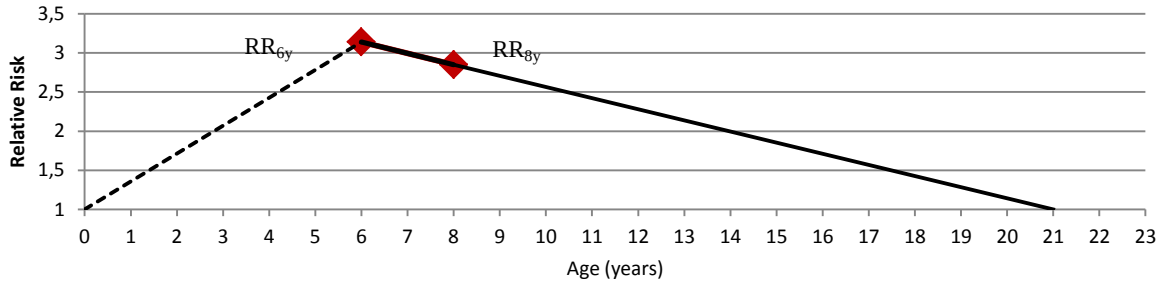


Figure 10: Exemplarily linear extrapolation of RRs for exposure to infant underweight of the relative risk from between target ages and prior and after target age.

The Relative Risks for ambient exposures ($PM_{2.5}$ and NO_2) are risk per unit exposure (RR○). In order to be able to use these estimates for the PAF calculation (Equation 5), the risk estimates had been converted into RR (Equation 7). The RR for $PM_{2.5}$ was 1.015 per µg m^{-3} and the RR for NO_2 was 1.007 per µg m^{-3}.

4.2.3 Exposure Levels and Estimation of Trends in Finland

Exposure observations from 1986 – 2012 have been used where available and future trends for 2013 – 2040 were projected based on the observed data (Table 5). This was not feasible for all factors due to the lack of exposure data for more than one year.

For exposure to SHS and smoking trends were estimated individually for different age groups (Figure 11). For SHS the age groups children (0-14 years) and adults (15-99 years) were estimated separately with no change in exposure during 1986 – 2040 for children. A trend was estimated for adults, based on data for 2003 and 2008 from three studies (Patja et al, 2009; Jaakkola et al, 2003 and European Commission, 2009). Four (4) age groups have been divided for smoking: young (15-24 years), middle (25-44 years), old (45-64 years) and elderly (65-84 years). The age groups were based on the available data on active smoking in Finland obtained from the National Institute for Health and Welfare (THL) (THL, 2013). The trend estimation was based on observed data for 12 years between 1985 and 2011. For the two younger age groups (young and middle) an exponential trend was used, whereas the observed data suggest no major change in the smoking prevalence in the older age groups (old and elderly) based on the last 5 years so that a constant trend was assumed.

Table 5: Exposures and their trend estimates for the selected factors.

Target		Stressor	Exposure estimate (Year), reference			Trend
I	Tobacco	SHS (children)	4 % (2003) Hugg, 2007		4 % (2006) Hänninen and Knol, 2011	No trend
		SHS (adults)	11% (2003) Patja, 2009	14 % (2003) Jaakkola, 2003	10,7 % (2008) European Commission Survey, 2009	LOGEST
		Smoking	Age specific values, see Figure 11			See Figure 11
II	$PM_{2.5}$	$PM_{2.5}$	9.1 µg/m^3(2005), Hänninen and Knol, 2011			Between 1986 and 1995 annually 3 % increase, after that 1.5 % increase
III	Dampness	Dampness and Mould	15 % (2004), Turunen et al, 2008			No trend
IV	Pet	Cat	21 % (2008), Hugg et al, 2008			No trend
		Dog	26 % (2008), Hugg et al, 2008			
V		Allergens	47 % (2007), Haahtela et al, 2008			No trend
VI		Formaldehyde	2% (2004) Hänninen and Knol, 2011			No trend
VII		NO_2	20 µg/m^3 (1997), Hänninen et al., 2004			EXPOLIS estimate from 1997 for 2005, same trend as $PM_{2.5}$
VIII		Infant underweight	3 %, Expert judgement			No trend
IX		Breast feeding	35 % (2008), OECD, 2009			No trend
X	Microbial	*Eurotium*	3.7 % (1996), Kilpeläinen et al, 2000			No trend
		Penicillium				

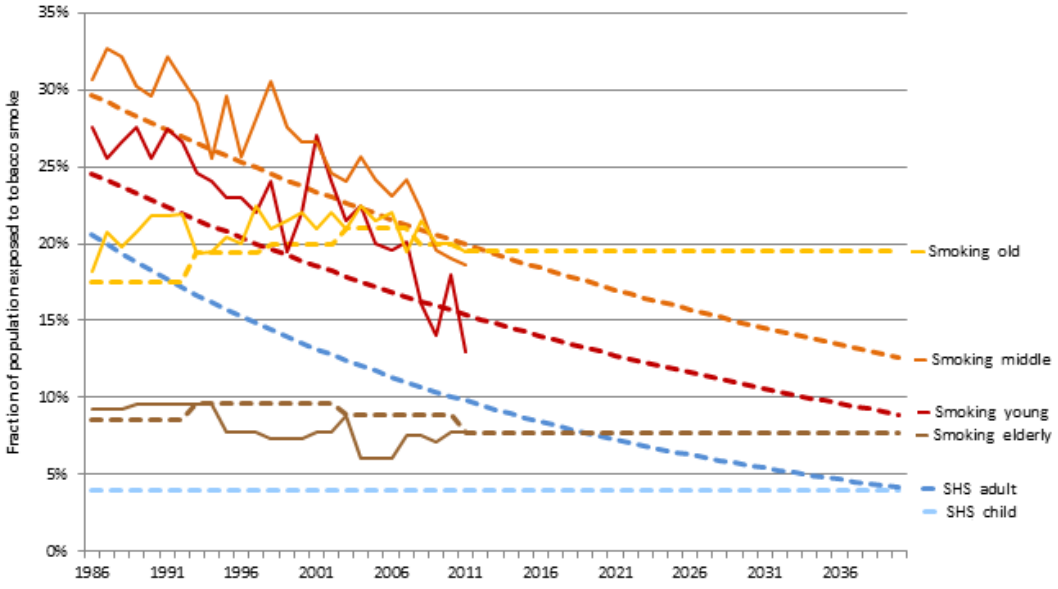


Figure 11: Prevalence of exposure to Second Hand Smoke (SHS) and active smoking observed data (solid line) and trend (dashed line) as % of the total age group.

The ambient concentration trend for $PM_{2.5}$ was estimated based on expert judgement and the recommendation by de Leeuw reported in the EBoDE report (Hänninen and Knol, 2011). An ambient concentration of 9.1 µg m^{-3} was used for the year as a baseline. A decrease in the concentration of annually 1.5 % was used for the years after 2005. For the years prior to the baseline year, an annual increase of 1.5 % until 1996 and between 1986 and 1995 of 3 % was used (Figure 11). A recommendation of 2 % decrease per year was reported in the EBoDE report, however, it was decided, to apply two trend estimations. A steeper decrease in the ambient concentration was applied until 1995 and a more conservative trend was applied from 1995 onwards. The $PM_{2.5}$ concentration is already quite low compared to other European countries and it seems unlikely, that the decrease continues in the magnitude. The same trend was used for NO_2, for which an estimate of 18 µg m^{-3} was used for the year 2005 (Figure 12).

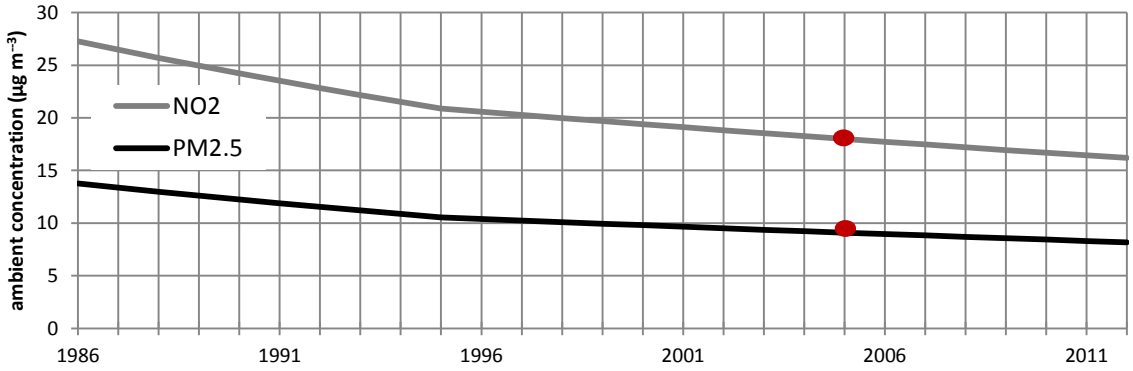


Figure 12: Average ambient concentration estimates for $PM_{2.5}$ and NO_2 with 2005 as baseline year (dot).

The exposure estimate for exposure to dampness and mould used in this work was the same as in the EBoDE and SETURI project. 15 % of the Finnish population was thought to be exposed to dampness and mould at home (Turunen et al, 2008).

The exposure to pets presents in atopic individuals a risk for asthma and in non-atopic populations the exposure to pets protects from asthma. As a risk factor, the exposure causes asthma and as a protective factor the exposure prevents cases of asthma. The exposure estimate for cat and dog allergens were derived from Haahtela et al.'s (2008) estimate of a prevalence of 15 % of allergies to animals in Finland. It was assumed, that only a small fraction (1 %) was allergic to other animals than cat and dog and therefore the prevalence of sensitization to cat and dog was assumed to be 7 % for each species. The exposure of the general population to cat and dog was obtained from Hugg et al (2008), too. For cat it was

21 % and for dog 26 %. It was assumed, that the population, which is regularly exposed to either of the animals resembles the general population and therefore that the allergy prevalence is 7 % in this sub-population. Merging these assumptions, the exposure estimate for cat as a risk factor was 1.5 % and for dog as a risk factor was 1.8 %. Since the exposures have protective properties for non-atopic individuals, the fraction, which is sensitized, was excluded for the exposure to pets as a protective factor. Therefore the exposed fraction estimates were 20 % for cat exposure and 24 % for exposure to dogs.

The fraction of the population being exposure to allergens was defined as the fraction of the population, which had at least one positive skin prick test result as an adult (Haahtela et al, 2008). The same prevalence, which is 47 %, was used for the sub-population of children.

About 2 % of the population was estimated to be exposed to formaldehyde in concentrations higher than 100 µg m^{-3} (Hänninen and Knol 2011). The estimation was based on a mean concentration of 41.6 µg m^{-3} in Finland (Jurvelin et al, 2001).

It was thought that a small fraction of all new-borns have a smaller length-to-weight ratio than the 85^{th} percentile. The estimation of 3 % of all infants being underweight was based on author's judgement.

For breastfeeding an estimate of 35 % of all new-borns being breastfed for four months was obtained from the OECD (2009).

The exposure to *Eurotium* species and *Penicillium* species is associated with living on a farm environment. According to Kilpeläinen et al. (2000) study results, about 4 % of children grow up on farm environment in Finland. This estimate is from the 1990s and for living on a farm during the first six years of live. However, it was assumes that the children do to move away from the farm during their childhood and that the prevalence of living on a farm did not change much during the last 20 years in Finland. It was not possible to quantify a change in the exposed fraction of population over the time under study for the protective factors due to a lack of sufficient exposure data.

4.3 SELECTION OF PRIMARY EXPOSURES FOR MITIGATION OPTIONS

Thirteen environmental exposures were identified in the literature review (Chapter 2.2.2) as potential targets for asthma reduction. For the selected exposures a number of exposure mitigation options were developed to reduce the asthma burden and the reduction potential was estimated using the life table model.

The final primary asthma mitigation targets were selected based on three criteria:

a) **Plausibility** of a causal exposure-asthma association

b) **Magnitude** of the attributable fraction of the asthma burden (Figure 22)

c) **Feasibility** of change in exposure (either the exposed fraction or the ambient concentration).

Causal relationship between the exposure and asthma is critical for the success of asthma reduction. The magnitude of the impact on population level was considered using an iterative approach. The life table model was executed for all the thirteen exposures and based on the attributable burden estimates and then minor factors were excluded. Third, the feasibility of controlling the exposures was considered. These three criteria were combined using an expert judgment approach to select the primary exposure control targets for this work (Table 6).

Table 6: Criteria for inclusion or exclusion of a factor in the control options

Target Group		Exposure	Risk or Protection	Division Criterion
Primary Exposures				
I	Tobacco	**SHS** **Smoking**	Risk Risk	Plausibility, Magnitude, Feasibility Feasibility, Plausibility
II	$PM_{2.5}$	**$PM_{2.5}$**	Risk	Magnitude, Feasibility, Plausibility
III	Dampness	**Dampness and Mould**	Risk	Magnitude, Feasibility, Plausibility
IV	Pet	**Cat** **Dog**	Protection Protection	Magnitude
		Cat **Dog**	Risk Risk	Due to inclusion of protection (same exposure)
Secondary Exposures				
V		**Allergens**	Risk	Plausibility, Feasibility
VI		**Formaldehyde**	Risk	Magnitude
VII		**NO_2**	Risk	Plausibility
VIII		**Underweight**	Risk	Plausibility, Feasibility, Magnitude
IX		**Breast feeding**	Protection	Plausibility, Feasibility
X	Microbial	***Eurotium*** ***Penicillium***	Protection	Plausibility, Feasibility

Tobacco smoke was included as primary exposure. Second hand tobacco smoke (SHS) was selected as a primary exposure because a causal relationship of exposure to SHS and asthma seems very plausible (Chapter 2.2.2). Furthermore, it attributes a big fraction to the total asthma burden (Figure 22) and by changing the active smoking prevalence the exposure is easily changed. Smoking was included as a primary exposure, because the evidence for a causal relationship between smoking and asthma is high (Chapter 2.2.2, Appendix III). Additionally, the adjustment of the exposure is very feasible, because smoking is a lifestyle choice and underlies the Finnish legislation.

Particulate Matter was included as primary exposure, because evidence for a causal relationship was considered sufficient (Chapter 2.2.2, Appendix III). Additionally, $PM_{2.5}$ is an important contributor to the overall environmental asthma burden in Finland (Figure 22). Reduction of the ambient concentration has been assessed in previous works (Kutvonen, 2014) and therefore it was considered feasible.

As $PM_{2.5}$, dampness and mould was included as a primary exposure, because of sufficient evidence of a causal relationship between exposure to indoor dampness and mould and asthma. Furthermore, it contributes significantly to the total asthma burden (Figure 22). Its exposure reduction potential has been assessed already in previous works (Hänninen and Asikainen, 2013).

Exposure to pets, including exposure to cats and exposure to dogs, was considered to be a primary exposure. This selection was mostly on the high fraction of the asthma burden prevented by the preventive component of the exposure (Figure 22). It is not very easy to readily adjust this exposure and the evidence for a causal relationship is limited (Chapter 2.2.2, Appendix III).

Allergens were not selected as a primary exposure, because of the controversy about the causality of the association. Additionally it is deemed very challenging to adjust this exposure, especially for ambient exposures, such as pollens.

Formaldehyde was considered to be a secondary exposure because of the very low fraction of the total asthma burden attributable to this exposure (Figure 22).

NO_2 was not selected as a primary exposure due to the limited evidence of a causal association of NO_2 and asthma (Chapter 2.2.2, Appendix III).

Underweight, breast feeding and the microbial exposures were not selected as primary exposure due to the very limited evidence for a causal association. Additionally, adjustment of the exposures seems not easily feasible, because for underweight and breast feeding there might be underlying morbidities as a causal factor for the limited weight gain or making it impossible to breast feed for the mother. Increasing microbial exposure to chosen fungi is challenging, because of the uncertainties about the route of exposure and the mode of action of these exposures.

4.4 RISK MITIGATION OPTIONS

Only primary exposures have been considered in the mitigation options. The developed mitigation options are based on adjustment of exposures (Table 7). For tobacco, dampness and pets this means a change in the exposed fraction of the population, whereas for $PM_{2.5}$ it means a change in the ambient concentration.

Table 7: Summary of control options and developed scenarios

Target	Mitigation option		Change in Exposure
Tobacco	*I.1*	Ban	100 % reduction in 2015
	I.2	50 % Reduction	50 % reduction in 2015
	I.3	Smoke free Finland	10 % annual reduction from 2015 until 2040
Particulate Matter	*II.1*	Ban Residential Small Scale Wood Combustion (SSWC)	100 % reduction of $PM_{2.5}$ fraction due to urban, supplementary small scale wood combustion in 2015
	II.2	50 % Reduction Residential Small Scale Wood Combustion (SSWC)	50 % reduction of $PM_{2.5}$ fraction due to urban, supplementary small scale wood combustion in 2015
	II.3	Speed Limit of 35 km/h	40 % reduction of $PM_{2.5}$ fraction due to re-suspension in 2015
Dampness	*III*	Dampness and Mould	50 % reduction in 2015
Pets	*IV*	Cat (Risk)	Increase to 50 % in 2015 leading to 3.5 % exposure of atopic population and 46.5 % exposure of non-atopic population
		Cat (Protection)	
		Dog (Risk)	
		Dog (Protection)	

4.4.1 Tobacco Mitigation Options (I.1-3)

The tobacco mitigation options target both, SHS and smoking equally. It is assumed that a change in smoking is mirrored directly in the exposure in SHS. As mitigation options three (3) options based on changes in exposure have been chosen: total ban of tobacco, 50 % reduction of the current smoking and 10 % annual reduction in smoking (Figure 13). The first two policies are based on Kutvonens (2014) work. As a measure to reach the exposure goals, he proposed a higher taxation of tobacco products. The change in exposure is assumed to happen once in 2015 and after that the exposure stays constant at the level of 2015. In the last years of the estimation, this exposure estimate is higher than the Business as Usual (BaU) estimate, because it is based on the exposure in 2014 and the BaU is decreasing based on the observed smoking trend However, the third policy is based on the announcement of the Finnish Government, that the country shall be smoke, which shall be accomplished by limiting the sales of tobacco products (Savuton Suomi, 2014). This goal is supposed to be reached by a 10 % annual decrease in the smoking population from 2015 onwards.

