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Non-response in the West Sweden Asthma Study Questionnaires

Degree Project in Medicine

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Gothenburg, Sweden 2020

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Abstract in English

Degree Project, Programme in Medicine
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Introduction: The West Sweden Asthma Study is an ongoing project aiming to investigate the respiratory health in West Sweden. In 2016, a postal questionnaire in the field of respiratory epidemiology was sent out to 50 000 subjects with a response rate of 50 %. It is of great importance to investigate the population of non-responders since they may differ from the responders and thereby possibly cause non-response bias.

Aim: The primary aim was to investigate the validity of the questionnaire results by comparing the responders against the non-responders**,** regarding demographic data and respiratory health.

Methods: A sample of 700 subjects were randomized from the non-response population. They were interviewed by telephone with questions composed by a shortened version of the postal questionnaire.

Results: A total of 311 non-responders participated in the telephone interview. Non-responders were more often males, smokers, living in an urban area and younger than responders. Attacks of shortness of breath were more common among non-responders, while physician diagnosed chronic bronchitis, COPD (chronic obstructive pulmonary disease) or emphysema, longstanding cough and sputum production were more prevalent among responders. Post-stratification weighting for non-response presented that the prevalence estimates for the weighted data were similar to the unweighted data.

Conclusions: Non-responders and responders differed in demographic data but not for most of the investigated respiratory symptoms and diseases. The results of prevalence data of symptoms and diseases from the postal questionnaire study are considered as representative for the population in West Sweden. Future studies are recommended to explore if digital methods can replace postal questionnaires and if register data can be used for weighting procedures regarding non-responders.

Key words: non-responders, non-response bias, respiratory epidemiology, cross sectional cohort study

Introduction

Asthma

Asthma can be described as a heterogenous disease that most often includes chronic airway inflammation. Symptoms are commonly wheeze, shortness of breath, chest tightness and cough (1). Asthma affects both children and adults and usually develops during childhood but may also have an onset later in life. Asthma during childhood is more common in boys while adult asthma is more common in women. The prevalence of asthma varies between different countries worldwide. An increase in prevalence of asthma has been reported since the second half of the 20th century from different developed countries. It seems to have reached a plateau in high-income countries but continues to increase in low- and mid-income countries (2). It has therefore been suggested that exposure for Westernization may increase the risk for asthma (3). The prevalence of asthma in West Sweden was stable around 8 % between 1990 and 2008, leading to the assumption that a plateau in this area had been reached (4). However, new data from 2016 reports that the prevalence again has been increasing, to 10 % (5).

It has been suggested that asthma can be divided into various phenotypes such as allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation and asthma with obesity (1). Another way to divide asthma is by endotypes that reflects different immunological responses that can be seen, which enables the use of targeted therapies. Important pathophysiological factors to the development of asthma are for example allergens, infections, tobacco smoke and genetic mutations. These can activate both the innate and adaptive immune system to stimulate chronic airway inflammation, which later on leads to airway remodeling (6). Important tools in the diagnostics of asthma are to begin with presence of clinical symptoms such as wheeze, shortness of breath, recurrent cough and nocturnal awakening. In addition, reversible airway obstruction and/or airway hyper-responsiveness

should be documented. Reversible airway obstruction enough for diagnosis is, by the completion of spirometry, defined as at least a 12 % improvement in forced expiratory volume during the first second during exhalation (FEV1) and a total improvement of at least 200 milliliters, after administration of short acting beta$_2$-agonists. Airway hyper-responsiveness is evaluated by bronchial provocation testing by inhalation of methacholine or mannitol. The aspects of airway inflammation in asthma can be analyzed by the biomarkers eosinophil counts in sputum or blood and/or increased fractioned exhaled nitric oxide (FeNO) (7). The goals of asthma treatment in a long-term perspective are to obtain good symptom control and reduce the risk of exacerbations, persistent airflow limitation, side-effects of medications and asthma-associated mortality. Medications recommended for treatment are, depending on the severity of asthma and possibly in different combinations due to individual response, inhaled corticosteroids, short acting beta$_2$-agonists, long acting beta$_2$-agonists, leukotriene receptor antagonist and oral corticosteroids. In severe asthma with difficulties to treat, biological targeted therapies such as IgE monoclonal antibodies, may be an option (1).

A common co-morbidity to asthma is allergic rhinitis (7-9). The associating factor between these two conditions has suggested to be airway hyper-responsiveness (9). The inflammatory cell response seems to be similar in the mucosal tissue in both the upper and lower respiratory tracts among patients with asthma and rhinitis (10). Symptoms of allergic rhinitis are for example watery nasal secretion, nasal congestion, sneezing, itchy skin and eye symptoms (8). It is of importance to treat both conditions since treatment for one of them can likely ease the other one (10). Allergic rhinitis may impact the control of the asthma, and rhinitis should be considered among patients suffering from inadequately controlled asthma (8).

Respiratory epidemiology

Epidemiology can be defined as ”the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of

health problems" (11). Research in the field of respiratory epidemiology results in important knowledge about, for example, prevalence of respiratory symptoms and diseases, prevalence trends over time, environmental determinants that triggers respiratory diseases (2) as well as variations between different countries (12). The global environmental change is considered to affect respiratory health conditions and is another reason that states the importance of continuous research in respiratory epidemiology (13). Longitudinal epidemiologic studies are an important tool of following cohorts over time and identify risk factors for development of asthma (14).

One method of data collection in respiratory epidemiology is by questionnaires, administrated by for example mail (postal questionnaires; written self-reported questionnaires), telephone interviews (15), face to face interviews or by the Internet (16). Postal questionnaires with the aim to evaluate respiratory symptoms and diseases are a cost-effective method (17) and are therefore commonly used in respiratory epidemiological studies. To validate questionnaires regarding asthma and respiratory symptoms, the answers to the questions should be compared to a clinical diagnostic test for asthma or information about physician-diagnosed asthma from medical records (18). Validation studies have presented high agreement between questionnaires including questions about asthma symptoms and physician diagnosed asthma (19), as well as significant correlations between a variety of different respiratory symptoms investigated by a questionnaire and lung function tests such as spirometry and methacoline test (20). It has therefore been suggested that questionnaires are a suitable method in evaluating asthma and respiratory symptoms in large epidemiological studies, when it is often not reasonable to perform clinical diagnostical tests because of an extensive study sample (21).

Non-responders

In questionnaire studies, the individuals of the study population that for some reason not contribute with data, are called non-responders (11). The non-response in these types of studies can be divided into unit non-response and item non-response. Unit non-response appears when a subject in a study sample fails to participate fully or partially. Reasons for unit response are for example inability to contact the participant due to wrong or missing address or telephone number, unwillingness to answer, or inability to answer because of a health condition or lack of time. Item non-response means that an answer is missing to one or several questions in the survey from a participant. Reasons to this may be refusal or inability to answer a specific question, not following instructions, or problems for the investigator to interpret the fulfilled answer because of for instance unreadable handwriting or several fulfilled alternatives to a single answer question. Non-response can be correlated to characteristics such as health condition, education level, attitudes and behaviors that may systematically differ from the responders (22). Prospective population studies presented that non-responders had a higher mortality (23-25), higher hospitalization rates due to somatic and psychiatric diseases, lower socioeconomic status, overall worse health profile (24) as well as higher rate of death and hospitalization related to alcohol (25). Therefore, responders in a study may not be representative for the whole sample and conclusions made from data of the responders alone can be biased (26). Non-response bias has suggested to be consisting of both the non-response rate as well as at which extent the non-responders systematically differ from the responders (22). In questionnaire studies, possible non-response bias should be addressed before as well as after distribution of the questionnaires, and the potential effects of non-response bias should be reported. That will enable the reader to assess the quality and representativeness of the results (26).

Approaches to handle missing data and non-response

Non-response leads consequently to missing data of a fraction of the sample. When deciding how to handle missing data it is of importance to examine what type the missing data is categorized as. It has been suggested that missing data can be classified into three different forms. The first type is described as ’missing completely at random’ which implies that the non-responders are a total random sample from the study population and does not correlate with any data variable, this type is mostly harmless but very uncommon. The second type is ’missing at random’ and implies that the response tendency depends on the observed data but not on the missing data. The last type, ’not missing at random’, suggests that the response tendency depends on the missing data and this classifies as non-ignorable non-response. Different methods have been presented to handle missing data. One way is to ignore the observations in the analyses that lack data. However, this method neglects the possible fact of non-response bias and is insufficient in the cases of non-ignorable non-response (27). In epidemiological studies it is recommended to invest in additional examinations of the non-responders to obtain data from this population. That will enable comparisons between responders and non-responders and allow estimation of the extent of non-response bias (13). Methods to further investigate the non-response population in questionnaire studies are, for example, to obtain demographic data such as gender, age, health care use and income, from population and health registries. For a postal questionnaire study, it is useful to examine a sample of non-responders further through a different approach, such as a telephone interview or a home visit (28). If data among the non-responders have been collected from registries or a follow-up interview, it is possible to assess the potential non-response bias by weighting the data. That is a statistical procedure aiming to adjust for non-response by assigning weight to the responders utilizing non-responders characteristics (27). Moreover, if the non-response population is investigated by a follow-up interview, it should include questions about reasons

for non-response which will gain knowledge about the missing data mechanism (29). It will also enable categorization of the non-responders into subgroups according to reason for non-participation. The different reasons may impact the measured outcomes suggesting that non-responders may not necessarily be a homogenous group. For example, a questionnaire study by Etter and Perneger presented that participants who clearly stated uninterest of participation had high health care expenditures, while participants with no found address or failure to fulfil the questionnaire had low expenditures (30).