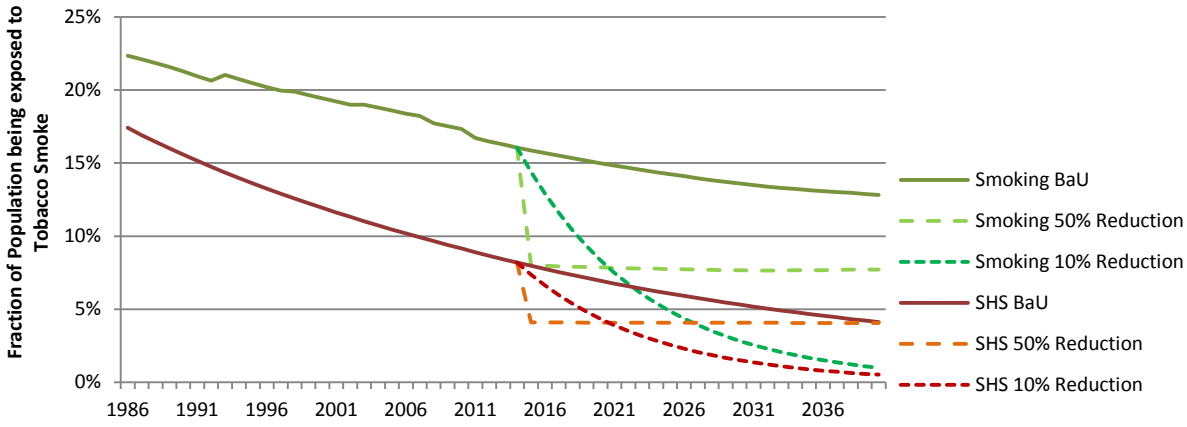


Figure 13: SHS and active smoking prevalence in the Finnish population with BaU, a 50 % reduction and an annual 10 % reduction.

4.4.2 Particulate Matter ($PM_{2.5}$) Mitigation Options (II.1-3)

The mitigation options targeting decreasing the exposure to $PM_{2.5}$, which includes three (3) options, are tackling the emissions of $PM_{2.5}$ from specific sources as suggested by Kutvonen (2014) (Figure 14). Firstly, supplementary residential small scale wood combustion in areas with a population density of ≥200 individuals / km^2 is either totally banned or decreased by

50 % in 2015. The contribution of supplementary residential small scale wood combustion to the total $PM_{2.5}$ concentrations in Finland is about 6 % and this fraction is either reduced by 100 % or by 50 % (0.6 µg m^{-3} and 0.34 µg m^{-3} respectively) and then subtracted each year from the total ambient $PM_{2.5}$ concentrations. The use of wood combustion in rural areas is not affected by these scenarios. Secondly, the speed limit in urban areas is decreased to 35 km/h in 2015 to decrease the exposure to resuspended $PM_{2.5}$. The speed limit will decrease the total $PM_{2.5}$ resuspension, which causes about 7 % of the total $PM_{2.5}$ concentrations in Finland, by 40 % (0.54 µg m^{-3}). In order to reach the decrease in small scale wood combustion, Kutvonen (2014) proposes the taxation of small scale wood combustion in urban areas.

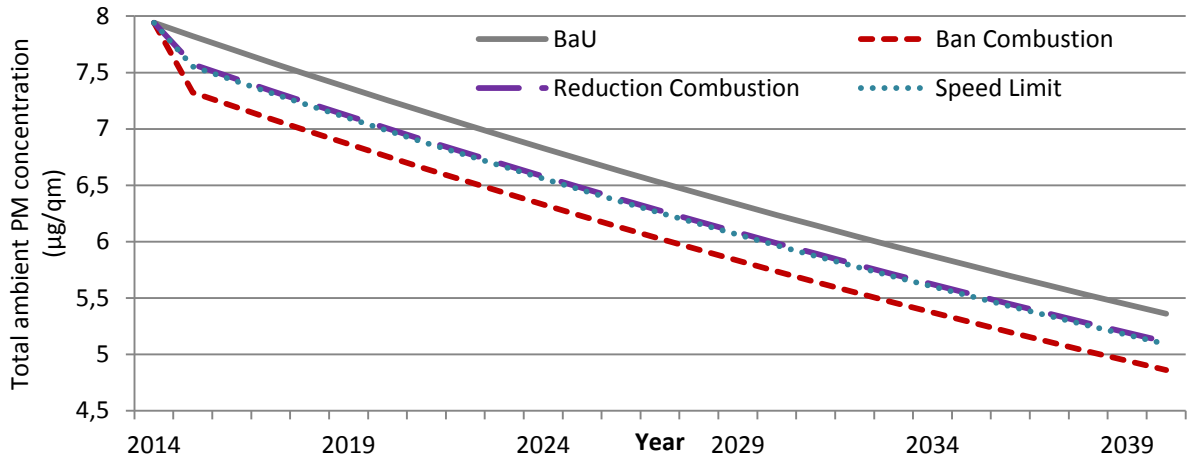


Figure 14: $PM_{2.5}$ ambient concentration for no change, ban and 50 % reduction of residential small scale wood combustion in urban areas and 35 km/h speed limit in urban areas.

4.4.3 Dampness and Dampness Mitigation Option (III)

For exposure to dampness and mould only one mitigation option has been developed: the decrease of exposure by 50 % in 2015. This policy is resumed from the HealthVent study (Hänninen and Asikainen, 2013). Hänninen and Asikainen (2013) suggest as hypothetical measures to reach a 50 % reduction a combination of improvements of the building structure and warning sensors.

4.4.4 Pet Mitigation Option (IV)

Exposure to furry pets, in this case cats and dogs, is a risk and a protective factor at the same time. In atopic individuals the exposure presents a risk for asthma and in non-atopic

populations the exposure protects from asthma. As a risk factor, the exposure causes asthma and as a protective factor the exposure prevents cases of asthma. In this mitigation option it is assumed that the exposure to cats and dogs is increased to 50 % in 2015, in both, the atopic and the non-atopic children. Therefore, some cases of asthma are caused (in the atopic population) and some are prevented (in the non-atopic population).

5 RESULTS

5.1 ASTHMA TREND

The total burden asthma in Finland was constantly increasing from 1986 to 2012 and a further increase in the future is expected (Figure 15). In 1986 the burden was 3009 DALYs and until 2040 it is going to increase more than three-fold to 10 857 DALYs. The younger age groups contribute less to the total burden than the older ones. From infants to young adults the burden reached a maximum of the sum for these age groups of 1732 DALYs in 2002. After that the burden decreased slightly until 2009 to 1302 DALYs and then stays nearly constant at around 1325 DALYs. In contradiction, the age groups of working age, pensioners and elderly increase during the whole study period with the elderly having the steepest increase. The age group of working age contributes the most to the total YLD_P, but this age group is the biggest age group in matter of number of individuals.

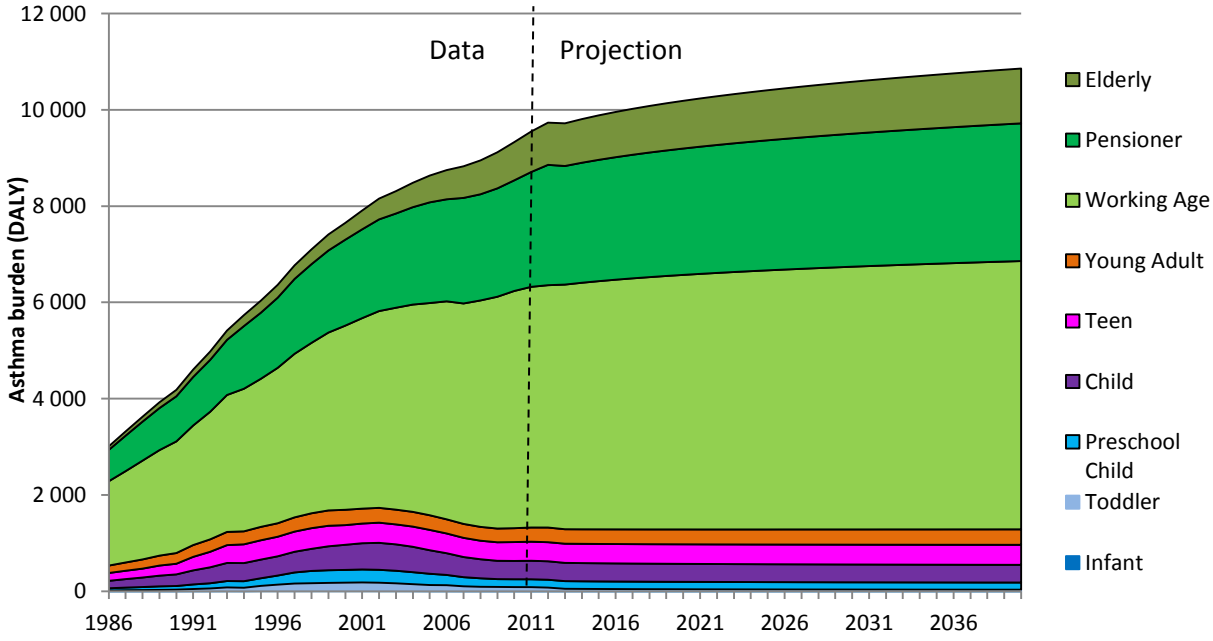


Figure 15: Trends in asthma burden (YLD) by age in DALYs in Finland from 1986 to 2040.

The incidence, which was defined as new entitlements to reimburse asthma medication from KELA during one calendar year, rose from 11 805 cases in 1986 to 18 328 cases in 1997 and declined again to between 14 000 and 16 000 cases for the other years. The prevalent cases, which were defined as the total number of individuals entitled to reimburse asthma

medication from KELA during one calendar year, increased constantly during the observational period from 75 213 in 1986 to 243 341 cases in 2012 and estimated 271 424 cases in 2040 (Figure 9).

5.2 ENVIRONMENTAL BURDEN OF ASTHMA

5.2.1 Asthma Attributable to Risk Factors

The model included ten (10) risk factors, from which six (6) were selected to be used in mitigation options (Table 8).

Table 8: Risk factors selected as primary exposures and secondary exposures

Primary Exposure			**Secondary Exposure**	
Target		*Factor*	*Target*	*Factor*
I	Tobacco	SHS Smoking	V	Allergens
			VI	Formaldehyde
II	$PM_{2.5}$	$PM_{2.5}$	VII	NO_2
III	Dampness	Dampness and Mould	VIII	Underweight
IV	Pets	Cat Dog		

At baseline (2011) 14 818 new person and a total of 238 716 individuals were entitled to reimburse their medical expenses for asthma medication from KELA. This led to an asthma burden of 9549 DALYs. With the ten (10) risk factors considered in the model 40 % of the burden (3823 DALYs) could be explained (Figure 16). The four (4) primary exposures (tobacco, $PM_{2.5}$, Dampness and Pets) caused 25 % (2405 DALYs) of the total asthma burden. The biggest fraction of attributable burden was caused by $PM_{2.5}$ (1108 DALYs) followed by SHS (766 DALYs) and dampness and mould (463 DALYs). Formaldehyde (0.02 DALYs) caused the smallest fraction of the asthma burden.

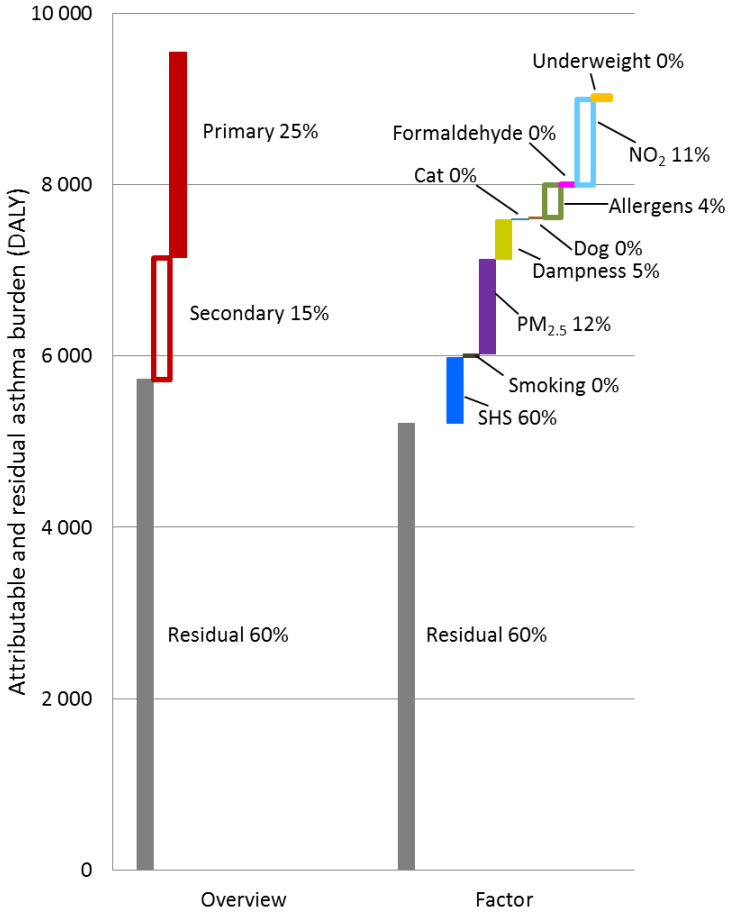


Figure 16: Attributable and residual fraction of total asthma burden (YLD) at baseline (2011) separated by primary (solid fill) and secondary (no fill) exposures.

Since some stressors only affect certain ages, the attributable fraction of the asthma burden differed for each age group (Figure 17). Second hand tobacco smoke (SHS), $PM_{2.5}$ and dampness and mould (and NO_2) were the only factors affecting all age groups. Formaldehyde had an impact only on infants and toddler, whereas smoking only had an impact on teens and older age groups. Dog, cat, allergens and underweight had an effect until the age of young adults. The biggest fraction of the burden could be explained in children (83 %) and preschool children (78 %). The smallest fraction could be explained in infants (28 %) and working age, pensioners and elderly with 36 % each. In the young age groups up until teens allergens caused the biggest fraction of the burden, whereas in the young adults and older $PM_{2.5}$ had the biggest contribution to the attributable burden.

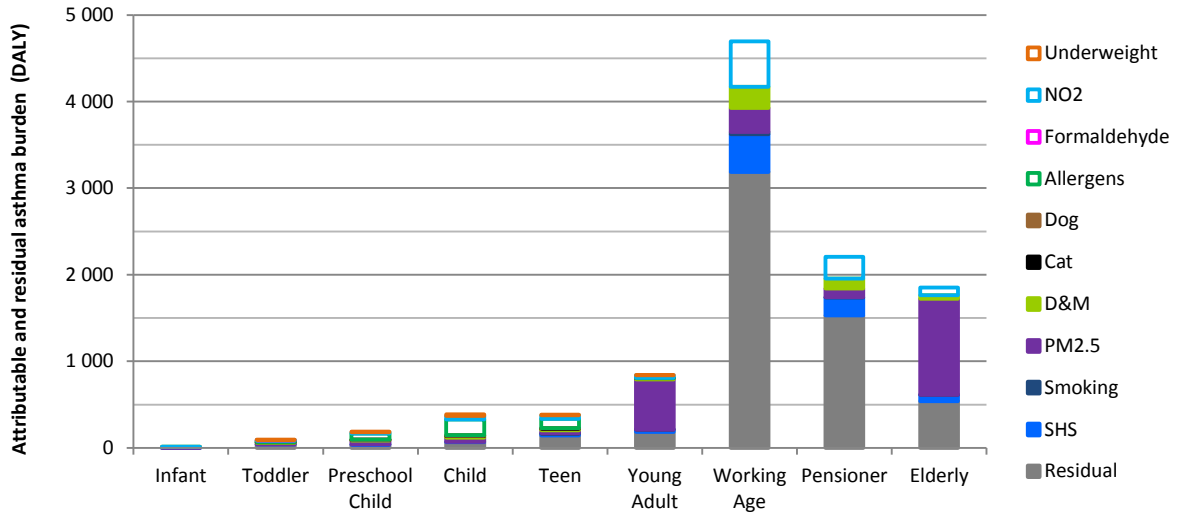


Figure 17: Attributable and residual fraction of total asthma burden (YLD) at baseline (2011) separated by primary (solid fill) and secondary (no fill) exposures by age group.

The attributable fraction of the total burden decreased between 1986 and 2040 (Figure 18). In 1986 it was more than 60 % of the total burden, whereas in 2040 it is less than half of it with 27 %. However, in absolute numbers the minimum of attributable burden was with 1846 DALYs in 1986, whereas the maximum of attributable burden was in 2004 with 3891 DALYs. From 2013 onwards the attributable burden decreases, whereas the total burden increases leading to an increasing unexplained fraction of the burden. The biggest contributors were SHS and $PM_{2.5}$. Cat and dog had the smallest contribution to the total burden. The exposure to smoking and SHS is based on the observed smoking trends in Finland. It is assumed that the past trend in the number of smokers in continuing in the future (Chapter 4.2.3) leading to a reduction of attributable burden from 759 DALYs to 436 DALYs, which is a reduction of 43 %, from 2015 to 2040. Furthermore, the ambient concentration of $PM_{2.5}$ is decreasing (Chapter 4.2.3). However, the attributable burden is increasing from 556 DALYs to 831 DALYs with a maximum of 1114 DALYs in 2012. The decrease in the exposure is compensated by the increase of asthma cases especially in the older age groups.

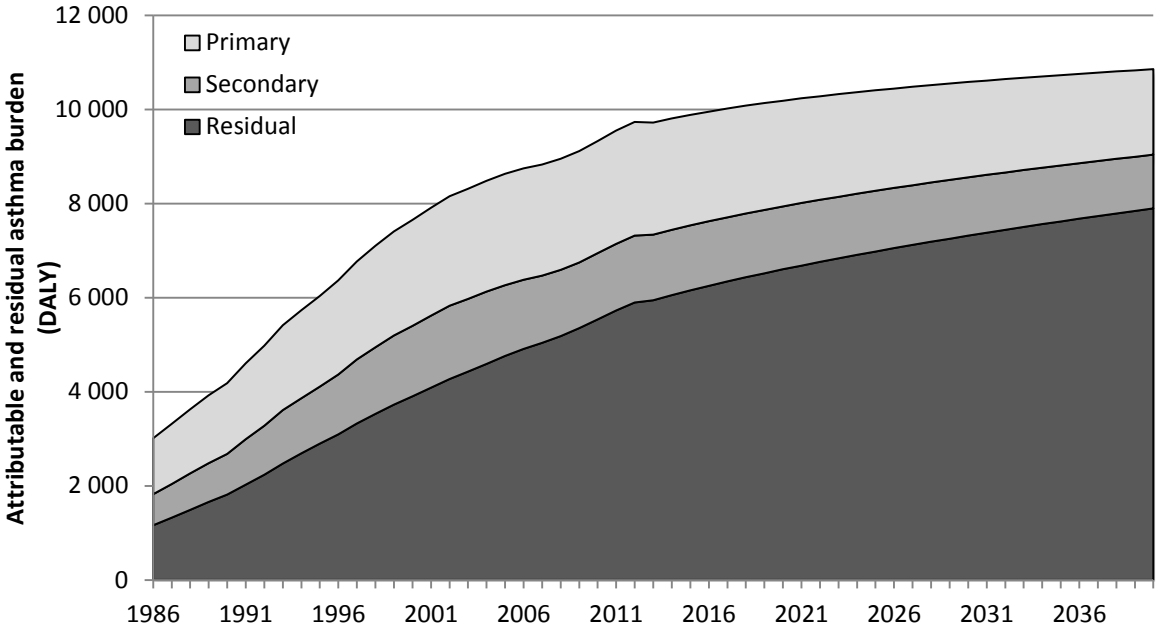


Figure 18: Timeline of the attributable and residual asthma burden (YLD) for 1986 to 2040.

5.2.2 Asthma Prevented by Protective Exposures

In this work five (5) protective factors have been considered: Cat, dog, breast feeding, *Eurotium* and *Penicillium*, from which only cat and dog were selected for inclusion in mitigation options (primary exposures) (Table 9).

Table 9: Protective factors selected as primary exposures and secondary exposures

Primary Exposure			**Secondary Exposure**		
Target			*Target*		
IV	Pets	Cat	IX		Breast feeding
		Dog	X	Microbial	*Eurotium*
					Penicillium

The exposure to protective factors prevented a total of 1467 incident cases and 8930 prevalent cases at baseline (2011). A total of 357 DALYs was prevented (Figure 19). This is about 4 % of the burden in that year. Exposure to dog of non-atopic individuals prevented the highest fraction of the burden (131 DALYs). Exclusive breast feeding for three (3) months had the second biggest protective effect (102 DALYs). The exposure of non-atopic individuals to cats prevented 92 DALYs. Exposure to *Eurotium* and *Penicillium* prevented together 30 DALYs.

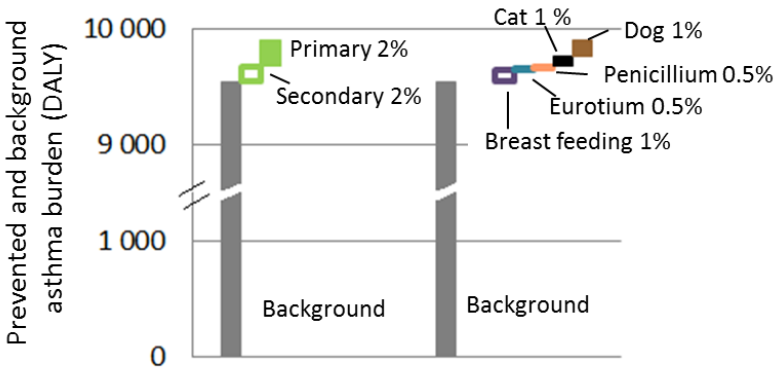


Figure 19: Prevented and background asthma burden (YLD) at baseline (2011) separated by primary (solid fill) and secondary (no fill) exposures.

All protective factors targeted the younger age groups and in the working age, pensioners and elderly no cases were prevented at all (Figure 20). In infants nearly no preventive effect could be observed as well. In young adults only about 4 DALYs (about 1 % of the total asthma burden) was prevented. In children about 41 % (157 DALYs) of the total asthma attributable burden was prevented, followed by preschool children with 40 % (65 DALYs).

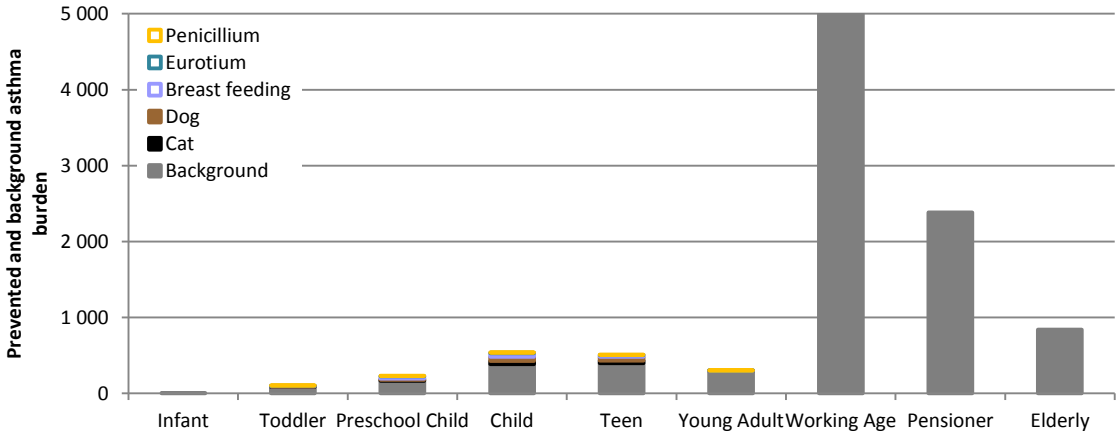


Figure 20: Prevented and background total asthma burden (YLD) at baseline (2011) separated by primary (solid fill) and secondary (no fill) exposures by age group.

Exposure to dog or breast feeding prevented the most cases. In toddler and preschool children breast feeding prevented the most cases, whereas in school children and teens exposure to dogs prevented most cases. In young adults breast feeding and exposure to dogs prevented about the same fraction of the burden. Exposure to *Penicillium* followed by exposure to *Eurotium* prevents the fewest cases in all age groups.

The prevented burden is changing relatively little during the years 1986-2040 (Figure 21). The smallest fraction of the total burden is prevented in 2040 and the biggest fraction was prevented in 1988 with 6 %. In 1986 the smallest fraction of the burden has been prevented with 134 DALYs. The biggest fraction of the burden was prevented in 2002 with 492 DALYs.

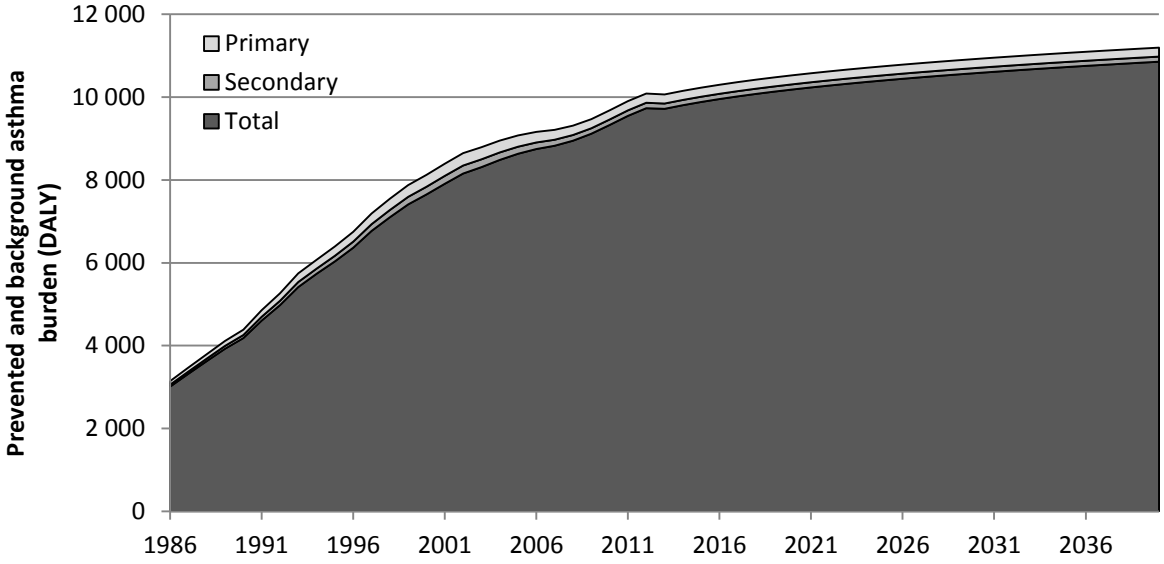


Figure 21: Timeline of prevented and background asthma burden (YLD) for 1986 to 2040.

5.3 ASTHMA REDUCTION POTENTIAL

At baseline (2011) 238 716 individuals were entitle to reimburse their expenses for asthma medication from KELA resuming in a burden of 9459 DALYs being attributable to asthma in Finland. Out of these cases about 40 % could be attributed to one of the risk factors included in the model. Furthermore, the protective factors prevented about 4 % of the background burden. However, in total the risk factors caused more asthma than protective factors could prevent (Figure 22). Based on the impact of the studied factors and the possibilities to adjust the exposed fraction of population, as well as the evidence for the association between the factor and asthma, the factors to develop control scenarios were chosen (Table 6). The magnitude of the attributable or prevented fraction caused by a specific risk or protective factor was determined by comparison between the attributable fractions (Figure 22).

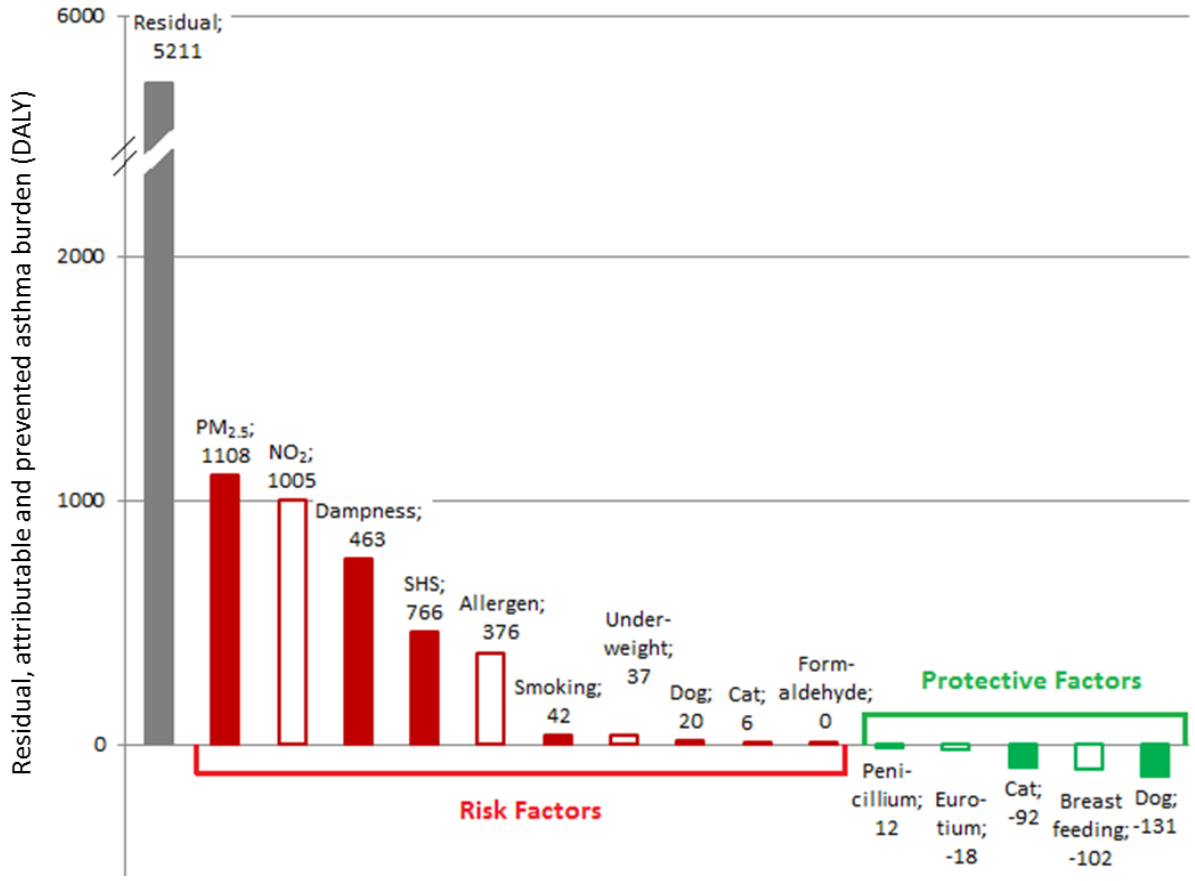


Figure 22: Attributable, prevented and residual fraction of total asthma burden (YLD) at baseline (2011) separated by factor and primary (solid fill) and secondary (no fill) exposures.

5.3.1 Tobacco Mitigation Options (I.1-3)

For exposure to tobacco smoke, which includes SHS and active smoking, three (3) mitigation options were developed: (i) total ban of exposure to tobacco, (ii) 50 % reduction of exposure to tobacco and (iii) annually 10 % reduction of exposure. The option of no measures are taken to reduce the exposure in the future and the current exposure trend is not changed, is referred to as Business as Usual (BaU) in the following. About 14 000 DALYs were attributable to exposure to tobacco smoke between 2015 and 2040. A ban of tobacco would eliminate all these cases in future. A 50 % reduction in exposure would reduce the burden in the 25 year period by about 3700 DALYs. An annual reduction of exposure by 10 % would lead to an exposed fraction of the population of 1 % in 2040. About 7500 DALYs due to asthma would be prevented between 2015 and 2040 if the Savuton Suomi aim would be reached (Figure 23).

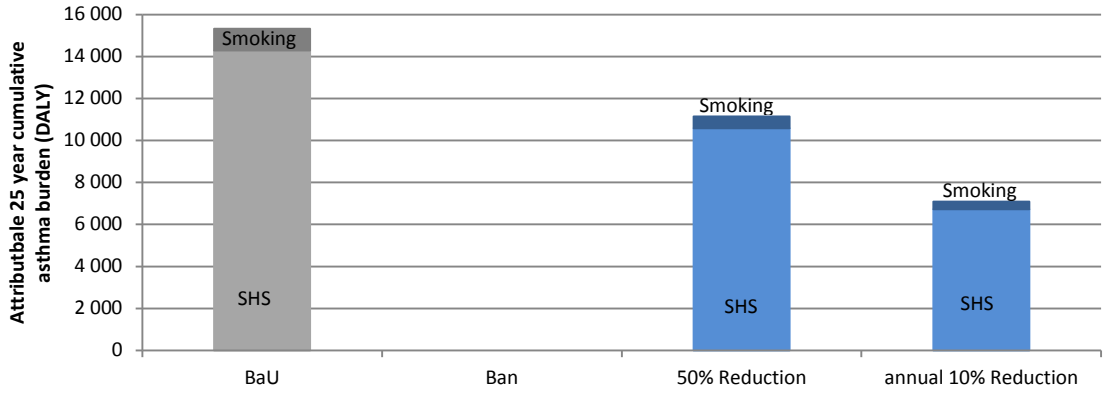


Figure 23: Tobacco (Second Hand Smoke (SHS) and smoking) attributable 25 year cumulative asthma burden (YLD) for Business as Usual (BaU), ban, 50 % reduction and annual 10 % annual reduction in exposure.

The annual 10 % reduction of exposure to tobacco smoke would reduce a higher fraction of the tobacco attributable burden each year (Figure 24). In 2015, the first year of 10 % reduction of the exposure to tobacco, 7 % of the tobacco attributable burden would be reduced compared to BaU. The reduction would increase until 2040 to 84 % of the burden that would be tobacco exposure attributable without any change in exposure to tobacco. The reducible burden would cumulate to 46 % of the business as usual attributable burden between 2015 and 2040 (Figure 23).

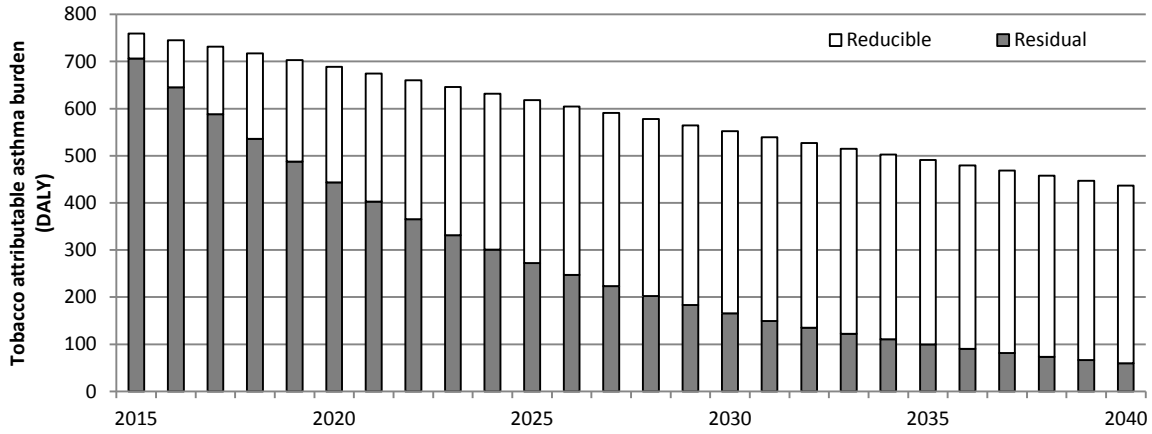


Figure 24: Timeline of tobacco attributable asthma burden (YLD) of the Business as Usual (BaU) and 10 % annual reduction of exposure to tobacco

5.3.2 Particulate Matter Mitigation Options (II.1-3)

Again, three (3) mitigation options were developed. Since $PM_{2.5}$ has various sources, two specific sources were chosen to be reduced: residential small scale wood combustion in urban

areas and resuspension of $PM_{2.5}$ due to traffic. The 25 year cumulative burden attributable to exposure to $PM_{2.5}$ was 24 980 DALYs. A total ban of small scale wood combustion in urban areas would decrease this number by about 1800 DALYs. A 50 % reduction of this type of combustion would lower the burden by about 900 DALYs. The same order of magnitude in reducing the attributable burden would be achievable by setting a speed limit of 35 km/h in urban areas. This option would eliminate 990 DALYs attributable to $PM_{2.5}$ exposure (Figure 25).