Non-responders in the field of respiratory epidemiology

In the field of respiratory epidemiology, several studies have reported non-responders as more frequently being smokers (31-34), males (32-37) and younger compared to responders (32-35). A literature review from 2002 (38) included eleven studies about respiratory epidemiology containing data from follow-ups of non-responders. The results of the different studies were not consistent because non-responders were reported to show both increased prevalence of respiratory symptoms and diagnoses, decreased prevalence as well as no reported difference between the responders and non-responders. However, all studies that included data about smoking reported that non-responders had a higher prevalence of smoking. Since 2002, three postal questionnaire studies regarding non-response have been published in the field of respiratory epidemiology according to the author's knowledge. They reported similar prevalence among responders and non-responders for the majority of respiratory symptoms and diagnoses (31, 34, 35). Overall, it does not seem to be a consensus in previous research if non-responders are causing decreasing, unchanged or increasing prevalence rates of respiratory symptoms and diagnoses. Non-response may increase the risk for non-representativeness of the sample. Some strata of the response population may be under-represented while some others may be over-represented which can affect the reported

prevalence. Therefore, it is of great need to still investigate the non-response population in respiratory prevalence studies.

Early and late responders

If the participants not responding to the first attempt of contact in population studies are attempted to be contacted again at one or several following time points, the population can not only be divided into responders and non-responders, but also into early and late responders. The number of contact attempts can be used to adjust for non-response and make assumptions about the non-response population. If a certain outcome is more prevalent among late responders than early responders, it is probable that it is even more prevalent among the non-responders (39). On the other hand, if the outcome among non-responders does not differ from the responders, it validates the results from the responding population and also that the amount of reminders sent out to the subjects not returning the questionnaire were enough to obtain information that mirrors the whole sample.

Several previous studies in research of respiratory epidemiology have reported late responders to more often being current smokers compared to early responders (17, 31, 34-38, 40, 41). Prevalence of respiratory symptoms and diseases have presented to be higher among early responders (17, 31, 35, 37, 38, 41, 42) as well as higher among late responders (36). In contrast, studies have presented no clear prevalence difference between early and late responders (34, 40).

Implications of response rates in respiratory epidemiology studies

Previous questionnaire studies in the field of respiratory epidemiology have presented different assumptions about response rate and risk for bias. De Marco et al (37) suggested that a higher non-response rate increases the risk of bias. With a response rate of 86 % in their study they reported a low to moderate bias for most respiratory symptoms, between 4-10 %. If

their response rate would have been 70 % the bias would have increased to between 15-21 % which led to the assumption that a non-response rate over 30 % generates enough bias to cause uncertain interpretations of the results. However, an increased response rate does not necessary increase the reliability of the results. Eagan et al (43) presented that an increase in response rate from 65 % to 89 % did not change the prevalence of respiratory symptoms and Brøgger et al (38) discussed that a raise from 60 % to 80 % in response rate most likely would not change their concluded assumptions of prevalence in their study. In contrast, a high response rate has even so been reported to present differences between responders and non-responders. Rönmark et al (33) performed a questionnaire study with a high response rate such as 85 %. Telephone interviews were conducted with the non-responders which showed that there were differences between the two groups in prevalence of asthma, respiratory symptoms and use of asthma medications. So, it seems that a high response rate may not guarantee less risk of bias caused by non-responders in this research field. There may be specific characteristics in the different studied populations leading to the importance of consequently investigate the non-responders both in individual questionnaire studies as well as the whole field of epidemiology.

The West Sweden Asthma Study

The West Sweden Asthma Study (WSAS) is an ongoing project aiming to investigate the prevalence of asthma, respiratory symptoms and allergic rhinitis in West Sweden. The study started in 2008 (WSAS I) with a questionnaire study with a response rate of 62 % (4, 44). A non-response study was conducted presenting no significant differences in respiratory diseases or symptoms comparing responders and non-responders. Non-responders were more often smokers, males and of younger age (34). In 2016, a similar questionnaire study (WSAS II) was conducted with the purpose to describe the changes in prevalence compared to the first study (5).

Aim

The aim of the thesis is to compare the responders from the 2016 questionnaire study against non-responders regarding demographic data, respiratory symptoms and respiratory diagnoses by telephone interviews.

Research questions

1. Are there significant differences between non-responders and responders regarding:
   -prevalence of respiratory symptoms and diagnosed respiratory diseases?
   -smoking (current smoking, ex-smoking, non-smoking)?
   -age, gender, living area, occupation, education level and work-related exposure to dust, gas or fumes?
2. Are there significant differences between subjects responding early or late to the questionnaire concerning above questions?
3. What risk does non-response implies when it comes to respiratory symptoms and diagnoses?
4. How does the prevalence of non-responders affect the defined prevalence from the postal questionnaires? Can the results be extrapolated to the population in the area?
5. Do the results differ from the recent non-response study (WSAS I), and if so, what reasons may explain that?
6. What were the reasons for not responding to the postal questionnaire? What suggestions of improvement are there to raise response rates in future questionnaire studies?

Material and Methods

Sample of the WSAS II questionnaire study (2016)

This thesis is a non-response study with the study design of a cross sectional cohort study based on the sample of the previously mentioned WSAS II questionnaire study from 2016. The sample of the postal questionnaire study consisted of 50 000 randomized selected subjects in the ages 16-75 years. The population sampled from were, at the date of randomization, residents in Gothenburg, Sweden, and its surrounding municipalities with a population centre located maximum 100 kilometers from Gothenburg city. The reason for this living area criteria was that the subjects could potentially be invited for other clinical studies and would therefore have a reasonable travel distance to the investigation clinic in Gothenburg. The 30 000 subjects randomized to the WSAS I questionnaire study in 2008 were excluded to enable comparisons between the two cohorts. The randomization process was performed by an external company. The sample was stratified regarding gender and in five-year age intervals with compositions matching the whole population. Names and addresses were conducted through the Swedish Population Register (45) and the postal questionnaire was mailed to the participants. The participants could complete the questionnaire and send it back in a prepaid envelope or fulfill it via a personalized Internet link. If the questionnaire was not returned after one month a reminder consisting of the same questionnaire was sent out, following a second reminder after another month and a third and final reminder following another two months. Responders to the first questionnaire were classified as early responders, responders to any of the reminders as late responders and in cases of no return as non-responders.

The postal questionnaire

The postal questionnaire included the Finland Estonia Sweden (FinEsS) questionnaire version (46, 47) of the Swedish Obstructive Lung Diseases in Northern Sweden (OLIN) Studies (48), the Swedish translated version of the Global Allergy and Asthma European Network (GA2LEN) questionnaire (49) and questions regarding socio economics, health status, airborne exposures and demographic data. The paper questionnaire was in Swedish and the Internet version was available in Swedish or English.

Participation in the postal questionnaire study

Of the 50 000 invited subjects, 817 questionnaires were returned because of unknown address, 89 could not answer due to disease, 60 were living abroad, 26 did not fit the inclusion criteria because they were also included in the previous study cohort and were accidently not excluded in the sample process, 24 did not understand the language and 16 were deceased. These groups were together classified as unreachable. The real study sample therefore consisted of 48 968 subjects. Out of these, 24 434 did not complete the questionnaire whereof 343 (0.7 %) subjects declared they did not want to participate and 110 (0.2 %) returned a blank questionnaire, giving a non-response rate of 23 981 (49 %). After three reminders 24 534 (50 %) participants had completed the survey (Figure 1). Among the responders, 10.6 % chose to respond using the Internet, 14.0 % among men and 7.8 % among women.

Sample of the non-response study

The population for the non-response study consisted of the 23 981 (49 %) subjects that not responded to the questionnaire. The subjects that were unreachable, had sent back an empty survey or had informed uninterest to participate, were thus excluded from the non-response population. A sample of 700 non-responders was randomized that matched the non-response population according to gender and age by five-year intervals (Figure 1). The randomization was made by using Statistical Package for Social Sciences (SPSS, version 24).

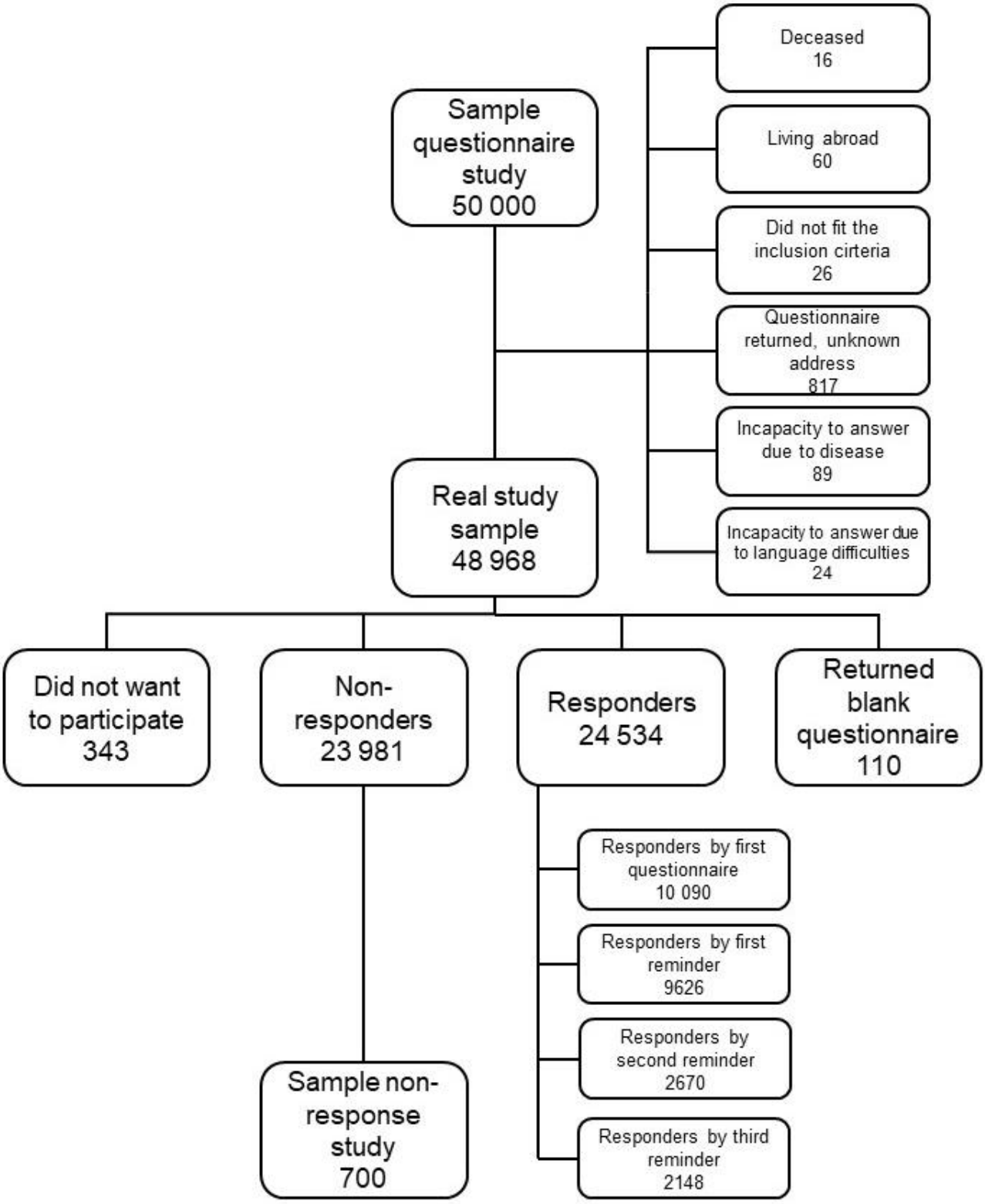


Figure 1. Flow chart demonstrating the population in the WSAS II questionnaire study (2016) and the non-response study.

Sample of the WSAS I questionnaire study (2008)

The questionnaire in the 2008 study was sent out to 30 000 subjects. Of these, 18 087 subjects participated in the study, leading to a response rate of 62 %. The number of non-responders were 10 732 subjects (37 %). The area sampled from 2008 covered a larger area of western Sweden than 2016. The subjects in the 2008 cohort that lived in an area not covered in the 2016 study, was in this thesis excluded in the analyses of comparing the non-responders in the 2008 cohort with the 2016 cohort. Of the 10 732 non-responders 2008, 1515 subjects lived in areas not covered 2016, leading to a sample of 9217 subjects.

Data collection procedures/Variable analyses/Statistical methods

Data collection

The sample of the 700 non-responders were investigated through telephone interviews. Telephone numbers to the subjects were collected from two commercial databases (www.eniro.se and www.hitta.se). Verbal consent was obtained before the interview was initiated. The interview took about five to ten minutes and consisted of a shortened version of the postal questionnaire including key questions about airway symptoms, diagnosed respiratory diseases, allergies, smoking habits and demographic data. It was also asked about reasons for not responding to the postal questionnaire and suggestions to changes in the study design that would have increased the probability to complete the postal survey. About half of the interviews were conducted by the author and the remaining half of another research investigator. It was done at least five attempts to contact the subjects during both daytime and evening time before classified as unreachable.

Variables regarding symptoms and diagnoses

The variables used regarding asthma was ever asthma (investigated by the question “Do you have, or ever had, asthma?”), physician diagnosed asthma (“Have you gotten the diagnose

asthma by a physician?") and use of asthma medications ("Do you use asthma medications, constantly or when needed?"). Further variables about symptoms and diagnoses were allergic conjunctivitis or rhinitis ("Do you have, or ever had, allergic eye or nose symptoms?"), ever eczema or skin allergy ("Have you ever had eczema or any other form av skin allergy?"), attacks of shortness of breath last 12 months ("Have you had any attacks of shortness of breath last 12 months?"), longstanding cough ("Have you had longstanding cough the last year?"), sputum production ("Do you usually cough up sputum or do you have sputum in your chest that you have difficulty getting up?"), recurrent wheeze ("Does it usually wheeze in the chest when you breath?"), wheezing last 12 months ("Have you experienced wheezing at any point the last 12 months?"), physician diagnosed chronic bronchitis, COPD (chronic obstructive pulmonary disease) or emphysema ("Do you have physician diagnosed chronic bronchitis, COPD or emphysema?"). All the above questions contained "yes" or "no" as answer alternatives, if the subject did not know the answer or if missing data, it was classified as a "no" to the specific question.

Variables regarding demographic data

The population were divided into age groups in ten years intervals (16-25, 26-35, 36-45, 46-55, 56-65 and 66-75 years) and exact age was used as a continuous variable for calculations of mean values. Living area was categorized into living in Gothenburg, which included Gothenburg and Mölndal municipality, and living outside of Gothenburg, including the remaining municipalities in West Sweden.

For smoking, current smoker was defined as being a present smoker, including smoking a minor number of cigarettes or pipe fillings per week, as well as a previous smoker that quit within the last 12 months. Ex-smoker was classified as a previous smoker that quit more than a year ago, and non-smoker was defined as never had smoked. The current smokers were asked to specify the number of cigarettes smoked per day, categorized into less than 5, 5-14,

5-24 or 25 and above. Ex-smokers and current smokers were inquired at what age they started to smoke and in addition ex-smokers at what age quitting smoking. Moreover, it was asked if smoking electronic cigarettes which was classified as never, sometimes or daily.

Further demographic variables included occupation that was categorized as employed, self-employed, unemployed, sick leave from work, student (full time), homemaker (full time) and retired. It was asked if being exposed to a lot of dust, gas or fume at work. Education level was categorized into primary school (including the answer alternatives schooling less than five years, junior secondary school or girls' school), secondary school (elementary school), high school (two year upper secondary school, vocational school or three to four year secondary school), and lastly university. It was also asked about length and height.

In the telephone interview, reasons for not responding to the postal questionnaire were classified as did not receive the questionnaire, forgot to answer, did not want to complete it or secrecy issues, lack of time, moved, considered the questionnaire as unimportant, did complete and mailed the questionnaire or other causes. Further, it was inquired for proposals of changes in the study design that would have increased the probability to complete the questionnaire. More than one suggestion was possible to present by each subject.