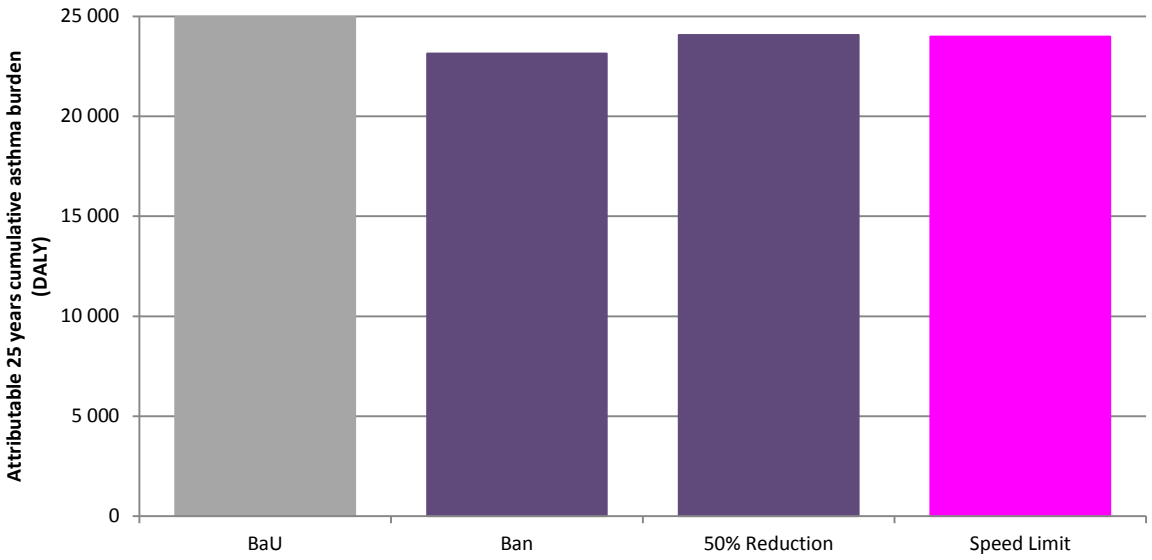


Figure 25: $PM_{2.5}$ attributable 25 year cumulative asthma burden (YLD) for BaU, ban of residential, supplementary urban small scale wood combustion, 50 % reduction of residential supplementary urban small scale wood combustion and a speed limit of 35 km/h in urban areas.

5.3.3 Dampness Mitigation Option (III)

In order to investigate the reduction potential of asthma attributable to indoor dampness and mould, one mitigation option was developed. Cumulated for the years 2015 to 2040 the burden was estimated to be more than 13 000 DALYs due as a result of exposure to damp and mouldy buildings. If the number of exposed individuals would be reduced by 50 %, the asthma burden would be halved, too (Figure 26).

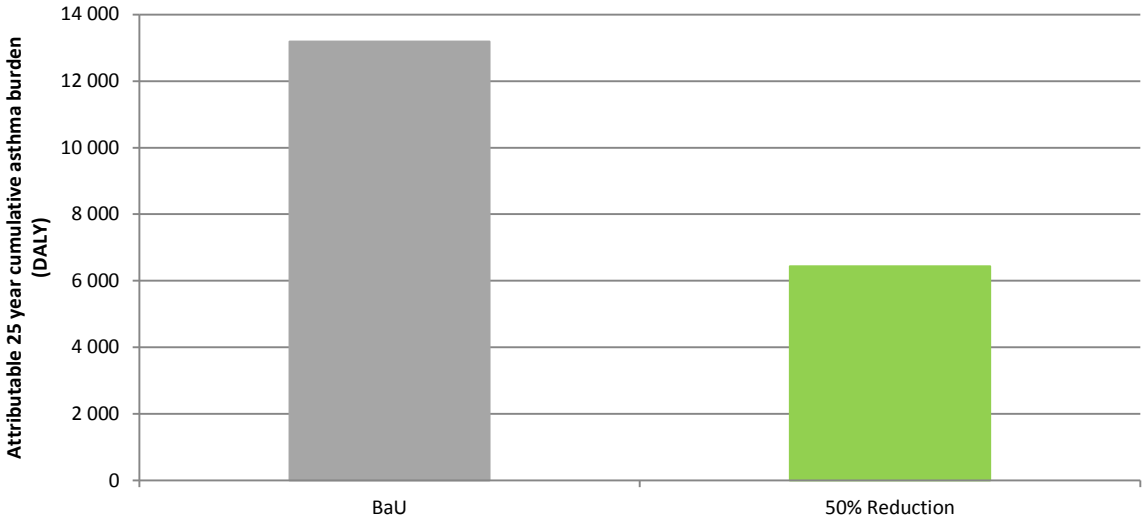


Figure 26: Dampness and mould attributable 25 year cumulative asthma burden (YLD) to for BaU and 50 % reduction in exposure.

5.3.4 Pet Mitigation Option (IV)

The mitigation option for exposure to pets included to contradicting effects: the atopic-population is at risk for asthma due to exposure to pets and the non-atopic population is protected based on the same exposure. As a result, this option increases the number of asthma cases in the atopic population and at the same time it prevents cases in the non-atopic population. In the option, where the exposure is not changed (BaU) nearly 5000 DALYs were prevented within 25 years If the exposure would be increased by 50 %, the net effect would be about additional prevented 5600 DALYs. The burden, which would be additionally caused in the atopic population, would be about 650 and 1300 DALYs respectively. The prevented burden in the non-atopic population would increase from about 5600 by about 6300 DALYs (Figure 27).

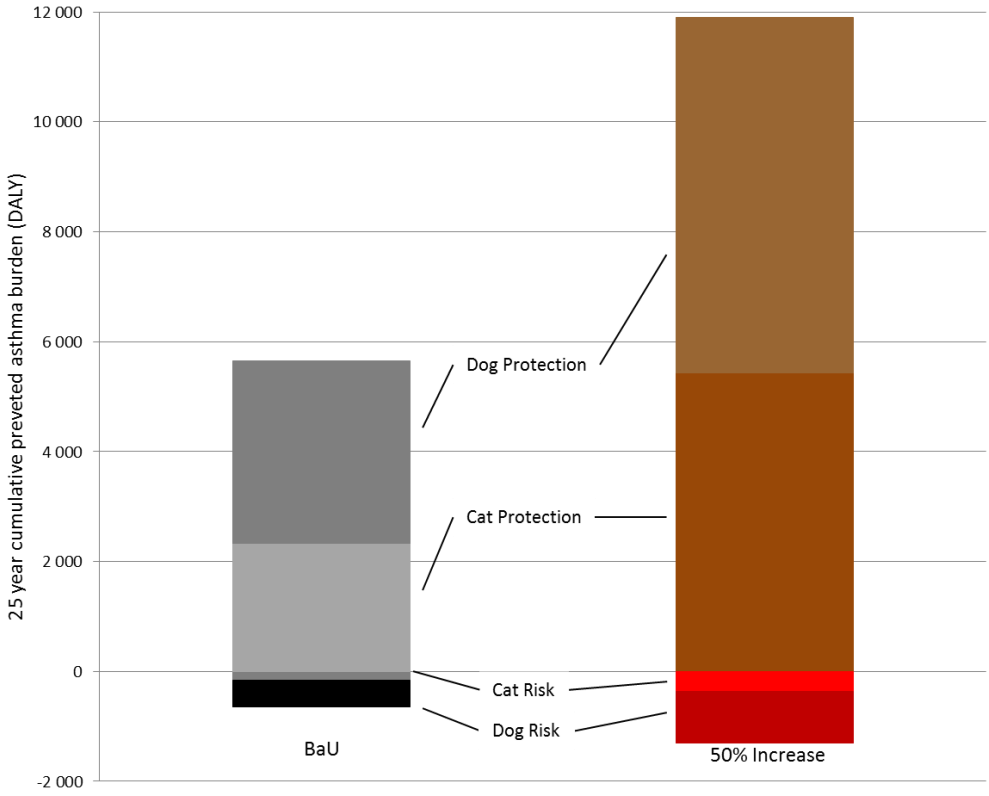


Figure 27: Pet prevented 25 year cumulative asthma burden (YLD) for BaU and 50 % increase in exposure.

5.3.5 Combined Mitigation Scenarios

In order to assess the overall potential of the developed mitigation options, they were combined. The combination was based on the reduction potential and the probability to apply the option in reality. The more the exposure is reduced, the more efficient is the mitigation option compared to BaU, meaning more asthma can be reduced. However, it becomes more difficult and unrealistic to decrease the exposure a lot within a short period of time.

Some mitigation options are clearly more effective in terms of potential to reduce the asthma burden (Table 10). The ban was most efficient for both, exposure to tobacco and residential small scale wood combustion. For tobacco exposure the annual 10 % decrease in exposure was more efficient than the one time 50 % reduction over a period of 25 years. Additionally, the gradual exposure decrease is more realistic than the sudden decrease. The mitigation options for exposure to ambient $PM_{2.5}$ target two different PM sources: residential small scale wood combustion in areas with a population density of at least 200 inhabitants/km^2 and resuspension due to road traffic. The total ban of residential small scale wood combustion was

more efficient than the 50 % reduction, however the second option seems more realistic. The option of the speed limit of 35 km/h in urban areas is not included in any combined scenario, because the analysis of Kutvonen (2014) showed that this scenario cannot be achieved in reality. Since for dampness and mould as well as pets only one option was developed, these were included in both combined scenarios.

Table 10: Reduction potential of mitigation options

Policy	Option	Changed Stressor	Change in Exposure	Reduced 25year cumulative burden [DALY]	
				Per stressor	Total
Tobacco	*I.1*	SHS Smoking	Ban	14 287 1042	15 329
	I.2	SHS Smoking	50 % Reduction	3711 464	4175
	I.3	SHS Smoking	Annual 10 % Reduction	7563 674	8237
$PM_{2.5}$	*II.1*	$PM_{2.5}$ via wood combustion	Ban	1839	
	II.2	$PM_{2.5}$ via wood combustion	50 % Reduction	918	
	II.3	$PM_{2.5}$ via speed Limit	35 km/h	991	
Dampness and Mould	*III*	Dampness and Mould	50 % Reduction	6432	
Pet	*IV*	Cat Protection Dog Protection Cat Risk Dog Risk	50 % Increase	3108 3149 -206 -445	5606

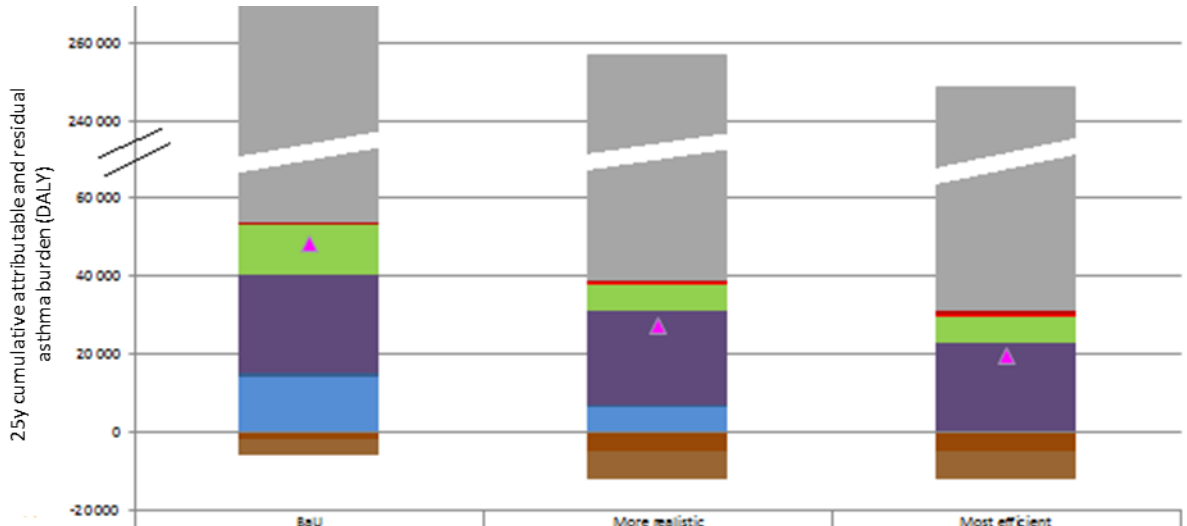
In summary, three (3) combined scenarios were assessed (Table 11, Figure 28): (i) Business as Usual (BaU), (ii) a more realistic scenario and (iii) the most efficient scenario.

Table 11: Combined mitigation scenarios and the included mitigation options

Combined Scenarios		Included mitigation options	Change
A	More realistic	I.3 Tobacco II.2 Wood combustion III Dampness and Mould IV Pets	Annual 10 % Reduction 50 % Reduction 50 % Reduction 50 % Increase
B	Most efficient	I.1 Tobacco II.1 Wood combustion III Dampness and Mould IV Pets	Ban Ban 50 % Reduction 50 Increase

All options included exposure to tobacco (SHS and smoking), exposure to $PM_{2.5}$, exposure to damp and mouldy buildings and exposure to pets and the residual cases. The residual burden includes the attributable burden to the secondary exposures and the not explainable cases. The protective factors, which were not included in any control scenario, are not taken into account (secondary exposures).

The "more realistic" combined mitigation scenario would decrease the burden within 25 years by 8 % (21 194 DALYs). The "most efficient" combined mitigation scenario would decrease the burden between 2015 and 2040 by further 8012 DALYs leading to a total decrease of 10 %. The biggest difference between the two combined mitigation scenarios is the total reduction of tobacco attributable asthma burden in the "most efficient" combined mitigation scenario compared to a gradual reduction in the "more realistic" combined mitigation scenario.



	BaU	More realistic	Most efficient
Residual	217698	217698	217698
Dog_Protection	-3321	-6470	-6470
Dog_Risk	492	937	937
Cat_Protection	-2324	-5432	-5432
Cat_Risk	157	362	362
Dampness	13191	6760	6760
PM2.5	24980	24063	23142
Smoking	1042	368	0
SHS	14287	6723	0
Net attributable	48504	27310	19298

Figure 28: Attributable 25 year cumulative asthma burden (YLD) for Business as Usual (BaU) "more realistic" combined mitigation scenario and "most efficient" combined mitigation.

The future trend estimation suggests an increase in the burden until 2040 with a changing attributable fraction and reducible fraction (Figure 29). The "more realistic" combined

mitigation scenario would be capable of preventing a growing fraction of the burden every year due to the stepwise reduction of exposure to tobacco. However, this combination of mitigation options would not bet capable of stopping the increase in asthma burden, but it was capable of slowing it down (Figure 29) The increase in the burden between 2015 and 2040 with BaUl is from 9885 DALYs to 10 857 DALYs. The fraction of reducible burden based on the "more realistic" combined mitigation scenario would increase in the same time from 6 % to 9 %. With this combined scenario the total burden would increase by only 7 % from 9343 DALYs to 9971 DALYs.

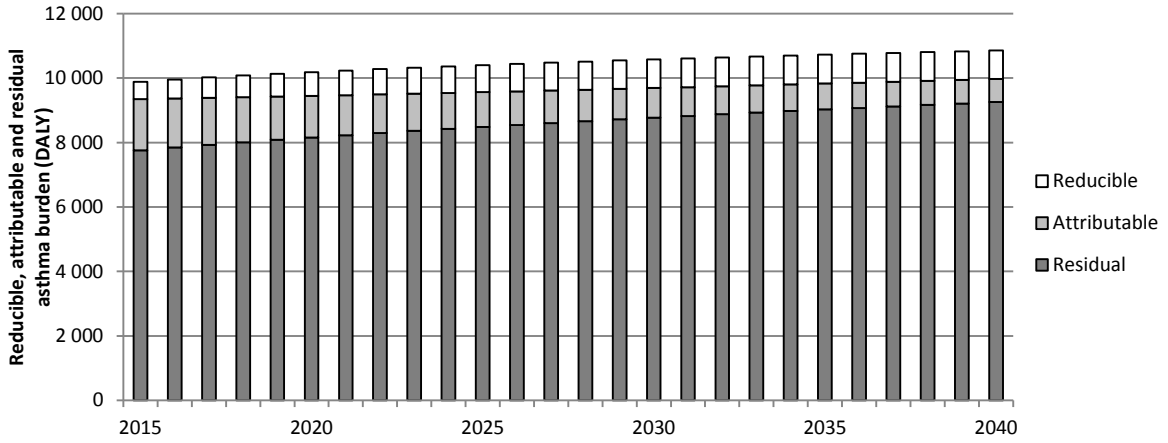


Figure 29: Asthma burden (YLD) for the years 2015 to 2040. The burden includes exposure to tobacco (SHS and smoking), $PM_{2.5}$, dampness and pets (cats and dogs). The reducible fraction is based on the "more realistic" combined mitigation scenario.

Since different factors target different ages, the fraction of the total burden between 2015 and 2040 that could be prevented by either the 'more realistic' combined scenario or the 'most efficient' combined scenario differs between the age groups (Figure 30). The biggest fraction of the burden could be reduced for both scenarios in children, followed by teens and preschool children. The infants were in both scenarios the age group with the smallest potential for reducing the asthma burden. The age groups of toddler, preschool children, children and teens had the higher reduction potential than the older age groups because of the selection of the factors of the mitigation options. The increase of exposure to pets reduced the burden a lot, but this exposure was thought to be only relevant during earlier life until the development of the immune system is finished. Therefore no cases were prevented in older age groups. If only those factors, which are relevant for all ages (SHS, $PM_{2.5}$, dampness and mould), were considered, the young adults showed the highest reduction potential, followed by the working age, pensioners and elderly with about the same potential. Infants, toddler,

preschool children and children had a lower reduction potential, which was about the same for these age groups. The reduction potential of asthma in teens was between those of the younger and the older age groups. In total 8 % and 11 % of the total asthma burden could be reduced by applying more realistic and most effective combined scenarios respectively.

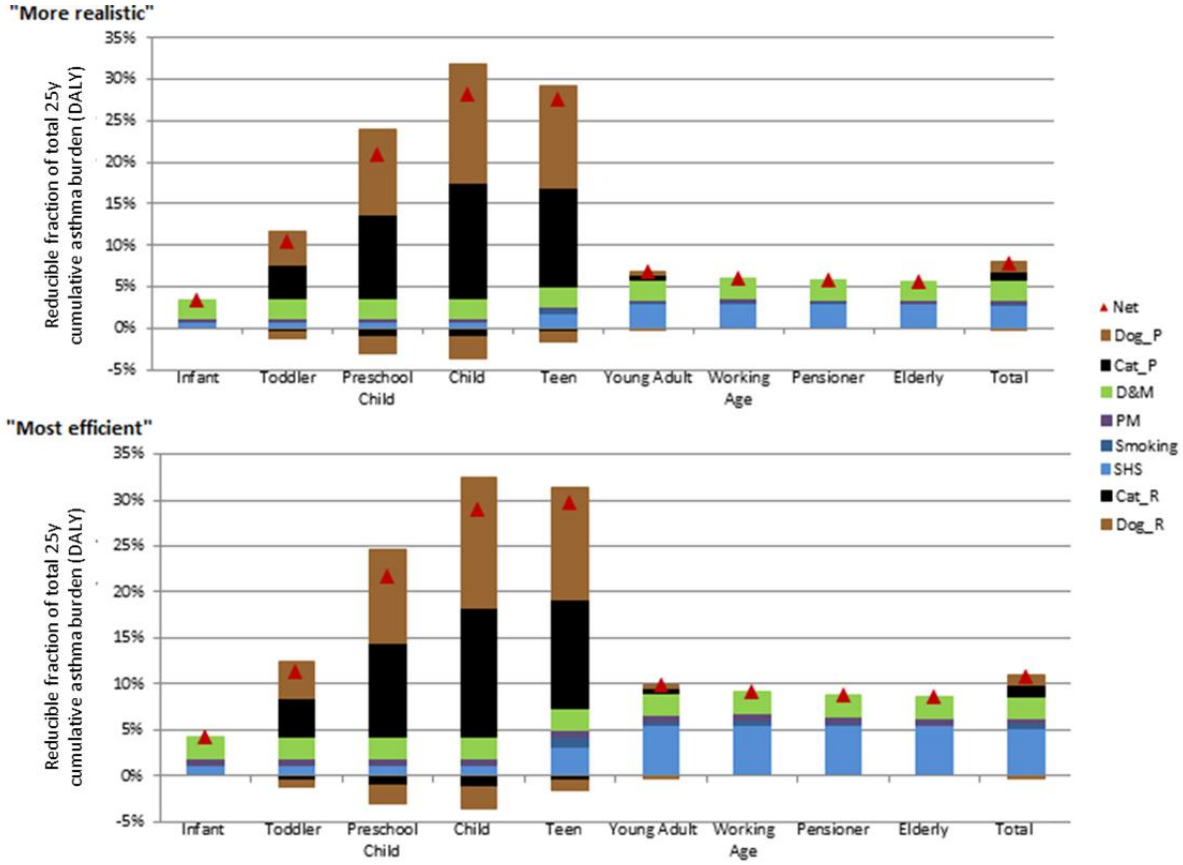


Figure 30: Fraction of total attributable 25 year cumulative asthma burden (YLD) that can be prevented by applying the "most efficient" (top) and "more realistic" (bottom) combined mitigation scenarios per age group. _R marks the exposure to pet as a risk factor, whereas _P marks the exposure as a protective factor.

5.4 DURATION OF THE ASTHMA ENTITLEMENTS

5.4.1 Average Duration of Asthma Entitlements

From the different methods to calculate the YLD (Chapter 2.3.1), an estimation for the duration of a disease can be derived, assuming that both estimates of the YLD should be the same.

$YLD_P = n_P \times L \times DW$ *with* $L = 1$ (Equation 4) *And* $YLD_I = n_I \times L \times DW$ (*Equation* 1)

$\rightarrow$ $YLD_P = n_P \times DW$ *And* $YLD_I = n_I \times L \times DW$

$YLD_P = YLD_I$

$\rightarrow$ $n_P \times DW = n_I \times L \times DW$

$\rightarrow$ $L = \frac{n_P}{n_I}$ Equation 8

As an estimation of the duration of asthma, the ratio of prevalence (n_P) to incidence (n_I) can be derived (Equation 8). In comparison to the WHO estimate of 15 years for the duration of asthma, the estimation derived using Equation 8 was age-dependent and changes over time (Figure 31).

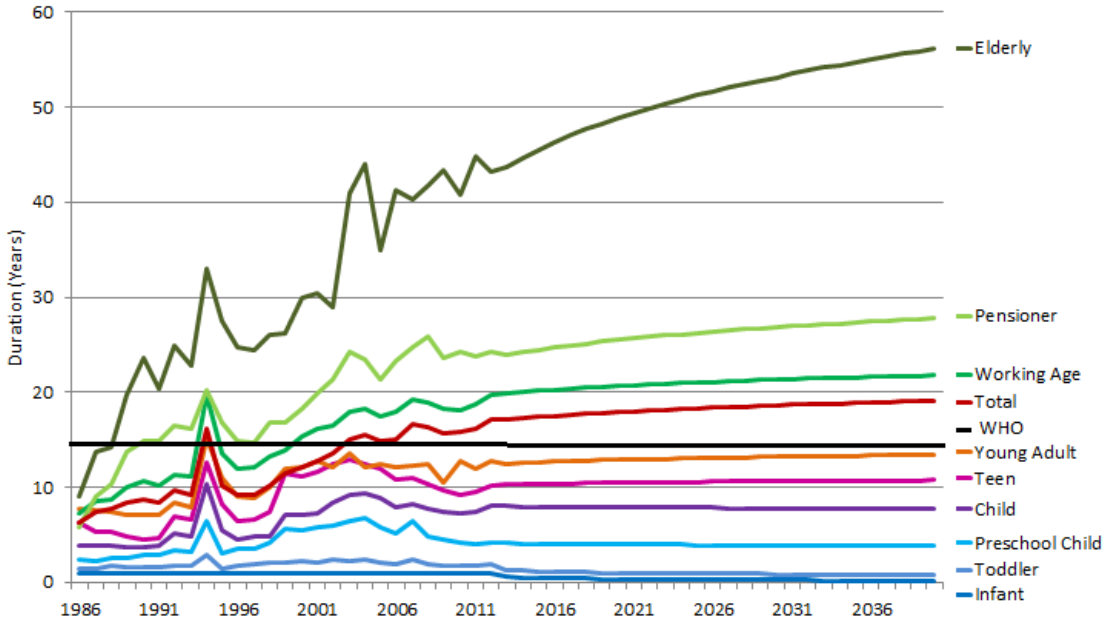


Figure 31: Asthma duration comparison between the WHO asthma duration estimate of 15y (black line) and the asthma duration estimation using the quotient of prevalence to incidence for all age groups.

5.4.2 Incidence-based and prevalence-based asthma burden estimation

Incidence and prevalence differ in the future trend estimation (constant vs. increase) and in the ages being affected the most (Figure 8 and Figure 9). The incidence rate is higher in young age groups, whereas the prevalence is highest in the older age groups. This has already an impact on the different YLD estimates. Another difference is the estimate for the asthma duration. The WHO estimate of 15 years used in the derivation of the incidence-based YLD_I

is a constant estimate for all years and age groups. However, the duration estimate based on the quotient of prevalence and incidence suggested an increasing duration with age and year of the study period (Figure 31). Due to these discrepancies in the input data, the estimates for the two YLD approaches differed. In 1986 the YLD_I was clearly higher than the YLD_P (7083 DALYs and 3009 DALYs respectively). In contrast, at the end of the study period in 2040, the YLD_P estimate is higher than the YLD_I estimate (10 857 DALYs and 8518 DALYs respectively). YLD_I increased between 1986 and 2040 only by 20 %, whereas YLD_P increased during the same 55 years more than three-fold (260 %). Not only the increase in the estimates discriminate the two approaches, but also the change in the contribution of the different age groups. In 1986 the fraction of asthma attributable YLD_I attributable to individuals being 19 years old or younger was 20 %, whereas the same age group only causes 13 % of the total asthma attributable YLD_P. The difference is even bigger in 2040: 29 % of the asthma YLD_I is attributable to teenagers or younger, whereas it is only 9% of the asthma YLD_P. The fraction of YLD_P that is less attributable to the young ages compared to YLD_I is attributable to the older age group, especially pensioners and elderly.

6 DISCUSSION

6.1 ASTHMA BURDEN ESTIMATES COMPARED WITH PREVIOUS STUDIES

Several other studies have been conducted aiming at the estimation and assessment of burden of disease and the environmental burden of diseases (see Chapter 2.3). However, the comparability with these studies is mostly limited due to the very limited focus of this work: burden of asthma Finland only taking morbidity (YLD) and not mortality (YLL) into account. Most other studies use the BoD as sum of YLD and YLL as a measure and focus at effect of one factor and not one outcome or if the outcome is the focus, the factors are not the same as in this work. The studies used for the comparison used the incidence-based YLD and not the prevalence-based except of the IHME study. Since the model used for this work was designed in a way that both, YLD_I and YLD_P, can be estimated, the YLD_I is reported in this chapter in order to achieve a higher comparability between the estimates although the YLD_I is considered not as suitable as the YLD_P (Table 12, Table 13).

Table 12: Comparison methods of environmental burden of disease studies

	Burden of Disease		***Environmental burden of disease***			
	WHO	**IHME**	**EBoDE**	**SETURI**	**HealthVent**	**Thesis**
Target year	2004	2010	2004	2004	2004	2011
YLD estimate	YLD_I	YLD_P	YLD_I	YLD_I	YLD_I	YLD_I YLD_P
Disability Weight	0.04	0.009-0.132	0.04	0.04	0.04	0.04
Duration (years)	15	-	15	15	15	15 -
Discounting	yes	no	yes no	no	yes	no
Asthma Data	?	?	BoD estimates from GBD 2004 update (WHO, 2009b) used			Incidence Prevalence
Reference	WHO, 2009b	Murray, 2012	Hänninen and Knol, 2011	Asikainen et al, 2013	Hänninen and Asikainen, 2013	

The WHO estimates for background asthma YLDs in Finland and the estimates in this work correlate rather well with a difference of 6 to 9 % (for 2002 and 2004 respectively). The

estimates in this work are always lower than the WHO estimates. The source of the incidence and prevalence data used by the WHO is unknown and the data used in this work are rather conservative. KELA applies very strict criteria who is entitle to reimbursement for medication expenses and it might be that very mild asthma cases are not entitle to reimbursement by KELA, but are counted in the WHO data source.

The HealthVent study (Hänninen and Asikainen, 2013) aimed at assessing the burden of disease due to poor indoor air quality, hence only stressors associated with poor indoor air quality are included and the focus is on the impact of the factors and not each outcome. Furthermore, as BoD background data the WHO 2004 estimate has been used and the results are only published as total BoD. This means that the mortality is considered in contrast to this work. This leads theoretically to lower estimates in this work compared to the HealthVent results. Furthermore, the BoD estimates of the HealthVent study include not only asthma, but other diseases associated with a specific factor. However, an YLD was published for poor indoor air caused asthma (2023 DALYs). As stressors have been included in this estimate: $PM_{2.5}$, outdoor bioaerosols, volatile organic compounds, home dampness and SHS exposure of non-smoking adults at home. If only $PM_{2.5}$, dampness and mould and SHS exposure of adults are taken into account, the estimation for the YLD is 2037 DALYs based on this work. This estimate is only slightly higher than the HealthVent estimation. The other HealthVent results always include other outcome than asthma in the estimation. The $PM_{2.5}$ is clearly higher than the estimate in this work, but it takes lung cancer, cardiovascular diseases and COPD into account and especially the later ones have a high incidence and prevalence and a higher mortality rate than asthma. As a result the HealthVent estimate is clearly higher than the estimate of this work. In contrast to $PM_{2.5}$, the estimate for SHS in the HealthVent study is only the half of the estimate of this work. The HealthVent study does only take the exposure of non-smoking adults into account, whereas this works assumes an exposure of all adults, the smoking ones and the non-smoking ones. Furthermore, the HealthVent study does only take indoor exposure into account, whereas this work takes all exposures to SHS into account. Although respiratory infections are considered as an outcome additionally to asthma in the HealthVent study for exposure to dampness and mould, the YLD estimate is slightly lower than the one from this work (340 DALYs and 397 DALYs respectively).

The EBoDE study (Hänninen and Knol, 2011) results have been available for asthma as the outcome and measured in YLDs. The YLD estimates for exposure to SHS are in the same range in both works (692 DALYs (EBoDE) and 604 YLDs (this work)). In this work, the impact YLD estimate for formaldehyde was very small with 0 DALYs. The EBoDE estimation of 9 DALYs is about in the same range.

Table 13: (Environmental) Burden of Disease studies and their results

Study	Reference	Factor	Study incidence-based YLD	Thesis incidence-based YLD
WHO	WHO, 2009b	Asthma	9000	8191
HealthVent	Hänninen and Asikainen, 2013	Asthma [a]	2023*	2037
		PM2.5 [1,a]	8653*	1049
		SHS [2,a]	278*	591
		Dampness & Mould [3,a]	340*	397
EBoDE	Hänninen and Knol 2011	SHS	692	604
		Formaldehyde	9	<1

* Included morbidity and mortality

[a] Includes only attributable to indoor air exposures

[1] includes asthma, lung cancer, cardiovascular diseases, COPD

[2] includes lung cancer, ischaemic heart disease, asthma

[3] includes respiratory infections, asthma

Overall, the results of this work are mostly in agreement with the results of previous studies. The estimates are in about the same range taking into account the differences in the studies. The only slightly odd result is the difference of estimates for SHS between this work and the HealthVent study. But because the estimate of this work is in line with the estimate of the EBoDE study, the big difference is probably based on differences in the definition of the exposed population (total exposure vs. indoor exposure and all adults vs. non-smoking adults).

6.2 EVALUATION OF UNCERTAINTIES IN THE MODEL

6.2.1 Accuracy of the Population Development in the Life Table

The population life table was developed as described in Chapter 4.1.1 for the period of 1986 to 2040 with 2011 as baseline year. Birth- and death rates have been used for the trend estimation prior to and after 2011. However, (im-)migration was not taken into consideration

in the estimation. Overall, the trend estimation seems to be rather accurate with an overestimation of about 3 % compared to the observed data in 1986 and with less than 5 % underestimation of the population in 2040 compared to the population projection of Statistics Finland. The net migration in Finland increased from 667 (1986) to 17 433 (2012) individuals (Statistics Finland, 2014e). This is 0.01 % and 0.3 % of the observed population in 1986 and 2012 respectively. Considering the rise in the numbers in net migration, it seems likely that the net migration is going to increase during the second half of the study period. Additionally, the number of migrated individuals cumulates over the years and if from 2012 onwards a net migration of 15 000 individuals is assumed, this number of sum up to 345 000. The underestimation compared to the Statistics Finland Population Projection is about 285 000. If the migration is roughly taken into account, the difference between the two future estimations decreases to a negligible number.

In summary, the population life table is considered accurate and reliable bases on the quality of input data and the comparison with the official population projection.

6.2.2 Considerations on the Method Accuracy

Incidence and Prevalence Data of Asthma

The data used to characterize asthma in Finland are considered to be reliable, because they are based on register data with huge monetary impact. The asthma background data have been provided by KELA, which applies very strict guidelines who is entitled to medical expenses reimbursement. Based on that, the asthma definition used in this work is very conservative. In contrast to that, in many epidemiological studies the asthma definition is less conservative or even very vague. In Chapter 2.2.1, Table 2 and Table 3 a more detailed description of the asthma definitions used in the reviewed studies is given. These differences in the disease definition lead to different estimations of incidence and prevalence and therefore asthma burden. Cases of very mild asthma are probably not included in the background data used in this work because the patients are not able to meet the criteria set out by KELA, leading to a lower estimation of the burden of asthma compared to studies using less conservative asthma definitions. This is supported by higher prevalence estimates reported in other studies: According to Pallasaho and colleagues (2011) the self-reported physician diagnosed asthma

prevalence was 9.4 % in Helsinki in 2007. The Global Initiative for asthma reports a slightly lower prevalence of 8.0 % in Scandinavia in 2001 (GINA, 2004).
The prevalence based on the total number of entitlements to reimburse drug expenses has one major uncertainty: KELA does not report if and if yes, when, entitled adults are re-evaluated if they still meet the criteria for entitlement. Therefore, it is possible, that a fraction of the entitlements is not used because the medication is not needed anymore. This leads to an overestimation of the prevalence. However, it seems unlikely that this overestimation is bigger than the underestimation of the total prevalence due to the missing mild asthma cases.

The input data of this work are all prone to errors. The used asthma data are likely to partly underestimate the total asthma cases in Finland because of the very conservative disease definition cutting out the mild cases. The used risk estimate are a source of error due to different biases, which in total more likely overestimate the risk than underestimate it (Appendix IV). Connected to that, the evidence for a relationship between an (environmental) exposure and asthma is mostly sparse (Chapter 2.2.2 and Appendix III). This is discussed in chapter 6.2.4 below.

However, in summary the input data used for this work and the results are considered to be robust estimates for the magnitude of the burden of asthma in Finland and the environmentally attributable fraction, as well as the fraction that can be prevented by controlling the environmental factors.

Uncertainties in exposure trend estimates

Since this work is life-table based, it was favourable to obtain exposure trends for the whole study period rather than one fixed exposure estimate for the whole period, as well as age-dependent exposure estimates rather than exposure estimates for the whole population. Anyhow, this was only possible for some factors, such as smoking and Second Hand Smoke (SHS). The data sources for the exposure estimates differ between the factors: for some factors estimates published as part of some studies have been used, whereas for smoking the data published by the Finnish National Institute for Health and Welfare (THL) have been used. These different sources have a different reliability: the data published by Statistics Finland or the THL are considered to be more reliable than data published in studies. For some factors, such as childhood underweight, it was not possible to obtain estimates from reliable sources, so the estimate is based on author's judgement, making it least reliable.

The trend estimates are always based on at least two data points between 1986 and 2012. If more data points have been available, all data points have been used (Chapter 4.2.3). A future trend estimation is always connected to a big uncertainty. In this work, the future trend estimation was not the aim of the work, but only a small step to obtaining the data needed for the life table model, therefore the methods used for the estimation are rather simple. Additionally, no statistical evaluation of the trend estimates has been done. Therefore, the trend estimations are a major source for error. The exposure trends influence the attributable burden directly via the population attributable fraction. If the future trend is over- or underestimated, the attributable EBD will also be over- or underestimated, too. The future trend in smoking is based on yearly observed data, which leads to a relatively robust estimation. On the other hand, the trends for $PM_{2.5}$ and NO_2 are based on recommendations from personal communications (Hänninen and Knol, 2011) and author's judgement, which makes them less reliable. Especially the application of a more conservative trend compared to the recommendation leads to a smaller decrease in the ambient concentration and with that to a bigger fraction of the attributable burden compared to the recommended trend.