Statistical methods

The data were analyzed statistically with help of Statistical Package for Social Sciences (SPSS) version 24 and 26. The prevalence measured from the telephone interviews as well as the whole population of non-responders were compared with the prevalence from the postal questionnaires with a p-value of < 0.05 considered as significant. For dichotomous variables, Fisher's Exact Test were used and for variables with more than two categories, Pearson's Chi-Square Test were used. Prevalence comparisons between early versus late responders were done by Linear-by-Linear Association test for trends for variables with ordinal outcomes with

even intervals between them (such as education level), and Pearson's Chi-Square Test for variables with nominal outcomes (such as employment status). Independent Samples t-Test was used for comparisons of mean values for continuous variables between the groups. To estimate what risk non-response implies, binary logistic regression analyzes and multivariate logistic regression analyzes were performed by calculations of Odds ratios with 95 % confidence interval. For the binary logistic regression analyzes, responders to the questionnaires versus responders to the telephone interviews were set as independent variables and respiratory symptoms and diseases as dependent variables. The multivariate logistic regression analyzes had respiratory symptoms and diseases as dependent variables and responders versus non-responders, gender, age and smoking as independent variables. Model-based weighting of the data was completed to assess the impact of non-response in the prevalence estimates of respiratory symptoms from the postal questionnaires. A logistic regression modelling strategy constructed the model with covariates likely to predict the probability of response to the questionnaire. The covariates were physician diagnosed asthma, chronic cough, exposure to dust, gas or fume at work, age, gender, smoking and educational status. These factors were regressed against the outcome (response to the questionnaire). Each individual's predicted probability from the full model was calculated and the weighting adjustment was calculated as the inverse of each individual's predicted probability.

Ethics

An ethical consideration in the thesis is that the study material consists of coded sensitive personal data that can be connected to the respective individuals in the sample. Personal data and other data were kept in different files separated from each other with a code key. Another ethical question involves if it is defensible to contact study subjects that did not respond to the postal questionnaire by telephone. The subjects not to responding to the postal questionnaire

may consider it as intrusive with a follow-up telephone interview. However, the subjects declaring they did not want to participate in the questionnaire study were not included in the telephone interview sample. Also, verbal consent was obtained before the telephone interview was initiated. Ethical reviews for the study have been approved by the regional ethics review board in Gothenburg; WSAS I (2008): 034-08, WSAS II (2016): 052-16.

Results

The WSAS II study (2016)

Participation and non-participation in the postal questionnaire

Regarding the subjects classified as unreachable, there was a difference between living in the city of Gothenburg and living outside Gothenburg ($p < 0.001$), as well as between men and women ($p < 0.001$). Living area and gender differed among non-responders as well as responders ($p < 0.001$). Responding to the questionnaire was more prevalent if living outside Gothenburg compared to living in the city of Gothenburg ($p < 0.001$), and being female compared to male ($p < 0.001$). The prevalence of non-responding was consequently the opposite of responding when it comes to living area and gender (Table 1).

The frequency of returned questionnaires declined with every reminder. When looking at which of the sent-out questionnaires the responders returned, there was a difference in living area ($p = 0.008$) and gender ($p < 0.001$). Responding to the first questionnaire had a higher prevalence among women, and in contrast, responding to the second or third reminder were more prevalent among men. Responding to the third reminder was more common if living in the city of Gothenburg (Table 1).

Table 1. Initial study sample, real study sample, responders, non-responders, early responders and late responders based on living area and gender with its p-values.

Study population		**Gothenburg**	**Outside Gothenburg**	**p-value**	**Men**	**Women**	**p-value**	**Total**
Initial study sample	N							50 000
Deceased	N							16
Living abroad	N (%)	35 (0.1)	24 (0.1)		32 (0.1)	28 (0.1)		60 (0.1)
Did not fit the inclusion criteria	N (%)	20 (0.1)	6 (0.02)		9 (0.04)	17 (0.1)		26 (0.1)
Questionnaire returned due to unknown address	N (%)	467 (2)	348 (1.3)	**<0.001^**	490 (1.9)	327 (1.3)	**<0.001^**	817 (1.6)
Incapacity to answer due to disease	N (%)	28 (0.1)	59 (0.2)		54 (0.2)	35 (0.1)		89 (0.2)
Incapacity to answer due to language difficulties	N (%)	19 (0.1)	5 (0.02)		3 (0.01)	21 (0.1)		24 (0.05)
Real study sample	N	23285	25619		24655	24313		48968
Did not want to participate	N (%)	135 (0.6)	207 (0.8)	0.437§	149 (0.6)	194 (0.8)	0.825§	343 (0.7)
Returned blank questionnaire	N (%)	48 (0.2)	62 (0.2)		46 (0.2)	64 (0.3)		110 (0.2)
Non-responders	N (%)	11896 (51.1)	12049 (47.0)	**<0.001§**	13256 (53.8)	10725 (44.1)	**<0.001§**	23981 (49)
Responders, total	N (%)	11206 (48.1)	13301 (51.9)		11204 (45.4)	13330 (54.8)		24534 (50.1)
Responders by first questionnaire	N (%)	4550 (40.6)	5530 (41.6)		4468 (39.9)	5622 (42.2)		10090 (41.1)
Responders by first reminder	N (%)	4395 (39.2)	5220 (39.2)	**0.008^**	4376 (39.1)	5250 (39.4)	**<0.001^**	9626 (39.2)
Responders by second reminder	N (%)	1207 (10.8)	1460 (11)		1321 (11.8)	1349 (10.1)		2670 (10.9)
Responders by third reminder	N (%)	1054 (9.4)	1091 (8.2)		1039 (9.3)	1109 (8.3)		2148 (8.8)

^ Pearson's Chi-Square Test, § Fisher's Exact Test

Participation in the telephone interview

Of the 700 subjects selected to the telephone interviews, non-available telephone number or untraceable number due to a new address were seen among 13 % (n = 90) and 32 % (n = 222) had an available number but could not be contacted in at least five attempts. A total of 55 % (n = 388) was successfully contacted, and a majority of these subjects were willing to respond to the interview (80 %). There were no differences in living area or gender of the subjects that agreed to participate in the telephone interview, not willing to participate, lacked telephone number or could not successfully be contacted. Living area and gender did not differ among the subjects successfully contacted either (Table 2).

Table 2. Sample of non-responders in the telephone interview described by living area and gender with p-values (Pearson's Chi-Square Test).

		Gothenburg	**Outside Gothenburg**	**P-value**	**Men**	**Women**	**P-value**	**Total**
Sample of non-responders		329	371		377	323		700
Agreed to participate	N (%)	149 (45.3)	162 (43.7)		162 (43.0)	149 (46.1)		311 (44.4)
Not willing to participate	N (%)	35 (10.6)	42 (11.3)		40 (10.6)	37 (11.5)		77 (11.0)
Missing phone number or had moved	N (%)	43 (13.1)	47 (12.7)	0.960	52 (13.8)	38 (11.8)	0.735	90 (12.9)
No contact	N (%)	102 (31.0)	120 (32.3)		123 (32.6)	99 (30.7)		222 (31.7)
Successfully contacted	N (%)	184 (55.9)	204 (55.0)	0.803	202 (53.6)	186 (57.6)	0.288	388 (55.4)
Percent of successfully contacted and agreed to participate	%	81.0	79.4		80.2	80.1		80.2

Demographic data

Non-responders were younger than responders, the mean age was 39.5±15.1 vs. 48.9±16.6 years ($p < 0.001$). Differences were seen in smoking status between non-responders and responders ($p < 0.001$). Current smokers were more prevalent among non-responders than responders (18.6 % vs. 12.6 %), whereas ex-smokers were more common among responders than non-responders (27.5 % vs. 20.6 %). When dividing the population into age groups, differences in smoking status were seen among ages 26-35 and 36-45 years. In the group 36-45 years, current smokers were almost three times higher among non-responders (28.1 % vs. 10.7 %). Non-responders and responders differed from each other regarding employment status ($p < 0.001$). Non-responders were more often employed (73.3 % vs. 54.8 %), while responders were more commonly unemployed (2.7 % vs. 0 %) and retired (22.7 % vs. 7.7 %). Education level also differed between non-responders and responders ($p < 0.001$). Among non-responders the most prevalent education level was high school but among responders it was university. Responders and non-responders differed in the three youngest age groups regarding education level but not in the three oldest. Work-related exposure to dust, gas or fumes were more prevalent among non-responders in total ($p = 0.032$) and among women ($p = 0.029$), but not among men ($p = 0.525$, Table 3).

Table 3. Demographic prevalence data for responders and non-responders regarding smoking status, employment status, education and work-related exposure with p-values based on gender, age groups and in total.

Demographics	Men		Women		Age 16-25		Age 26-35		Age 36-45		Age 46-55		Age 56-65		Age 66-75		Total	
	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR
Smoking status																		
Current smoker	12.4	19.1	12.9	18.1	15.5	20.2	12.0	16.2	10.7	28.1	12.6	8.9	14.8	21.1	11.0	14.8	12.6	18.6
Ex-smoker	27.9	22.2	27.1	18.8	6.3	6.7	14.7	27.0	20.2	21.1	25.2	22.2	39.3	31.6	44.1	37.0	27.5	20.6
Non-smoker	58.8	58.6	59.1	62.4	77.1	71.9	72.5	56.8	68.4	50.9	61.2	68.9	44.9	47.4	43.7	48.1	58.9	60.5
p-value^		**0.022**		**0.027**		0.458		**0.005**		**<0.001**		0.590		0.668		0.684		**<0.001**
Employment status																		
Employed	53.2	74.1	56.2	72.5	36.5	60.7	75.3	90.5	80.2	89.5	78.3	93.3	60.3	52.6	4.2	14.8	54.8	73.3
Unemployed	3	0.0	2.4	0.0	4.4	0.0	3.9	0.0	3.1	0.0	3.3	0.0	2.6	0.0	0.04	0.0	2.7	0.0
Sick leave from work	1.7	0.6	3.2	2	1.2	1.1	1.6	0.0	2.4	1.8	3.7	2.2	5.4	5.3	n/a	n/a	2.5	1.3
Student	7.3	10.5	8.7	7.4	52.8	30.3	10.0	1.4	3.3	0.0	1.1	0.0	0.2	0.0	0.04	0.0	8.1	9
Retired	23.4	4.9	22.1	10.7	0.1	0.0	0.1	0.0	0.8	0.0	2.1	0.0	18.8	31.6	90.1	66.7	22.7	7.7
Self-employed	9.5	8	3.8	4	0.8	4.5	4.4	5.4	7.4	7.0	9.2	4.4	9.5	10.5	4.5	11.1	6.4	6.1
p-value^		**<0.001**		**0.003**		**<0.001**		0.085		0.663		0.520		0.904		**<0.001**		**<0.001**
Education level																		
Primary school	2.6	1.9	3.9	7.4	0.7	3.4	1.1	1.4	1.2	3.5	1.2	4.4	2.6	5.3	10.5	18.5	3.3	4.5
Secondary school	16.1	13.0	12.2	4.7	13.2	4.5	2.9	8.1	4.7	10.5	8.5	11.1	17.2	15.8	31.2	14.8	14.0	9.0
High school	41.9	57.4	34.4	51.0	59.2	73.0	31.7	51.4	35.5	54.4	44.7	40.0	39.1	36.8	24.9	37.0	37.9	54.3
University	38.3	27.2	48.1	35.6	25.9	18.0	63.4	39.2	57.6	31.6	44.5	44.4	39.9	31.6	31.6	29.6	43.7	31.2
p-value^		**0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		0.251		0.857		0.141		**<0.001**
Work-related exposure to dust, gas or fumes	27.3	27.8	10.6	16.1	14.1	15.7	18.0	23.0	16.2	28.1	18.0	26.7	20.1	15.8	20.5	25.9	18.2	22.2
p-value§		0.525		**0.029**		0.532		0.154		**0.017**		0.121		1.000		0.304		**0.032**

R: responders, NR: non-responders, ^Pearson's Chi-Square Test, §Fisher's Exact Test

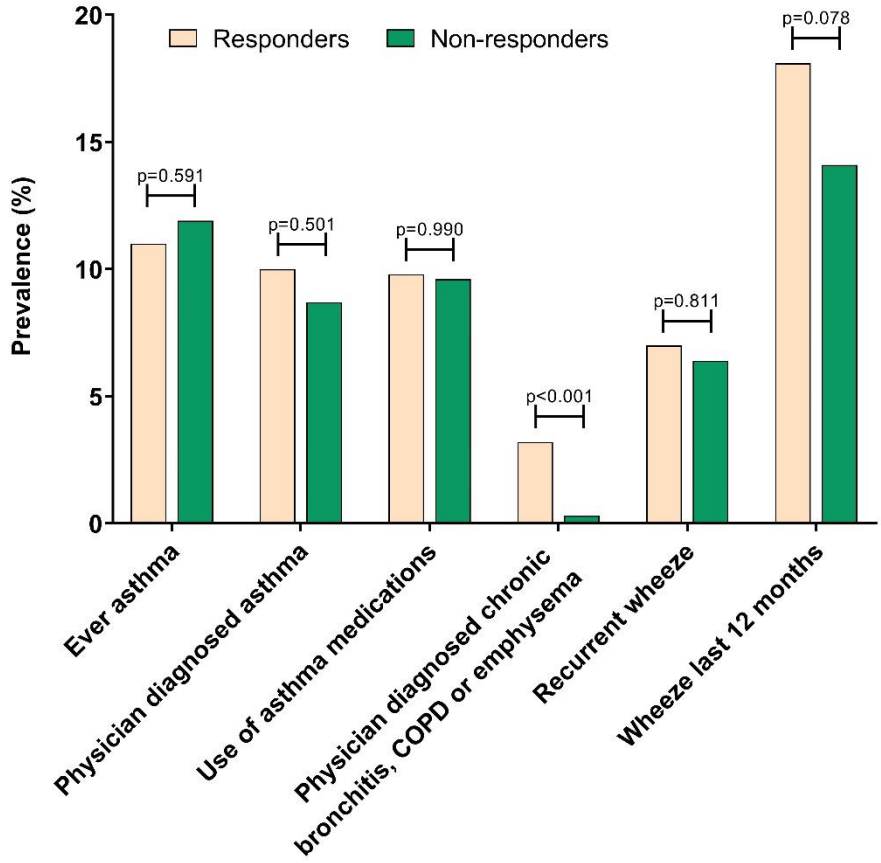
Respiratory diseases, symptoms and medications

There were no differences between responders and non-responders regarding prevalence of physician diagnosed asthma, ever asthma, use of asthma medications, wheeze last 12 months, allergic conjunctivitis or rhinitis and eczema or skin allergy. Physician diagnosed chronic bronchitis, COPD or emphysema were more prevalent among responders ($p < 0.001$). Also, longstanding cough and sputum production were more common among responders ($p = 0.037$ respectively $p < 0.001$). Recurrent wheeze had a higher prevalence among responding women ($p = 0.048$). Attacks of shortness of breath last 12 months were more common among non-responders in total and among women, but not among men (Table 4, Figure 2A and 2B).

Table 4. Prevalence of diseases, symptoms and medications among responders and non-responders, p-values (Fisher's Exact Test) for men and women.

Diseases, symptoms and medications		**Men**			**Women**		
		R	**NR**	**p-value**	**R**	**NR**	**p-value**
Ever asthma	%	9.8	10.5	0.803	12.0	13.4	0.621
Physician diagnosed asthma	%	8.9	8.0	0.889	10.9	9.4	0.681
Use of asthma medications	%	7.8	9.9	0.301	11.6	9.4	0.513
Physician diagnosed chronic bronchitis, COPD or emphysema	%	2.6	0.6	0.134	3.7	0	n/a
Attacks of shortness of breath last 12 months	%	8.6	12.3	0.120	12.2	19.5	**0.009**
Longstanding cough	%	12.0	9.3	0.329	14.0	8.7	0.079
Sputum production	%	15.5	9.3	**0.032**	15.1	6.0	**0.002**
Recurrent wheeze	%	7.1	9.9	0.166	6.9	2.7	**0.048**
Wheezing last 12 months	%	16.8	13.0	0.245	19.3	15.4	0.296
Allergic conjunctivitis or rhinitis	%	27.6	32.1	0.215	29.5	31.5	0.592
Ever eczema or skin allergy	%	33.1	30.9	0.612	46.7	39.6	0.099

R: responders, NR: non-responders.



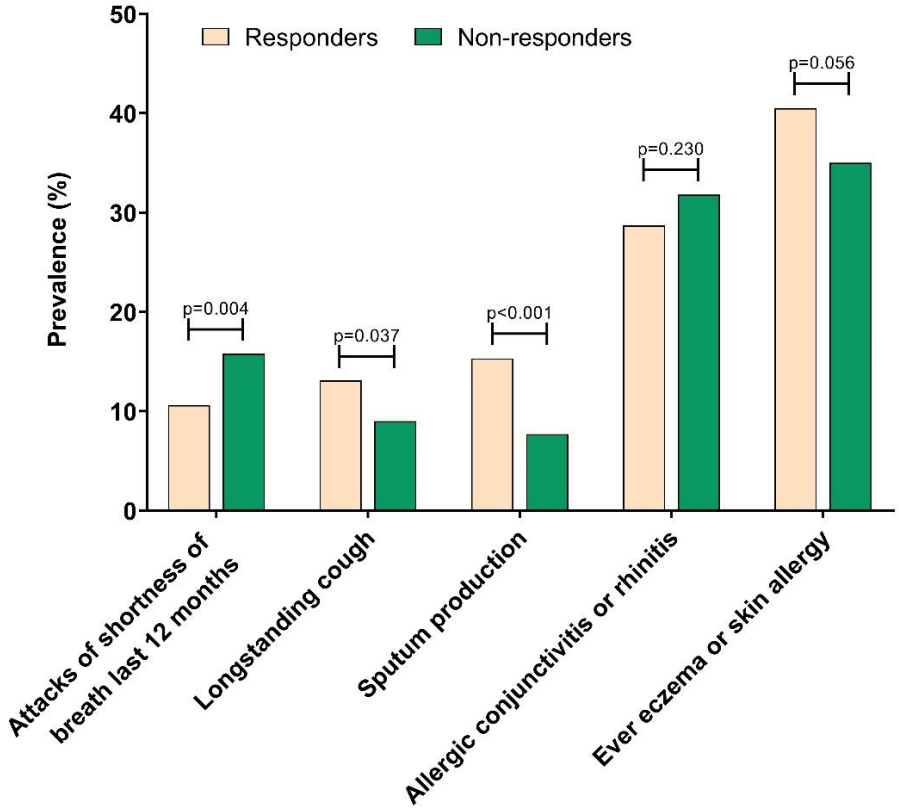


Figure 2A and 2B. Comparison of prevalence of symptoms, diagnoses and use of medications in total among responders and non-responders with its p-values (Fisher's Exact Test).