Nevertheless, is it believed that a future trend based on reliable observed data is more accurate than using the same estimates for the 55 year study period, especially, if a clear increase or decrease in exposure has been observed in the past. Additionally, the control options are evaluated relative to the Business and Usual (BaU) and an over- or underestimation due to an error in exposure trend, has an impact on the absolute attributable burden, but not on the relative effectiveness.

In general, the risk factor attributable fraction of the asthma burden is decreasing (Figure 18). This is due to the counteracting trends in asthma prevalence and exposures. The asthma prevalence is increasing, especially in the older age groups (Figure 16), whereas the exposures are decreasing, especially these, which target the older age groups. The exposure to SHS, smoking and ambient air pollutants ($PM_{2.5}$ and NO_2) are decreasing in the future (
Figure 11, Figure 12). Besides dampness and mould, these factors are the only ones targeting age groups older than 21 years. This decrease in exposure reflects directly in a decrease of the attributable fraction of the burden. The increase in the unexplainable fraction of asthma shows clearly, that asthma is not well understood by now and that the onset and the symptoms are associated with factors, which are not taken into account so far.

Impact of neglecting mortality

In this work, only the morbidity (YLD) and not the mortality (YLL) due to asthma is considered. Years of Life Lost (YLL) have been neglected because the data, which are only available for the years 2009 – 2012, published by Statistics Finland suggest only a small number of deaths due to asthma (Statistics Finland, 2014f). Additionally the most cases of deaths caused by asthma in Finland happen in the older population (Table 14). The older population has a shorter remaining life expectancy to standard age, which leads to lower YLL estimates. In general, the fatality rate of asthma is with 1.6 in 100 000 asthmatics globally one of the lowest (GINA, 2004), supporting the negligible impact of mortality in this work.

Table 14: Number of deaths caused by asthma in Finland

Year	Age [years]			Total
	0-14	15-64	≥65	
2009	0	16	79	**95**
2010	0	12	76	**88**
2011	1	11	95	**107**
2012	0	10	96	**106**

Discounting and age weighting in Burden of Disease studies

In this work no age weighting or discounting was applied, which leads to the fact that the same value is given to each year of life, independent of the age and if the year of healthy life is in the present or future. In previous studies, discounting has been used to give a bigger value to past years and 3 % less value for every year further in the future. Non-uniform age weighting has been used to give a higher weight to the years lived in the middle age groups and less value to younger or older years. These approaches are based on studies assessing society's preferences on health, although the outcomes have not been unambiguous. The main differences between the studies have been the value given to present and future healthy years as well as the age and the weight of preferred years of healthy life (WHO, 2014c). The WHO changed the policies of discounting and age weighting between the different published studies. The earliest used discounting and non-uniform age weighting, the 2001 update used discounting, but uniform age weighting, whereas the 2004 update used the same method as the earliest study. However, also non-discounted and uniform age weighted DALYs have been published (WHO, 2014c). The non-uniform age weighting was not applied in this work, because economic aspects have not been considered. When there is a focus on economic aspects of BoD, such as the monetary loss due to sick leaves from work, the non-uniform age weighting might be useful, because it sets the focus on the population in the working age. If non-uniform age weighting would have been applied used in this work, a focus on the younger age groups might have been favourable, because one of the aims of the work has

been the possibility to decrease the future burden by changes in the exposure. However, in total any kind of non-uniform age weighting does not seem useful in this work, because the focus of the age weighting, for example on the younger individuals or older individuals, would change the impact of the assessed control scenarios, because the younger ones are more likely to survive the study period than the older ones and therefore more asthma cases can be attributable. Additionally, the asthma prevalence increase with increasing age, so putting a weight on the older ages would intensify this increase. The age and how much weight is put on it, is completely based on expert judgement and policies of previous studies (WHO, 2014c).

Discounting has not been applied in this work, because the aim of this work was to assess the impact of control options on the burden of asthma. Discounting puts emphasis on present years because studies suggest that the public values future years less than present years. This view is contradicting with the aims of this work, because a focus is put on the future years, when the control options are in place. Furthermore, giving a certain value to healthy present or healthy future years seems to be a highly subjective matter and especially the commonly used 3 % discounting is not based on scientific evaluation, but more on an agreement on expert judgement (WHO, 2014c). Since the control options in this work are applied for a future period of 25 years, each year of this period is considered to have the same value despite of how far in the future it is.

Onset versus aggravation of asthma and epidemiological study designs

The articles practically never clearly stated if the study investigated the relationship to asthma onset or aggravation of symptoms. Theoretically, it should be possible to divide exposures into categories (Figure 32). The first type of risk factors (R_O) is associated with the onset of asthma, whereas the second type (R_S) is associated with the occurrence of asthma symptoms. The same stressor may be equally associated with onset and symptoms ($R_{O\&S}$). Protective factors are associated to either onset (P_O) or symptoms (P_S), too. An association with onset or symptoms determines its

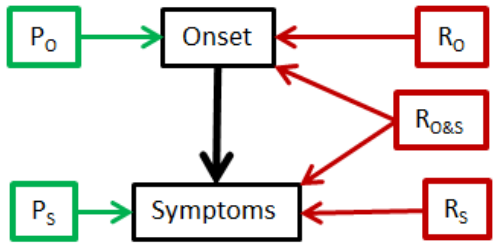


Figure 32: Conceptual categorization of types of risk factors (R) and protective factors (P), with an association between a factor and onset (R_O and P_O), symptoms (R_S and P_S) or both ($R_{O\&S}$) in epidemiological studies.

impact on population's health. If an exposure is only associated with asthma aggravation, only the asthmatics in the population are at an increased risk due to this exposure and the exposure does not have any effect non-asthmatic population. On the other hand, exposure associated with asthma onset, only affect the non-asthmatic population, because it causes additional asthma cases. Epidemiological studies should be designed that they can investigate both relationships in order to gain a better knowledge about the etiology of asthma and the relationship between onset, symptoms and aggravation, as well as the impact of exposures to it.

Additionally, studies investigate the relationship between an exposure and an outcome during a specific time period. The follow up time can, depending on the investigated outcome, be anything between hours and decades. The statistical assessment between the exposure and the outcome, meaning the estimation of a risk estimate, is not done as a timeline, but only at specific time points. For the epidemiological studies used in this work, a scientific justification has never been given for the choice of the follow up time. It appears as if studies either investigate early childhood exposure with the follow up until the school age or teenage years, or adult exposure and the outcome sometime later in the adulthood. If a study investigated the relationship at more than one point in time after exposure, it was obvious, that the risk estimate differed between the different follow ups. This highlights the problem that the knowledge about the asthma pathogenesis is so sparse and there is no information about the timeframe between exposure and effect, that it is not possible to scientifically choose the best follow up period. Therefore, it seems as the follow up period is chosen due to convenience. This might lead to the risk, that the maximum risk and its time after exposure, is missed, because it was outside of the follow up period. Additionally, it seems scientifically not very likely, that the an exposure only has an effect in one or two years after the actual exposure, especially considering that most exposure investigated in the studies are factors, last for years and not short periods of time and the outcome in this work is a chronic disease. Because of that, the determination of the actual exposure, meaning the time of exposure and the quantity of exposure, is hardly achievable.

As explained in Chapter 4.2.2 the used risk estimates have been extrapolated over a longer period time aiming at a more realistic characterisation of the risk with an increase to a maximum and a decrease to no extra risk. However, there is a significant uncertainty about

the duration of the effect and therefore, it was chosen by convenience and the thought that an effect of a childhood exposure might vanish when the development of the organs associated with the immune system is finished in early adulthood. But, it has to be mentioned, that there is no literature support of this approach.

The epidemiological study design determines also the chance for bias and error especially if the studies are using questionnaires. If the exposure and the outcome, as well as other exposure that can influence the exposure-response relationship, so called confounders, are not measured directly, there is not only the chance of parameter error, such as errors in the measurements itself, but all information are based on statements and memories of individuals. This makes the assessment of confounding rather complicated and furthermore, if information about exposures in the past is needed, individuals might have problems to remember the exposures in sufficient detail. Errors and bias can alter the quantitative dose-response relationship estimate. In more detailed possible bias in questionnaire based epidemiological studies are discussed in Appendix IV.

Sensitivity of the burden of disease estimates on the Disability Weights

The Disability Weight (DW) is needed as an input for both approaches, incidence- and prevalence-based Years Lived with Disability (YLD), to estimate the Burden of Disease (BoD). The DW is obtained from the World Health Organization (WHO). The WHO published only a very short explanation for the choice of estimate, stating that it is based on expert judgement. In this work, the same DW is applied for all ages and years, because only this one estimate is available. In contradiction to this uniform application of the same DW on all ages and years stands the high variability of the severity of asthma and the published results of the Finnish Asthma Programme presented in Chapter 1. Although the number of individuals entitled to reimburse their medical expenses for asthma rose, the number of days spent in hospital due to asthma decrease by nearly 70 %. This suggests that the severity of asthma in Finland is decreasing and asthmatic individuals face less impairment compared to 20 years ago. Supported is this idea by the development in asthma medication and management leading to a more efficient supressing of symptoms and a better management of acute attacks. If the severity is decreasing, the DW should be adjusted to this change mirroring the changes in impairment. Furthermore, the reported results of the Finnish Asthma Programme suggest differences in the severity of asthma in different age groups. The biggest fraction (39 %) of all days spent in hospital because of asthma was observed in individuals

over 65 years, whereas only 15 % and 12 % have been attributable to individuals younger than 15 years and younger than 5 % years respectively. In the asthmatic population of individuals being 65 years or older, women have been more prone to spent days in hospital. Overall, the severity seems to increase with age and being higher in females than in males. Based on these observations, it seems realistic that the DW must be adjusted to age and gender of the individual.

It is not possible to quantify the differences in the DW needed to adjust for year, age and gender. It seems likely that the used DW is an overestimation after the beginning of the 2000s, which was the time of the last two WHO GBD studies. Before this time, the DW is probably an underestimation. There is no information available if the WHO standardized the DW for all ages and gender, but it seems likely that it was done. In that case the DW used for the future estimation leads to an underestimation of the burden, because more elderly are asthmatics, so more severe cases of asthma enter the pool of all asthma cases.

6.2.3 Uncertainties in the Asthma Duration

The asthma duration is a crucial point in the difference between the incidence-based and prevalence-based YLD estimation, because the incidence base approach needs the duration estimation, whereas the prevalence-based estimate does not need it as an input parameter.

Although the KELA data are considered to be very reliable in terms of characterisation of asthma in Finland, there is one notable uncertainty: Only for entitlements ending due to death concrete numbers and the reason for the ending are available, for all other ending entitlements no reason was reported. It seems as if adult asthmatics with an entitlement are not re-evaluated regularly if they still comply with the criteria set out for entitlements. Therefore, it is unclear if the entitlement is ending timely close to the remission of symptoms or if there is a big fraction of “unused” entitlements, which are not used because the medication is not needed anymore. In this case, it is not identifiable which fraction of all entitlements is “unused” and an overestimation of the total number of asthmatics. Based on the very strict entitlement criteria and the in comparison low prevalence estimation in this work, the impact of that uncertainty is assumed to be rather small in view of the overall reliability and accuracy of the used data.

Currently, there is no information available on the average duration or entitlement to medical expenses reimbursement and with that the average duration of asthma. As presented in Chapter 5.4.2 the WHO estimate for the duration and the estimation based on the prevalence-incidence-quotient differ significantly. For the year of the WHO study update (2004) the 15 years duration estimation correlates with the quotient estimation, but in general, the WHO estimate seems to overestimate the duration in the past, whereas it underestimates the duration in the future. When looking at the incidence and prevalence trends over the years, it is noticeable, that the prevalence cases increase much more than the incidence cases. This can only be justified by a longer duration of asthma. Looking at the prevalence-incidence-quotient for the different age groups, the quotient increases with increasing age.
Incidence is the number of new cases within one year and prevalence of all cases in one year. With other word, prevalence is the sum of all incidence cases of all previous years minus the dropouts due to death or the remission of asthma. Prevalence is a retrograde measurement, looking at the past, whereas the incidence describes the present. When dividing the prevalence by the incidence to obtain a duration estimate, both are taken from the same year. The incidence numbers used for the quotient will be included in the future prevalence numbers. The quotient only gives an estimate, how many years it would have taken to accumulate the prevalence cases, if the incidence would have been the same in the previous years. However, the incidence is fluctuating each year, therefore this estimation might be hypothetical correct, but does not give a realistic estimation. Overall, the prevalence divided by incidence approach to estimate the duration of asthma, does not give an estimation for the duration of asthma, if the disease is developed that year, but it gives an estimation how long the asthmatics in that year have been suffering from asthma. In practise that does not mean that the individuals in the elderly, who develop asthma at that age, will suffer from asthma for 50 years, but that these individuals, who already suffer from asthma, did develop the disease on average 50 years ago.

I tried to obtain data from KELA on the duration of the entitlement of reimbursement. However, their database is not designed in a way that these data could have been retrieved easily, so KELA kindly declined the inquiry. The period of available data of 27 years leads to the cases, in which the asthmatics would have entered the system before 1986 or would not have left the system by 2012. Therefore, only few complete durations (one individual entering the system after 1986 and leaving it before 2012) would have been obtainable and most other

datasets would have been fractions, for which the early years of asthma would be missing (the individual entered the system before 1986) or it would be unknown how long the individual will suffer in the future (the individual did not leave the system before 2012). The case of people entering the system before is most prominent at the beginning of the life table and the case of people not leaving the system until 2012 is most prominent at the later years of the life table. Due to that, the duration could only be estimated for the middle years of the life table and only for a small number of individuals, which would increase the uncertainty a lot.

In conclusion, more sophisticated modelling or observational studies are needed to give a more realistic estimation of the future asthma duration. Since the estimations are not available at this point, the quotient based estimation is considered to be more realistic than the fixed 15 years duration; however the uncertainties are so big in both approaches, that the data are unsuitable for the use in estimating the burden. Therefore, the incidence based YLD estimates are considered to be not reliable for most parts of the investigated time period. The problem is circumvented by the prevalence based approach, because it does not need the disease duration as an input.

Additionally, the increasing duration proses another problem: the WHO data, which have been published in the scope of the 2004 update, have been published several years later than the target year (WHO, 2009b). In 2009 the duration has already been longer than in 2004 leading to an underestimation in 2009. The same problem applies to other studies using the WHO BoD estimates from the 2004 update as input data for their estimations.

Differences of incidence-based and prevalence-based YLD estimations

In most previous studies the incidence-based approach to estimate the YLD has been used. Only the most recent Global Burden of Disease (GBD) study done by the IHME (University of Washington) used the prevalence-based approach (WHO, 2014b and Lim et al, 2012). None of the both approaches is the better or more correct one in general. However, for complex diseases with a long duration, it seems more appropriate to use the prevalence based approach, because for such disease is might be difficult to estimate a precise duration. Especially, if long periods of time are analysed and the duration undergoes changes during that time period, or a population in which the duration differs, the prevalence-based approach might be more suitable. In this present case, there are major uncertainties in the duration estimation of asthma, as discussed in the previous subchapter under “Asthma duration and the

impact on the BoD estimate". The WHO estimation of 15 years seems only suitable for the years, when the WHO study has been conducted, whereas the quotient duration (prevalence divided by incidence) seems to fit rather well in the past years, but to overestimate the duration in the future to unrealistic long estimates. Since there is no reliable asthma duration estimation, it is considered scientifically more justified to use the prevalence-based YLD approach, because it circumvents the duration problem.

6.2.4 Evidence and Multicausality of Exposure-Asthma Relationships

The evidence of the in the model considered factors varies greatly with in general more uncertainties in the causality of protective factors and asthma than in the causality of risk factors and asthma. It is not possible to draw a final conclusion on the sufficiency of the evidence, because there is controversy about nearly all factors. The evidence for a causal relationship between each factor and asthma is discussed in detail in Appendix III.

In epidemiology different kinds of factors in causal relationships have been defined according their necessarily and sufficiency. If a factor is necessary, the outcome only develops in the presence of the factor, but the presence of the factor alone is not enough to cause the outcome. If a factor is sufficient, the presence of the factor always leads to the outcome, whereas without exposure to the factor, the outcome never occurs (Bonita et al, 2006). As for most chronic diseases, it has not been possible so far to identify necessary or sufficient factors for the development of the disease or occurrence of symptoms of asthma. Because of that, the uncertainty about the actual interaction of the exposures with each other is big. It seems certain, that asthma is developed due to a mixture of exposures and internal factors, such as the genetic background. The mode of the interdependent effect is not known. There are no information if the risk factors work in a synergistic way, which would increase the attributed risk to exposure to several factors to more than the sum of the individual risk, or if risk and protective factors work in an antagonistic way, which would mean that the joint effect is less than expected or if these contradicting factors completely prohibit the effect of the other factor. However, it seems most likely, that the factors interact with each other.

In this work, all factors have been assessed independently and each asthma case has been theoretically attributed to exposure to one factor, not taking into account that the factors are

neither sufficient nor necessary and might interact. In reality, it is more likely, that the factors interact with each other. Especially the exposure to risk and protective factors at the time point manipulates the outcome. By assuming that every factor is sufficient, the contribution of each factor to the total burden is overestimated. Additionally, the used risk estimates are the statistical average of increase in risk in the specific study population, but each individual has a different susceptibility to develop asthma, for example due to the genetic background. Therefore, each factor presents a different risk or protection to each individual. These considerations highlight the problem of the results of the control scenarios: If the exposure to one factor is decreased or deleted, other factors are still affecting the individual. Since none of the included factors has been identified as necessary or sufficient, it is likely that a substantial part of all exposures needs to be changed (reduction of the risk factors and increase of the protective factors) to really prevent a case of asthma. Therefore, the reduction potential in reality is most likely be much lower than estimated in this work.

6.3 EVALUATION OF MITIGATION OPTIONS

In the context of this work, the focus was set on the impact on public health in the context of asthma. The evaluation of the feasibility of the mitigation options is not an objective of this work and therefore it is discussed only shortly in the following.