Risk analysis

Binary logistic regression analysis showed that non-responders had a significantly increased risk of attacks of shortness of breath the last 12 months (OR = 1.58 (1.16-2.15)) and a decreased risk of physician diagnosed chronic bronchitis, COPD or emphysema (OR = 0.10 (0.01-0.69)), longstanding cough (OR = 0.66 (0.44-0.97)) and sputum production (OR = 0.46 (0.30-0.70)).

Multivariate logistic regression analysis resulted in similar significant risks of symptoms and diseases among non-responders as for the binary analyses, but in addition there was seen a reduced risk of wheeze the last 12 months (OR = 0.69 (0.49-0.95), Figure 3).

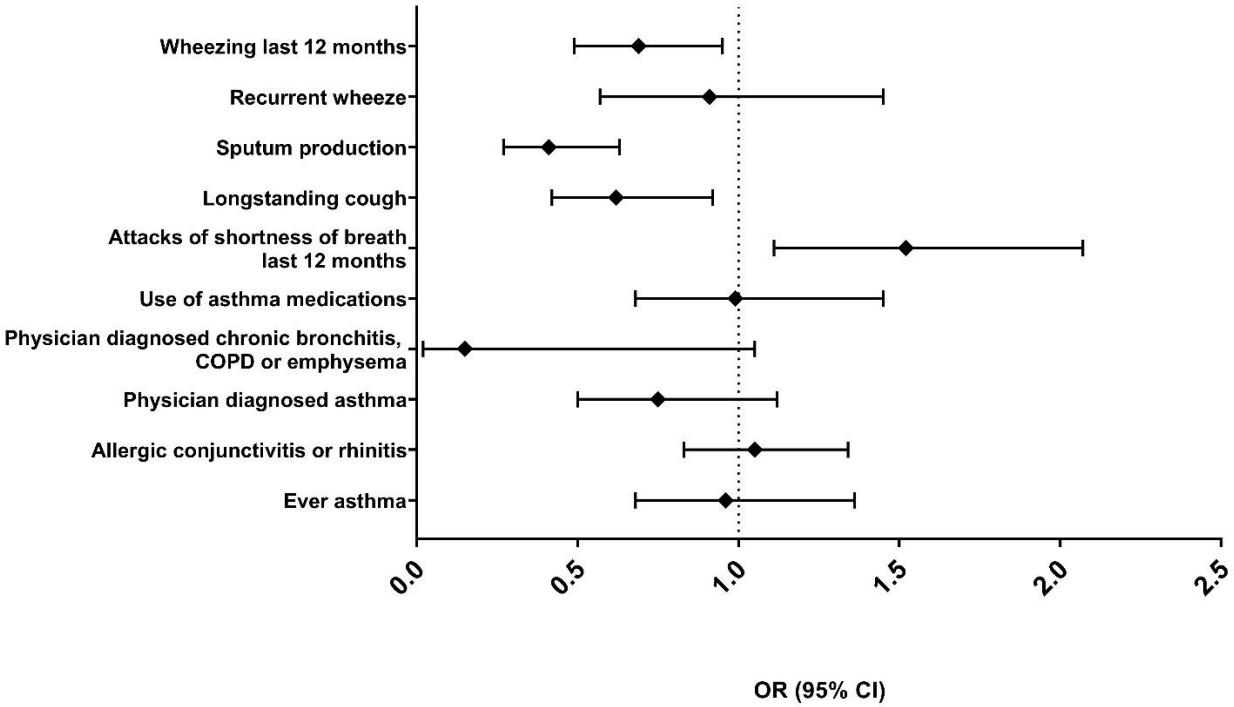


Figure 3. Multivariate logistic regression analysis with respiratory symptoms and diseases as dependent variables and responders versus non-responders as independent variable. Gender, age and smoking were also included as independent variables in the model.

Post-stratification weighting

The unweighted prevalence of physician diagnosed asthma, longstanding cough, sputum production, recurrent wheeze and wheezing last 12 months, were similar to when the data was weighted for non-response (Table 5).

Table 5. Prevalence estimates of respiratory symptoms for unweighted and weighted data, for men, women and in total.

Respiratory symptoms		Men		Women		Total	
		Unweighted	Weighted	Unweighted	Weighted	Unweighted	Weighted
Physician diagnosed asthma	%	8.9	8.6	10.9	10.4	10.0	9.6
Longstanding cough	%	12.0	11.2	14.0	12.9	13.1	12.1
Sputum production	%	15.4	15.2	15.0	14.7	15.2	14.9
Recurrent wheeze	%	7.1	6.9	6.8	6.5	7.0	6.7
Wheezing last 12 months	%	16.8	16.4	19.2	18.9	18.1	17.7

Reasons for non-response

The most frequent reason of non-response among both men and women was lack of time (23.5 %), considering the questionnaire as unimportant (19.0 %), not receiving the questionnaire (18.0 %) and forgot to answer (16.1 %). Within the “Others” category the dominating reason was no memory of receiving the questionnaire (28 subjects, Table 6).

Table 6. Reasons for non-response among men, women and in total.

Reasons for non-response		Men	Women	Total
Did not receive the questionnaire	N (%)	24 (14.8)	32 (21.5)	56 (18.0)
Moved	N (%)	14 (8.6)	6 (4.0)	20 (6.4)
Forgot to answer	N (%)	24 (14.8)	26 (17.4)	50 (16.1)
Considered the questionnaire as unimportant	N (%)	34 (21.0)	25 (16.8)	59 (19.0)
Did not want to complete it and secrecy	N (%)	0 (0)	1 (0.7)	1 (0.3)
Did complete and mailed the questionnaire	N (%)	4 (2.5)	3 (2.0)	7 (2.3)
Lack of time	N (%)	36 (22.2)	37 (24.8)	73 (23.5)
Other causes	N (%)	26 (16.0)	19 (12.8)	45 (14.5)
Total	N	162	149	311

Improvement suggestions

Of the 311 subjects responding to the telephone interview 269 of them agreed to give in total 291 suggestions, more than one suggestion was possible to present by each subject. The most prevalent replies were being able to answer via telephone, via email, via Internet or through some form of digital solution, offer a shorter questionnaire, advertisement for the questionnaire through social media as Instagram or Facebook, and offer the questionnaire in different languages.

Early and late responders

There were differences regarding if fulfilling the original questionnaire or the following reminders in aspect of smoking status, employment status, education level, gender and work-related exposure to dust, gas or fumes. Current smokers, non-smokers, employees, self-employees, unemployed, homeworkers, students, subjects with high school as highest education level, men and work-related exposure to dust, gas or fumes tented to be late responders. Ex-smokers, retirees and women were more commonly among early responders (Table 7).

Table 7. Prevalence of demographic data among early responders (responders by first mailed questionnaire), late responders (responders to the reminders) with its p-values.

Demographic data		Responders by original questionnaire	Responders by first reminder	Responders by second reminder	Responders by third reminder	p-value
Smoking status						
Current smoker	%	10.9	13.1	15.5	15.4	**<0.001^**
Ex-smoker	%	30.8	26.2	23.6	22.2	
Non-smoker	%	57.5	59.7	59.4	61.8	
Employment status						
Employed	%	52.3	56.3	56.7	57.7	**<0.001^**
Self-employed	%	5.9	6.4	7.5	7.8	
Unemployed	%	2.2	2.6	3.7	4.1	
Sick leave from work	%	2.5	2.3	3.0	2.3	
Homeworker	%	0.2	0.4	0.3	0.6	
Student	%	6.7	8.2	10.0	11.0	
Retired	%	28.3	20.9	15.8	13.1	
Education level						
Primary school	%	3.7	3.1	3.3	2.8	**0.003***
Secondary school	%	14.0	13.8	15.1	13.2	
High school	%	35.8	38.1	41.9	41.6	
University	%	45.7	43.7	38.4	40.3	
Gender						
Men	%	44.3	45.5	49.5	48.4	**<0.001***
Women	%	55.7	54.5	50.5	51.6	
Work-related exposure to dust, gas or fumes	%	17.3	18.6	20.1	18.2	**0.005***

^Pearson's Chi-Square Test, *Linear-by-Linear Association

For most of the investigated respiratory symptoms there were no difference in prevalence regarding early and late responders, except from allergic conjunctivitis or rhinitis that were somewhat more common among late responders ($p = 0.043$) and physician diagnosed chronic bronchitis, COPD or emphysema ($p = 0.042$) that were somewhat more prevalent among early responders. Ever eczema or skin allergy were more common among early responders ($p < 0.001$, Table 8).