6.3.1 Tobacco Mitigation Options (I.1-3)

The tobacco mitigation options are explained in detail in Chapter 0. The first two options (total ban of tobacco; 50 % reduction of tobacco) are based on Kutvonens (2014) work. The total ban of tobacco products and with that the decrease of exposure to tobacco smoke to zero, does not seem achievable from 2015 onwards. Such a major, sudden difference cannot be accomplished in practise. The second option is based on the analysis of how the price of cigarettes influences the consumption. Kutvonen claims that the price of a cigarette package has to be increased by 135 % to stop 50 % of the smokers to buy cigarettes and smoke. The price increase from 5.10 € to 12.35 € would be achieved by increasing the taxes on cigarettes. This approach seems doable, especially since the Ministry of Social Affairs and Health of Finland (STM) announced increase in taxes on tobacco products as a measure to decrease the

attractiveness of tobacco products (STM, 2014). At the same time the import of tobacco from aboard would need to be lightly limited and controlled. Furthermore, it is claimed that the income out of the taxes on tobacco products would even slightly increase with that change. However, it is not realistic that the increase in taxation can be accomplished until 2015, because the legislative procedure needs some time. The third option has been developed on the basis of the Finnish Tobacco Act (No. 693/1976) with its amendments that entered into force on the 1st October 2010. Section 1 (20.8.2010/698) states that "[the] aim of the Act is the end of use of tobacco products containing compounds that are toxic to humans and create addiction". By decreasing the annual smoking prevalence by 10 % it is possible to achieve a nearly smoke free Finland until 2040. A gradual decrease in the smoking prevalence seems realistic, because it can be reached with a combination of different measures: increase in the taxation, limiting the availability of tobacco products, support of smokers willing to quit smoking as well as campaigns to prevent the start of smoking. The idea of a totally smoke free country is becoming more popular across Europe. The British Medical Association (BMA) agreed at the annual representative meeting in 2014 to push for a ban of smoking for anyone born in the year 2000 or later, which would lead according to the BMA to a smoke free United Kingdom in 2035. However, they did not provide suggestions how this ban exactly should look like and so far, the government took no actions in order to establish this demand in the legislation (British Medical Association, 2014).

6.3.2 Particulate Matter ($PM_{2.5}$) Mitigation Options (II.1-3)

The particulate matter mitigation options are explained in detail in chapter 4.4.2. As the first two tobacco mitigation options, the options developed to decrease the exposure to PM are based on Kutvonens work (2014). Two different PM sources are controlled by the options: residential supplementary small scale wood combustion in urban areas and re-suspension due to road traffic. The residential small scale wood combustion is supposed to be reduced by introducing taxation on it. Due to the option design, small scale wood combustion in rural areas and as primary heating source are not included to be reduced in the future. Therefore, only recreational wood combustion is affected by these scenarios. It is claimed that a tax of 155 €/m^3 would reduce that type of combustion to zero, because it would be more expensive than all other energy supplies. For the halving of the current small scale wood combustion a tax of 78 €/m^3 is considered necessary. However, residential small scale wood combustion is

a common Finish tradition and the population might be adverse to such taxation, because they value the benefits of small scale wood combustion more than the improvement of health. Furthermore the legislation aiming at an increase in the use of renewable energy encourages the use of wood combustion by reporting is as positive in the energy certificate of a building. This shows the contradicting legislation targeting different problems but affecting the same exposure, which makes the control of $PM_{2.5}$ via supplementary small scale wood combustion rather unrealistic. The same problem was identified by Kutvonen for the third option, the implementation of a stricter speed limit in urban areas, to decrease the average ambient concentration: the population values the right to drive faster more than an improvement of health due to a smaller $PM_{2.5}$ ambient concentration. Therefore, it seems difficult to accomplish a speed limit of 35 km/h in urban areas to reduce the resuspension $PM_{2.5}$.

6.3.3 Dampness Mitigation Option (III)

Damp and mouldy buildings have been identified as major public health and society problems by the Finnish Government. In 2009, the “Kosteus- ja hometalkoot” (Moisture and Mould Programme) has been launched aiming at reducing the moisture damaged buildings, the health effects, economic losses and methods to assess the moisture problem in buildings. As part of the programme no quantitative aim has been published, but it clearly targets the decrease of the exposed population (Kosteus- ja hometalkoot, 2014). It is not likely, that half of all damp buildings can be remediated until next year as it is proposed for the dampness and mould mitigation option in Chapter 4.4.3, because the work needs time and issues such as the financing and relocation during the work has to be clarified. Therefore, the developed dampness and mould option is a little too optimistic about the control potential, but in long term the set goal of 50 % reduction can be achieved. Especially, if care is taken that newly built houses are built using the current standards to prevent the development of indoor dampness and if more attention is paid by the inhabitants and real estate sales person to indoor dampness so that actions can be taken before the problem can increase from only dampness to mould. Additionally, the population might be in favour of this policy, if the remediation of the buildings is partly financed by the government or would come with tax benefits if the energy efficiency is improved at the same time.

6.3.4 Pet Mitigation Option (IV)

The pet mitigation option described in Chapter 4.4.4 is probably the most controversial mitigation option included in this work. Firstly, the evidence for a causal association of exposure to pets, in this case cats and dogs, and asthma is very sparse and not sufficient. This seems true for both, the presenting of a risk to atopic individuals as well as a protective property for non-atopic individuals. Secondly, the intentional long term exposure of atopic individuals to pets, which might cause the development of asthma and/or the worsening of symptoms, in order to prevent asthma in non-atopic individuals, is ethically highly problematic. It is unethical to take the risk of people suffering more, to prevent the suffering in another group of people. Especially considering that the evidence for exposure to pets preventing the asthma onset or symptoms is even smaller than this exposure being a risk factor for atopic people. Thirdly, it is hard to accomplish an exposure of about half of the under 22 years olds to cats and dogs on a daily basis. Pets could be part of the day-care or school routine, by for example teacher bringing their dog to classes, but this might cause a lot of distraction for the children. Additionally, children might feel uncomfortable in the presence of a dog and parents, especially of atopic children, will be against this kind of practise, because it would decrease the children's health. Even if the exposure would not affect asthma at all, atopic children would have allergy symptoms, what probably affects their performance in school negatively, because they have to take more medication or feel sick.

6.3.5 Economic Considerations of the Mitigation Options

A summary of the efficiency of the different mitigation options has been presented in Figure 28 (Chapter 5.3.5) above. As discussed above, some mitigation options are hardly achievable, whereas some are likely to be achievable. The most realistic option is considered to be the yearly decrease in exposure to tobacco smoke, because it is legislatively set out as an aim of the Tobacco Act and its gradual change. A substantial decrease in the fraction of the population being exposed to dampness and mould is realistic, but only in long term and not as quickly as proposed in this work. The other mitigation options are hardly achievable. The annual reduction to tobacco smoke by 10 % would decrease the total number of asthmatics (prevalence) in Finland from 2015 to 2040 by 205 930 individuals. Haahtela et al (2006) estimated the average cost of each asthma patient in Finland in 2003 being 1031 €. Assuming that the costs did not change since 2003 and stay the same in the future, reaching the aim of a

smoke free Finland until 2040 would save more than 212 million € within these 25 years. Obviously, the State would lose tax incomes from tobacco products, which decreases the benefit of the policy. On the other hand, tobacco exposure is not only associated with asthma, but with cardiovascular diseases and especially lung cancer, which prevalence would decrease a lot, too. Kutvonen (2014) estimates that even the total ban of tobacco products would yield an overall profit of 100 billion €. Therefore, it can be assumed that the gradual smoking reduction would be cost-benefit efficient, too.

Trying to reduce asthma in Finland by controlling the ambient PM concentrations proves to more difficult as discussed above. Nevertheless, the total ban of residential small scale wood combustion in urban areas would decrease the cumulative 25 year prevalence by 45 971 cases. This would reduce the medical costs for asthma in 25 years by more than 73 million €. Kutvonen's (2014) analyses suggest that the net profit of this policy would be between 0.5 and 1 billion €. PM are associated with not only asthma, but as tobacco smoke exposure with cardiovascular and other diseases. The benefits due to a reduction in these outcomes are significant.

The net profit of the Dampness and Mould Control Scenarios is going to be smaller, because the remediation of dampness damages buildings is very expensive. Nevertheless, in about 160 000 asthmatics symptoms would be prevented with this policy.

The monetary impact of the pet mitigation option is very uncertain. On the one hand, money for medical reimbursement would be saved due to the decrease of asthma cases, but on the other hand the costs due to allergic symptoms of the atopic individuals would rise. Additionally it is not clear, who is paying for the costs for the pets, if it is the private owner, the school or city or if there would be a governmental programme paying. Additionally money would be needed to be spent on campaigns promoting the idea of increased exposure to pets in day-care centres and schools.

7 CONCLUSIONS AND SUMMARY

The prevalence of doctor diagnosed asthma in Finland is currently about 5 %. The data show a rather constant level in incidence in reimbursement entitlements and potentially asthma, in the last decade, whereas the prevalence is increasing, especially in the older population. These contradictory trends suggest an increase in duration. The main aims of this work have been to quantify the environmental attributable fraction of asthma in Finland, as well as the prevented fraction due to exposure to protective factors. Based on this assessment control scenarios have been developed in order to identify the magnitude of reduction potential of the asthma risk.

The in most previous burden of disease studies used incidence-based Years Lived with Disability estimates have been found not to be suitable for long term diseases with changes in the disease duration, as for example asthma, because of difficulties in the duration estimation. This problem has been circumvented by the use of the prevalence-based estimation approach as a measure of burden of disease. In a systematic literature review 235 articles were retrieved and exposures were selected with pre-defined criteria for risk assessment. In order to quantify the environmental attributable fraction of asthma ten (10) risk and five (5) protective factors have been analysed. The risk factors included in the mitigation options are: Second Hand Smoke (SHS), active smoking, particulate matter ($PM_{2.5}$), damp and mouldy buildings, cat and dog; excluded as mitigation options were: allergen, formaldehyde, NO_2 and underweight. The included protective factors were: cat, dog as mitigation options and excluded as mitigation options were exclusive breastfeeding for 4 months, *Eurotium* and *Penicillium*. The biggest attributable fraction was due to exposure to $PM_{2.5}$ (12 %) and SHS (8 %). In total 40 % of the burden of asthma was attributable to the included risk factors, with 25 % being attributable to exposure included in mitigation options, in 2011. Only 4 % of the total burden of asthma has been prevented due to exposure to protective factors in 2011.

Based on the analysis of the exposures and mitigation options, combined mitigation scenarios to decrease the burden of asthma have been developed. The most efficient mitigation scenario can reduce about 11 % of the total burden of asthma by applying the following mitigation options: ban of tobacco and residential small scale wood combustion in urban areas, 50 % reduction of the exposure to and 50 % increase in the exposure to pets in 2015,. This combination of mitigation options would reduce the number of asthmatics between 2015 and 2040 by 730 141. A more feasible combination of mitigation options can reduce the annual asthma patients by nearly 390 000 cases by applying the following mitigation options: annual 10 % reduction in exposure to tobacco, halving of exposure to residential small scale wood combustion and damp buildings, doubling of exposure to pets. This would be about 8 % of the total burden of asthma. The most efficient mitigation option is the total ban of tobacco, followed by an annual 10 % reduction of tobacco. Reduction of residential wood combustion and urban speed limits of 35 km/h are the least efficient mitigation options.

The number of asthma patients is increasing despite all efforts and new ways of dealing with the problem should be considered. This work suggests that adjustment of exposure to risk and protective factors is capable of decreasing the burden of asthma. Additionally, many information gaps regarding asthma remain until today and more studies are need. Especially studies investigating the cellular mechanisms behind asthma are needed. This would support epidemiological studies by increasing the understanding of the association between asthma and risk or protective factors. Furthermore, it would support a clear, globally agreed definition of asthma with the same diagnosis criteria applied in all studies to increase the comparability of the results.

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APPENDIX I: EXCLUDED ASTHMA ASSOCIATED FACTORS

In the conducted systematic literature review 235 articles have been retrieved, from which most were not selected for further consideration in this work. These selection steps included among others the requirement of an exposure being environmental and a likelihood of exposure in Finland. In this Appendix articles are summarized, about exposures excluded due to these reasons. The variety of stressors, which have been proposed to be associated with asthma, is enormous. Roughly, they can be divided into anthropogenic and natural environmental, lifestyle related, pharmaceuticals, internal and co-morbidity factors. This chapter gives a broader overview over the risk and protective factors that have been studied repeatedly. Those factors, which have already been reviewed in Chapter 2.2.2 are not presented again.

Studies among migrating populations in Germany after reunification support the idea of the importance of local environmental factors (Subbarao et al, 2009). Migration was suggested as a stressor for asthma (Antó, 2012).

Anthropogenic Environmental Exposures

Exposure to phthalates has been suggested to present a risk associated with asthma. As a measure of phthalate exposure PVC flooring is mostly used. Epidemiological studies suggest a positive association between exposure to PVC and asthma symptoms (Bornehag and Nanberg 2010). The same conclusion was reported from Hsu and his colleagues (2012), especially for the phthalates benzylbutyl phthalate (BBzP) and dibutyl phthalate (DBP). Results of animal studies with mice suggest that the prenatal exposure to bisphenol A is positively associated with the onset of asthma (Nakajima et al, 2012).

The effects of single air pollutants are not often studied, but the effect of a mixture of air pollutants, such as coal and biomass exhaust. This exhaust contains particulate matter (PM) carbon monoxide (CO), sulphur dioxide (SO_2), nitrogen dioxide (NO_2) and volatile organic compounds (VOCs). The indoor exposure to this kind of exhaust is proposed to be associated with the development of asthma and asthma symptoms (Jie et al, 2011). Long term exposure

to NO_2 was reported to be associated with an increase in hospitalizations in elderly individuals (Andersen et al, 2012). Furthermore, evidence is accumulating that prenatal exposure to air pollutants is associated with asthma by altering the immune competence of the offspring (Antó, 2012). Long-term exposure to ozone (O_3) and PM_{10} are related to a decrease in asthma control (Jacquemin et al, 2011).

Volatile Organic Compounds (VOCs) have been reported to be associated with asthma symptoms, too. Often the effect of a single VOC is investigated in studies and not the cumulative effect of a mixture of VOCs, which would be more realistic. Nevertheless, a concentration-dependent relationship between VOCs concentrations indoors and asthma prevalence could be observed (Jie et al, 2011).

Natural Environmental Exposures

Natural environmental stressors include for example allergens such as pollen, animal dander and moulds. Respiratory tract infections are associated with the onset of asthma, too. Most convincingly this relation was demonstrated for infections with *Rhinovirus* and *Respiratory Syncytial Virus*. *Chlamydia* and *Mycoplasma* infections have been implicated with the onset of asthma, too. Upper respiratory infections are associated with asthma prevalence (Lemanske and Busse, 2010).

Allergens, which are associated with development of asthma in sensitized individuals, are pet allergens such as cat allergens and Der p 2, the allergen of the house dust mite. The risk of asthma exacerbation is increased in sensitized individuals in relation to the exposure to the allergen. This relation was shown for sensitization to German cockroach (Bla g 2), mouse urine protein (Mus m 1), dust mite (*Dermatophagoides farinae* allergen Der f 1), cat dander (Fel d 1), dog dander (Can f 1), common ragweed (*Ambrosia artemisiifolia*), tree (*Acer negundo, Betula verrucose, Corylus avellana, Quercus alba, Platanus acerifolia*) and grass (*Cynodon dactylon, Lollum perenne, Phleum pretense, Poa pratensis, Sorghum halepense, Paspalum notarum*) pollen (Olmedo et al, 2011). The positive association of exposure to pollen and asthma symptoms in sensitized populations was reported in different studies (DellaValle et al, 2012).

The association between exposure to cat and dog in infancy and the development of asthma is controversial in not sensitized individuals. Still, a meta-analysis of 63 peer-reviewed articles suggests, that this exposure does not increase the risk of asthma development (Chen et al, 2010). Additionally, according to Hugg and colleagues (2008) an inverse relation between exposure to pets, such as cat, dog and bird, and the risk of asthma exists. Therefore, exposure to pets in early life as a protective factor for later asthma is proposed.

Lifestyle Related Exposures

The lifestyle or personal behaviour seems to play a certain role in both, the onset of asthma and the exacerbation of asthma. In many asthmatic individuals physical exercise causes bronchospasms and asthma symptoms (Lemanske and Busse, 2010).

The role of diet in the disorder is not very clear yet. Most studies focus on food with antioxidant properties, for example fish oil, and only investigate small time windows (Subbarao et al, 2009). Omega-3 fatty acids, non-refined carbohydrates and Vitamins C, D and E are regularly put under study, but there is no evidence, yet (Yeatts et al, 2006 and Stanwell Smith et al, 2012). As discussed in Chapter 2.3, the cells of the immune system are important factors in the development of asthma symptoms. Vitamin D is essential in the function and regulation of these cells, as well as in the development of the respiratory tract in utero. Therefore, Vitamin D deficit is suggested to be a risk factor for asthma, too (Weiss and Litonjua, 2011). However, there is no evidence yet and the study results remain controversial (Mai et al, 2012).

The socioeconomic status, the family size and the number and order of siblings are regularly thought to be connected with asthma (Subbarao et al, 2009). According to Almqvist and colleagues (2005) an increase in the risk of asthma onset is associated with a decrease in the socioeconomic status. However, they note that these findings can be biased by different pattern of exposure to air pollutants and differences in the diet in different socioeconomic groups. Therefore, the association of the socioeconomic status as an independent factor on the asthma risk remains controversial (Antó, 2012).

Pharmaceutical Exposures

Approximately 5 to 10 % of asthmatic individuals experience worsening of asthma symptoms after the use of non-steroidal anti-inflammatory drugs. A side-effect of this type of drugs is the modulation of eicosanoid, which are asthma-provoking, production (Lemanske and Busse, 2010).

Another group of drugs, which is related to asthma, are antibiotics. Prenatal maternal antibiotic use is dose-dependent connected with persistent wheezing and asthma (Subbarao et al, 2009). The usage of antibiotics is suggested to be associated with asthma symptoms, too, with a stronger association for antibiotics to treat Gram-positive bacteria and broad-spectrum medication than for narrow spectrum antibiotics (Almqvist et al, 2011).

Internal Factors and Co-Morbidities

The co-occurrence of asthma and gastroesophageal reflux in 45 to 65 % of asthmatics suggests a correlation, but a causative factor could not be determined so far (Lemanske and Busse, 2010).