Table 8. Prevalence of diseases, symptoms and medications among early responders (responders by first mailed questionnaire) and late responders (responders to the reminders) with p-values (Linear-by-Linear Association).

Symptoms		Responders by original questionnaire	Responders by first reminder	Responders by second reminder	Responders by third reminder	p-value
Ever asthma	%	10.6	11.6	10.2	11.4	0.373
Allergic conjunctivitis or rhinitis	%	28.1	28.8	29.1	30.0	**0.043**
Physician diagnosed asthma	%	9.9	10.3	8.8	10.5	0.958
Physician diagnosed chronic bronchitis, COPD or emphysema	%	3.4	3.1	3.4	2.4	**0.042**
Use of asthma medications	%	9.7	10.1	9.3	10.0	0.846
Attacks of shortness of breath last 12 months	%	10.2	10.9	10.8	10.3	0.528
Longstanding cough	%	12.6	13.3	14.0	13.1	0.138
Sputum production	%	14.8	15.7	15.7	15.3	0.288
Recurrent wheeze	%	6.7	7.1	7.2	7.2	0.272
Wheeze last 12 months	%	17.8	18.6	18.4	17.2	0.927
Ever eczema or skin allergy	%	42.3	40.5	36.7	37.1	**< 0.001**

Comparisons of non-responders in the WSAS I study (2008) and WSAS II study (2016)

Gender, living area and age

More men than women were non-responders both 2008 and 2016. Living in the city of Gothenburg was more common among non-responders 2008, whereas living outside Gothenburg was more common 2016. This difference in living area was not significant when only looking at the non-responders that participated in the telephone interview.

Regarding all non-responders and the non-responders that not participated in the telephone interview, there was a decrease of non-responders among men 2016 and consequently an increase among women 2016 (all non-responders $p = 0.002$, non-responders not participating in the telephone interview $p = 0.018$). Living in the city of Gothenburg was less common 2016 ($p < 0.001$ for both all non-responders and non-responders not participating in the

telephone interview). These described differences were not seen among the non-responders participating in the telephone interview (Table 9).

Table 9. Gender and living area for non-responders 2008 and 2016 with its p-values (Fisher's Exact Test). Non-responders analyzed in the groups all non-responders, non-responders not participating in the telephone in the telephone interview as well as non-responders participating in the telephone interview. Not participating in the telephone interview included no found telephone number, no contact and successfully contacted but declined to participate in the interview.

		2008	2016	p-value
All non-responders				
Men	N (%)	5273 (57.2)	13 256 (55.3)	**0.002**
Women	N (%)	3944 (42.8)	10 725 (44.7)	
Gothenburg	N (%)	5679 (61.6)	11 896 (49.6)	**<0.001**
Outside Gothenburg	N (%)	3538 (38.4)	12 050 (50.2)	
Non-responders, not participating in the telephone interview				
Men	N (%)	108 (66.3)	215 (55.3)	**0.018**
Women	N (%)	55 (33.7)	174 (44.7)	
Gothenburg	N (%)	103 (63.2)	180 (46.3)	**<0.001**
Outside Gothenburg	N (%)	60 (36.8)	209 (53.7)	
Non-responders, participating in the telephone interview				
Men	N (%)	107 (58.5)	162 (52.1)	0.190
Women	N (%)	76 (41.5)	149 (47.9)	
Gothenburg	N (%)	101 (55.2)	149 (47.9)	0.136
Outside Gothenburg	N (%)	82 (44.8)	162 (52.1)	

Non-responders in the 2008 cohort were younger compared to the 2016 cohort when looking at all non-responders (mean 38.3 SD ± 14.9 years vs. 39.5 ± 15.1, $p < 0.001$). The contrary was seen among non-responders participating in the telephone interview (mean 41.7 SD ± 15.2 years vs. 38.5 ± 15.7, $p = 0.029$). There was no difference in age concerning non-responders not participating in the telephone interview (mean 38.6 SD ± 15.3 years vs. 40.1 ± 14.9, $p = 0.282$). Not participating in the telephone interview included no found telephone number, no contact and successfully contacted but declined to participate in the interview.

Diseases, symptoms, medications, work-related exposure and smoking

There were no differences between non-responders 2008 and 2016 when it comes to prevalence of respiratory diseases, respiratory symptoms, use of asthma medications, eczema or skin allergy, and work-related exposure to dust, gas or fumes. Current smoking was less common 2016 compared to 2008, among women ($p < 0.001$) and in total ($p = 0.001$). There was an increase in non-smoking 2016, also among women and in total ($p < 0.001$ for both, Table 10).

Table 10. Diseases, symptoms, medications, work-related exposure and smoking status for non-responders 2008 and 2016, analyzed by gender and in total with its p-values (Fisher's Exact Test for variables referring to health status and work-related exposure, Pearson's Chi-Square Test for smoking status).

	Men			**Women**			**Total**		
	2008	**2016**	**p-value**	**2008**	**2016**	**p-value**	**2008**	**2016**	**p-value**
Diseases, symptoms, medications and work-related exposure									
Physician diagnosed asthma	6.5	8.0	0.813	9.2	9.4	1.000	7.7	8.7	0.738
Use of asthma medications	4.7	9.9	0.163	9.2	9.4	1.000	6.6	9.6	0.316
Physician diagnosed chronic bronchitis, COPD or emphysema	0.9	0.6	1.000	1.3	0.0	0.338	1.1	0.3	0.558
Longstanding cough	14.0	9.3	0.240	13.2	8.7	0.353	13.7	9.0	0.132
Sputum production	10.3	9.3	0.834	15.8	6.0	**0.027**	12.6	7.7	0.082
Recurrent wheeze	3.7	9.9	0.094	6.6	2.7	0.170	4.9	6.4	0.557
Wheezing last 12 months	16.8	13.0	0.383	22.4	15.4	0.203	19.1	14.1	0.162
Ever eczema or skin allergy	28.0	30.9	0.683	44.7	39.6	0.477	35.0	35.0	1.000
Work-related exposure to dust, gas or fumes	31.8	27.8	0.785	10.5	16.1	0.235	23.0	22.2	0.912
Smoking status									
Current smoker	25.2	19.1	0.312	42.1	18.1	**< 0.001**	32.2	18.6	**< 0.001**
Ex-smoker	25.2	22.2		23.7	18.8		24.6	20.6	
Non-smoker	49.5	58.6		34.2	62.4		43.2	60.5	

Reasons for non-response

The 2008 and 2016 cohorts differed when it comes to reasons for non-response ($p = 0.001$). For example, forgot to answer as a reason was more prevalent 2016 than 2008 (16 % vs 7 %),

and also moved had a higher prevalence 2016 (6 % vs 2 %). Not wanting to complete the because of secrecy matters had instead a higher prevalence 2008 (4 % vs 0.2 %, Figure 4A and 4B).

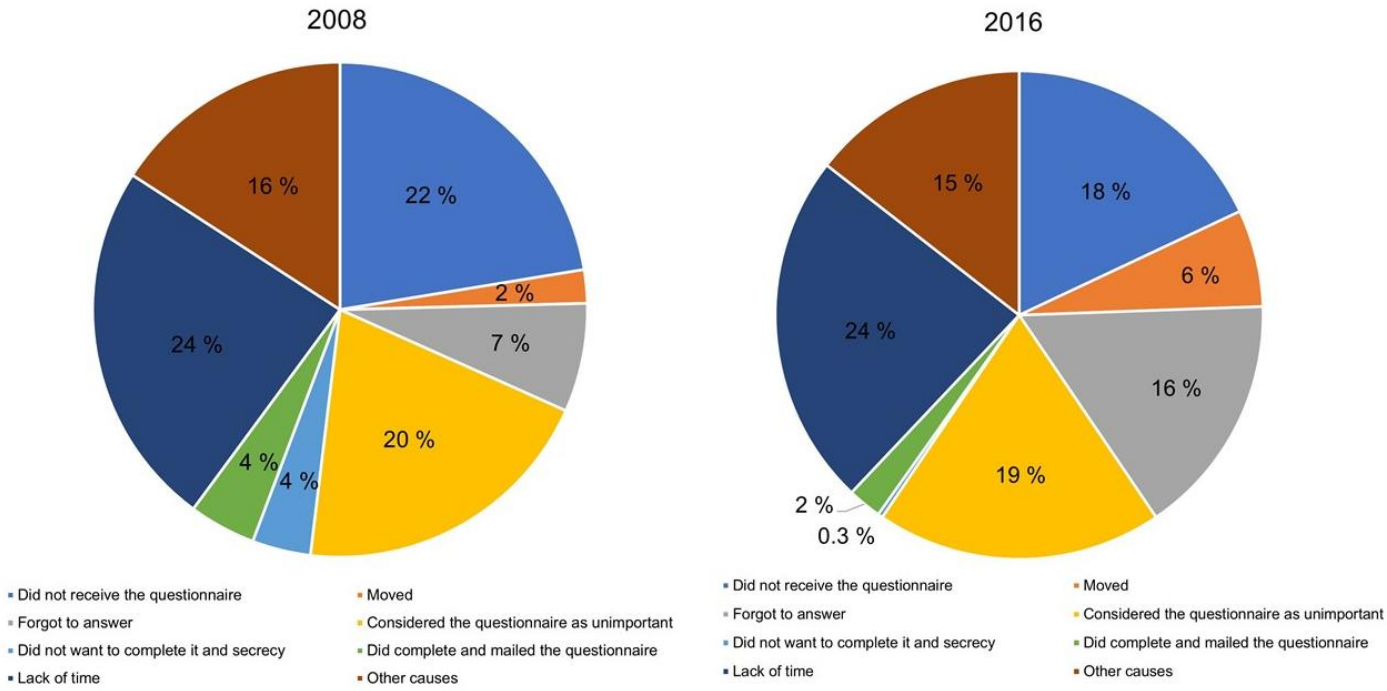


Figure 4A and 4B. Pie charts demonstrating the reasons for non-response (%) 2008 and 2016.