There is controversy about the role of stress in asthmatic conditions. Some publications propose evidence for an association between asthma symptoms and stress, whereas others to report that there is no association (Lemanske and Busse, 2010 and Subbarao et al, 2009).

Males develop asthma two to four times more often than females do in the first three years of life, but females are more prone to have persistent asthma. This suggests an impact of the sex on the probability to develop asthma (Yeatts et al, 2006).

The role of gut microbiota is frequently discussed. It is connected to the ‘Hygiene Hypothesis’. Gut microbiota are one of the earliest exposure to microbes in life at very high quantities. Therefore, it might play a major role in the development of the immune system and the onset of allergic diseases, such as atopic asthma (Weiss, 2011).

Obesity is named as a risk factor for asthma incidence, too, with an association, which is stronger for women than for men. A proposed mechanism for the relation is the chronic low-

grade systemic inflammation, which is characteristic for obesity (Yeatts et al, 2006 and Stanwell Smith et al, 2012). The American Thoracic Society workshop concluded that there was sufficient evidence for an association between obesity and asthma (Dixon et al, 2010).

The onset of asthma was suggested to be associated with nocturnal dyspnoea in a positive manner, too (Torén et al, 2004).

The frequency of emergency room and urgent care centre visits was reported to be increased in minority racial/ethnic groups, independent from the socioeconomic status. It was suggested that this is due to differences in the perceptions of barriers to access and the need of care and with that differences in the self-management of asthma (Law et al, 2011).

(The references are given in the reference list of the main document.)

APPENDIX II – EQUATIONS USED FOR THE POPULATION LIFE TABLE CALCULATIONS

In Chapter 4.1.1 are the methods described which were used for development of the population life table. Briefly, the observed population in Finland in 2011 was used as baseline. Trends based on the observed birth rate from 1986 – 2011 and the death rates at each year of age in 1986 – 2011 have been used to estimate the population from 2011 to t1986 and 2040. In this Appendix the exact mathematical formulas, which have been used to calculate the population in each year at each age, are presented.

Both, death rate trends and birth rate trend, were used to estimate the population for the time window of 1986 to 2040. Year 2011 was used as baseline year, meaning the observed population data for this have been used as start for the estimation to the past and the future. In the following the calculation for the estimates for the years prior 2011 and after 2011 are explained exemplary for the past and future years. The birth rate and death rates are described in Chapter 4.1.1.

Population estimation for age 0:

Only the new-borns belong to age 0. For the years 1986 to 2010 the calculation is done from the current year to the previous year (Equation A.II.1a) and for the years 2012 to 2040 it is done from the current year to the next year (Equation A.II.1b).The number of birth is calculated by multiplying the birth rate trend (b_y) with the total population of the previous year ($P_{t,y}$-1) and following year ($P_{t,y+1}$) respectively. The number of deaths in that age group is subtracted. The number of deaths is obtained by using the death rate trend ($d_{a,y}$) estimate for that year, followed by multiplication with the population one year older the previous year ($P_{a+1,y-1}$) and the next year ($P_{a+1,y+1}$) respectively.

$$P_{a,y} = b_y \times P_{t,y-1} - (d_{a,y} \times P_{a+1,y-1}) \qquad \text{Equation A.II.1a}$$

$$P_{a,y} = b_y \times P_{t,y+1} - (d_{a,y} \times P_{a+1,y+1}) \qquad \text{Equation A.II.1b}$$

Population estimation for ages 1 to 98:

Again, the calculation is done for the years 1986 to 2010 from the current year to the previous year (Equation A.II.2a) and for the years 2012 to 2040 it is done from the current year to the next year (Equation A.II.2b). The calculation is based on the assumption, that all individuals being alive at a specific age and year ($P_{a,y}$) is the number of individuals being in the age group one year younger the previous year ($P_{a-1,y-1}$) minus the individuals, who died ($d_{a-1,y}$ x $P_{a-1,y-1}$) or the number of people one year older the following year ($P_{a+1,y+1}$), subtracted by the number of individuals dying in this age group ($d_{a-1,y-1}$ x $P_{a-1,y+1}$) and year.

$$P_{a,y} = P_{a-1,y-1} - (d_{a-1,y-1} \times P_{a-1,y-1}) \qquad \text{Equation A.II.2a}$$

$$P_{a,y} = P_{a+1,y+1} + (d_{a-1,y} \times P_{a,y+1}) \qquad \text{Equation A.II.2b}$$

Population estimation for ages 99 to 100:

The estimates for this age group are calculated the same way as for the past and future years. For the two oldest age groups, the population estimates were calculated directly from the population trend. This trend was computed using the LOGEST function and the observed data for the two age groups, which were obtained from the Statistics Finland database. The population trend derived from the absolute numbers of population was used because the highest age group includes all individuals being older than 100 years in Finland. Since only a fraction of this group dies every year, but becomes new members, who turn 100 years old, this age group would grow infinitely big, if it would be calculated by adding all people who died to the number of individuals in this group the following year.

APPENDIX III – SCIENTIFIC EVIDENCE FOR CAUSALITY OF CONSIDERED EXPOSURE-ASTHMA RELATIONSHIPS

The evidence for a causal relationship between an exposure and an outcome, in this case asthma, is crucial for the reliability of an assessment based on epidemiological studies. If a factor is included, for which there is no evidence for causal relationship, it might be, that a fraction of BoD is theoretically attributed to that factor, although in practice the factor is not associated with the outcome at all. This leads to an over- or underestimation (depending on whether it is a risk- or protective factor), of the attributable or explainable fraction of BoD. Below, criteria to assess the level of evidence based on *in vitro*, *in vivo* and epidemiological studies are presented and applied for the assessment of the evidence for a causal relationship between the considered factors and asthma.

Currently, there are major uncertainties about the cellular mechanisms of especially the onset of asthma, but also the occurrence of symptoms. For some risk factors modes of action have been proposed and *in vitro* and *in vivo* test results support these suggestions. However, the suspicion of an exposure presenting a risk or protection for asthma, are based on epidemiological studies. Epidemiological studies assess a statistical correlation between an exposure and an outcome. If such a study shows a relationship between the exposure and outcome, it does not mean that there is evidence for a causal relationship. In 1965 Sir Austin Bradford Hill proposed 9 criteria, which can support the proposal of sufficient evidence for such a causal relationship. These criteria include: Strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy (Bradford Hill, 1965).

The exposures and studies, which have been presented already in Chapter 2.2.1 of the main document, are here discussed with a focus on their evidence for causality based on the Bradford Hill criteria (Bradford Hill, 1965).

There is a multitude of studies about asthma with different designs and qualities published. In general, risk factors gained more attention than protective factors in the past research, but the number of studies about protective factors is increasing. Furthermore, some (environmental) factors are studies more often than other. Unambiguous results of studies are rare, but

nevertheless, the evidence for the relationship between exposure and asthma onset or exacerbation is sufficient for some factors. However, even for those factors with sufficient evidence for a causal relationship, the risk estimate often varies a lot. To avoid the need to choose one risk estimate out of a pool of available studies, meta-analyses have been used whenever possible. In meta-analysis all studies with a certain quality are combined and an average risk estimate is calculated. In general, there is still a lot of controversy in the scientific community about asthma as such and the association between exposures and asthma onset or exacerbation. In the following all the factors included in the model will be discussed shortly with a focus on the evidence of a causal association.

Air pollutants, such as Particulate Matter (PM) and Nitrogen Dioxide (NO_2), are some of the most commonly studied factors in association with asthma. Due to the high number of studies, it is possible to assess the association between exposure to PM and onset of asthma and the exacerbation of asthma independently. Guarnieri and Balmes (2014) concluded that there is "substantial evidence" for a causal relationship between PM exposure and asthma symptoms and "some evidence" for the causal relationship between PM and asthma onset. A major difficulty in studying the effects of exposure to PM is the high variety of PM depending on the source, composition and size distribution. PM often constitute of transitional metal, organic compounds, free radicals as well as immunogenic substances. The specific composition and size of each particle determines its toxicological profile and there can be big differences between the potential to cause adverse effects (WHO, 2005). Under laboratory conditions it is difficult to achieve a composition of PM resembling the average composition of ambient PM for a bigger population, because the ambient PM concentration differs a lot between micro environments. Another problem in epidemiological studies is the co-exposure with other air pollutants. PM, ozone, NO_2 and sulphur oxides correlate strongly and therefore make it difficult to attribute the observed effect to one specific pollutant. Especially for NO_2 it is discussed if the effects seen in the studies are really attributable to the exposure to NO_2 or if NO_2 is in most cases just an indicator for the exposure to other traffic-related air pollutants (Guarnieri and Balmes, 2014). Guarnieri and Balmes (2014) suggest that the results of epidemiological studies are consistent enough to conclude that there is a causal relationship between NO_2 exposure and asthma symptoms, whereas the relationship is not clear for NO_2 exposure and asthma onset. In contradiction, they report that the toxicological data are weak and that there are some contradiction results in animal studies and controlled exposure trails in healthy and asthmatic humans. In epidemiological studies, confounding due to exposure to

other ambient air pollutants is critical and can interfere with the studied relationship. However, controlling of this confounding is very difficult and therefore there is always the risk of biased results (Guarniere and Balmes, 2014). An additional problem in epidemiological studies is the information gap, if long-term or short-term exposure is more important and if peak exposures or average exposures are more important. It seems as if peak exposure is associated with adverse asthma outcomes the day after the peak, but the data a rather sparse on this relationship (Guarnieri and Balmes, 2014).

Tobacco smoke, either from active smoking or from Second Hand Smoke (SHS) consists of various constituents. The above discussed PM are one of the constituents. In general, the exposure to smoking and SHS differs in the composition of the inhaled smoke. Nevertheless, the published studies are consistently suggesting an increased risk for asthma compared to non-exposed population. Although the studies consistently suggest an increase in risk, the size of the additional risk is differing a lot between the available studies. Additionally, most published studies have been designed to assess the relationship between exposure and asthma symptoms and only very few investigate the association between exposure to tobacco and asthma onset. Widely agreed modes of action for the effect of exposure to tobacco have been reported (Chapter 2.2.2). Taking that into account, the evidence is rather weak for the relationship tobacco exposure and asthma onset, whereas it seems sufficient for tobacco exposure and asthma symptoms. Again, the measure of exposure is problematic. For exposure to tobacco it remains unknown if the effects are due to the duration of smoking or the amount of tobacco being smoked.

Several meta-analyses are available of studies assessing the association between exposure to dampness and/or mould and asthma. The results seem to be consistent for the association between exposure to dampness and/or mould and asthma symptoms, but not for the association with onset of asthma. Different meta-analyses, one from 2005 and one from 2007, come to contradicting results (Richardson et al, 2005 and Fisk et al, 2007). Again, exposure to dampness and mould is not an exposure to a single specific factor, but to a number of chemicals, fungi and bacteria, whose composition differs between each micro environment and building. Additionally, so far it was not possible to identify, if all constituents of the mixture contribute to the effect or if specific constituents are responsible for certain adverse effects. Furthermore, the mechanism behind the observed effects is not known. In summary, the evidence for a causal relationship between damp and mouldy buildings and asthma seems

limited, while the evidence for the onset of asthma is even weaker than the evidence for dampness causing asthma symptoms.

Currently, the evidence for a causal relationship between childhood exposure to formaldehyde and asthma is very limited, because the results of different studies are contradicting greatly. Furthermore, the strength of the relationship seems rather weak based on a meta-analysis from 2010 suggesting only a very slight increase in risk (McGwin Jr et al, 2010).

The association between childhood weight and asthma is very controversial. Firstly, it is not agreed on, if the actual weight in early childhood is the important factor or the weight gain during childhood. Additionally, the number of available studies is quite limited. Therefore, it has to be concluded, that at this point there is no sufficient evidence for a causal relationship (Flexeder et al, 2012 and Zhang et al, 2010).

It seems as the association between asthma and allergy is one of the most studied one. The underlying mechanisms of both diseases are proposed to be partly similar. However, the studies are designed in very different ways. The scientific community seems to be divided into two groups: the ones claiming evidence for a causal relationship and the others claiming that it is just a statistical association and not a causal relationship. Many intervention studies do not show any effect of the decrease of allergen exposure on asthma. However, the Cochrane Society concluded that there is some evidence, that injection allergen immunotherapy does decrease asthma symptoms and the need for medication (Abramson et al, 2010). In general, it is difficult to assess the association between allergy and asthma, because the proposed mechanisms behind the diseases are so similar, that they might be not causally associated, but confounding each other because they share some risk factors.

For all included risk factors there is no sufficient evidence for a causal relationship between the exposure and asthma. Exposure to pets, as well as exposure to fungi, such as *Penicillium* and *Eurotium*, has been proposed as protective factors based on the Hygiene Hypothesis. This hypothesis claims, that the developing immune system needs certain challenges to develop properly and exposure to a mixture of bacteria, fungi, allergens and other factors found in a farm environment, would support this correct development of the immune system (Ege et al, 2011). However, the whole hygiene hypothesis is challenged by studies regularly. Especially, since it is not possible to identify the important factor: the diversity of exposure, specific

bacteria or specific fungi. The study results concerning breastfeeding are controversial: some suggest protective properties, while others suggest breastfeeding being a risk. Furthermore, it is uncertain if the breastfeeding has to be exclusively and for what duration for an effect. Moreover, the proposed mechanisms for the protective properties differ: one hypothesis is that the allergens and immune proteins in the milk support the development of the immune system, whereas the other hypothesis claims that the exposure to the bacteria on the skin of the mother helps to support the development of the immune system (Takemura et al, 2001 and Brew et al, 2012).

For most suggested factors associated with asthma only some of the criteria are fulfilled. For most factors the strength, which is the increase in risk due to exposure to the factor, and consistency, meaning that several studies by different working groups have the same findings, are rather well. The specificity is more limited, because the studies mostly do not exclude other possible explanations for the observed results. The occurrence of the outcome after the exposure (temporality) and an increase in risk when the exposure is increased (biological gradient) are often assessed due to the study design. Plausibility, coherence, experiment and analogy are very much connected in the area of research on asthma. For some factors, but not all, a plausible mechanism (plausibility) has been proposed and based on that proposal experiments (*in vitro* and *in vivo*) are conducted aiming at the proof of the proposed mechanisms. However, often the results of the epidemiological studies and the laboratory results differ, so the coherence is limited. For most associated risk factors, the same mechanism has been proposed: oxidative stress. The criterion of analogy is applied the other way round in such cases: instead of comparing the effects of similar factors, other factors are investigated based on their properties. Especially, the proposal of protective factors is nearly always based on exposure to a “dirty” environment, as it is proposed by the Hygiene Hypothesis, which is suggested to train the immune system correctly. Additionally, epidemiological studies do face the problem of study design. The knowledge about the pathogenesis is so sparse, that it is not known if the factors have the same effect on causing the onset and causing the symptoms. It might be that some factors affect both, whereas other factors only affect one of them. An investigation of this question would require studies on both: onset and exacerbation. However, studies investigating both are seldom available. Favourably, the investigation of the association with onset and symptoms should be done within the same project or working group in order to avoid differences in the results due to

differences in the used measurement methods, data handling and so on. Therefore, there is a major scientific uncertainty behind the differentiation between factors associated with the development of the disease or the exacerbation of symptoms. Another problem in the study design is the time frame: at present, there is no knowledge about the timeline between exposure and outcome, as well as the duration of the effect. Hence, there is the possibility that relevant outcomes are not observed in the studies because they happen outside of the observation period of the study. This is discussed more detailed in Chapter 6.2.2 under “Risk Estimate Extrapolation”.

In summary, the evidence for only few risk factors (Particulate Matter, SHS) seems to be sufficient, whereas for most factors the evidence is very weak. For the differentiating between risk/protective factor for onset and the occurrence of symptoms attributable to a specific exposure, is currently no scientific justification available.

APPENDIX IV – SOURCES OF BIAS IN QUESTIONNAIRE BASED EPIDEMIOLOGICAL STUDIES

The Relative Risk (RR) estimates used in this work to calculate the Population Attributable Fraction (PAF) are obtained from epidemiological studies. The quality of the study determines the reliability of the RR estimate. However, even high quality studies are sensitive for different types of errors and biases, which are shortly presented below.

In order to obtain risk estimates for the relationship between an exposure and asthma, different types of studies have been used: cohort studies, case-control studies, population based cross-sectional studies and meta-analysis. This presents a risk for an error in the risk estimate due to biases in the original studies. As a first general source of error the possibility of publication bias has to be taken into account. A publication bias is the preference of journals to publish studies attracting readers. In this case it means that studies showing a relationship between an exposure and asthma may be more likely to be accepted for publication than studies showing no effect, which would increase the risk estimate, especially in meta-analysis (Anderson et al, 2013). The definition of asthma in the study presents another source of error. A definition of asthma as wheezing for a specific time or the occurrence of coughing over a specific time period in a study, leads to a very low sensitivity to detect asthma cases. Especially Chronic Obstructive Pulmonary Disease (COPD) cases cannot be separated from asthma cases that way. This can alter the risk estimate, because the relationship between an exposure and asthma or COPD can differ significantly. Studies, using an interviewer for obtaining the needed data, are under risk for observer or interviewer bias. This kind of bias is the (unintended) influence of the study participant by the interviewer due to the way the question is asked or gestures (Delgado-Rodriguez and Llarca, 2004). Furthermore, a recall or reporting bias is likely to occur in epidemiological studies: affected individuals suffering from the outcome under study are more likely to remember exposures or to report exposure than these individuals not affected by the exposure (Delgado-Rodriguez and Llarca, 2004). Another type of bias likely to occur is the non-response bias, which is somewhat similar as the reporting bias. This bias is defined as the tendency to participate in epidemiological studies: individuals suffering from the outcome under study are more likely to participate in a study than healthy individuals. These two biases increase the risk estimate for the exposure asthma relationship (Delgado-Rodriguez and Llarca, 2004).

In epidemiological studies, confounding can change the risk estimate in both directions. Confounding is the influence of factors on the exposure-response relationship under study. For asthma, smoking is such a confounder, which needs to be controlled and taken into account. Furthermore, the exposure to other known asthma causing agents, for example in the occupational settings, has to be taken into account in epidemiological asthma studies, because asthma is a multi-causal disease. If the asthma case is not due to the studied factor, but a confounding factor, which has not been controlled in the study, the risk estimate for the aimed exposure-response relationship is greater than it would have been if confounding and biases would have been taken into account (Anderson et al, 2013).