Discussion

The main purpose of this thesis was to compare the responders with the non-responders, regarding respiratory health and demographic data, in the WSAS II questionnaire study. There was no difference between non-responders and responders regarding prevalence of asthma. Physician diagnosed chronic bronchitis, COPD or emphysema, longstanding cough and sputum production were more prevalent among responders, however, attacks of shortness of breath were more common among non-responders. Risk analysis concluded that non-responders had an increased risk of attacks of shortness of breath the last 12 months and a decreased risk of physician diagnosed chronic bronchitis, COPD or emphysema, longstanding cough and sputum production. Post-stratification weighting for non-response presented that

the prevalence estimates for the weighted data were closely like the unweighted data. Non-responders were more often males, smokers, living in the city of Gothenburg and younger than responders. Non-responders had a higher occurrence of employment and work-related exposure, but a lower education level than responders. Early and late responders differed in demographic data, but not for most of the investigated respiratory symptoms and diseases.

Results in relation to other research in the area

In agreement with several previous studies, the prevalence of asthma in this study did not differ between responders and non-responders (17, 34-36, 42, 43). The observed increased prevalence of longstanding cough among responders has also been reported by Abrahamsen et al (35) and that bronchitis or emphysema are more prevalent among early responders have been addressed by Bakke et al (17). In contrast to these findings, previous publications have both reported a decreased (32, 50) and an increased prevalence of asthma among non-responders (33). The situation of no consistent pattern in previous research regarding if the symptoms prevalence among non-responders are unchanged, elevated or lowered, continues the need for investigation of non-responders in respiratory epidemiology surveys. It is possible that the subjects suffering from requested symptoms and diseases have a higher response rate, because their personal experiences make them think that research in this area is of importance. On the other hand, suffering from a disease may decrease the likelihood of response because of low energy and motivation as a consequence of the illness. In the opposite, healthy subjects might have the energy to reply but less motivation for it. Leadbetter et al (51) suggested in their study that subjects are more prone to respond if they are interested of the subject or if it is promoted that their answers are of importance.

Regarding demographic data, non-responders in this study were, in consensus with several publications, more frequently younger (32-35), males (32-37) and smokers (32-34) compared to responders. Non-responders being younger than responders may however not be valid

when particularly investigating an older population. A non-response study of a postal questionnaire in the field of respiratory epidemiology that only included subjects of 70 years and older, presented an increased non-response rate with increased age. The oldest age groups had the highest non-response rate and the reasons presented were for example that a higher age led to an increased prevalence of mental impairment and living in nursing homes (31).

Non-responders in this study tended to be employed more often than responders, while responders were more often unemployed and retired. A suggestion is that unemployed and retirees possibly have more time to spend fulfilling the questionnaire, and employees are busier due to their work and more prone to be non-responders. This is in line with that the most common reason for non-response in this study was lack of time. Non-responders had a lower education level than responders, which also has been reported from previous studies about non-responders in general (24, 52). Lower educational level might suggest a possibility for lower socioeconomic status among non-responders in this study, however, data about income and economic status were not investigated and non-responders were more often employed which could contradict a lower socioeconomic status. Non-response was more common if living in the city of Gothenburg compared to outside of the city, which matches the non-response study in WSAS I (34). Also Björnsson et al (36) reported a higher non-response rate in Gothenburg compared to two areas with fewer inhabitants in Sweden. They explained this as a result of a higher prevalence of immigrants in Gothenburg with a possible risk of difficulties understanding the language and therefore also the questionnaire. Other presented reasons for higher non-response in urban areas are busier lifestyle, younger and more mobile population, and larger poverty (53). Overall, these differences in demographics between responders and non-responders in this study are in line with that non-response can be correlated to characteristics that may systematically differ from the responders, regarding for example health condition, education level, attitudes and behaviors (22). This confirms the

need of continuing addressing the possibility of non-response bias in questionnaire cross sectional cohort studies.

In the comparisons of non-responders in WSAS 2008 and 2016, there were no differences in prevalence of diseases, symptoms, medications or work-related exposure. Current smoking decreased 2016, a trend also seen among the responders in the same study population (5). The two cohorts differed regarding gender and living area when looking at all non-responders and the non-responders in the telephone interview sample that not responded. However, these differences were not seen when only analyzing the subjects that participated in the telephone interview. In other words, the sample that responded to the telephone interview did not match the distribution of gender and living area for the whole non-response population. This illustrates that unrepresentative sampling as well as non-response bias is not only possible issues in original questionnaire studies, but also in the following non-response studies. Silman (28) addressed that there will always be a fraction of the non-responders refusing to participate in a non-response study and it is therefore challenging to achieve a truly random sample in the follow-up studies of non-responders. Another reason for unmatching samples shown in this study could be loss of power since the sample to the telephone interview was smaller than the whole population of non-responders.

Methodological considerations

The method chosen to investigate the non-responders in this study was telephone interviews. The prevalence of symptoms and diseases from the non-responders were used for post-stratification weighting, as a further method to investigate if possible non-response bias occurred. The analyzes resulted in similar prevalence as for the responders, which lead to the assumption that the prevalence from the questionnaires are valid for the whole study population. One problem with follow-up attempts of non-responders, is that there is most commonly a fraction that will refuse participation in both the original study and the non-

response study, as mentioned above. A suggestion may be to make additional attempts to reach the participants not answering in the telephone interview, for example by home visits (38). That might though be a more expensive and time-consuming approach than only performing telephone interviews, as well as debatable if it is ethic correct to try to contact the subjects again that may wish to decline participation. Instead of follow-up strategies such as telephone interviews and home visits to collect data from the non-responders, data from this population could be collected from registries without the need to contact them (54). In Sweden, there is a register called The State's Personal Address Register (Statens Personadressregister) that contains data such as address, birthplace, deregistration from the population register due to emigration or deceased, income, spouse or caregiver, as well as ownership of a house, for all citizens that are nationally registered in Sweden (55). Additionally, Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) is a register with information about the Swedish citizens' education level, employment and unemployment, health insurance, parental insurance, and enterprises (56). These types of demographic data could be used to compare the non-responders with the responders in the weighted data analyzes, and by so not have to perform an additional non-response study. However, data about health status and exposure could not be collected from the registries mentioned above. It has been suggested as insufficient to only use gender and age as variables for the weighting analyzes since the unrepresentativeness may depend on other demographic data (57, 58) but, adding mortality as a variable for the weighting calculations could provide more representativeness of the sample (58). Bonander et al (57) used different Swedish register data (both demographic and health data) for a weighting procedure called inverse probability pf participation weighting (IPPW) for participants as well as non-participants in a cohort study. They presented promising results of this model since the representativeness of the results increased after the procedure.

The method to analyze the answers from the questions about symptoms and diseases, but not for exposure or demographic data, was to define the answer “don’t know” and missing data as “no”. The reasons for this were that only the answers of “yes” were used when calculating the prevalence data and therefore the distribution of the other answer alternatives did not matter in this case. For clinical applications it is suggested that it is of more interest to know how many in a population suffering from a symptom or disease, rather than how many who do not. The participants suffering from the symptom or disease are probably more prone to answer “yes” than missing to fulfill that question. Contrary to these suggestions, Leeuw et al (59) presented that missing data in a questionnaire should be considered as ’not missing at random’ and as its own group. There may be reasons for not fulfilling answers to certain questions, for example about alcohol and smoking, because of fear of undesirable interpretation. For these types of exposure questions, missing or “don’t know” was therefore kept as their own groups in this study.

Strengths and weaknesses

A strength in this study was the use of the Swedish Population Registry that provided names and addresses of the randomized stratified sample. The majority of the Nordic non-response studies in the field of respiratory epidemiology have used mandatory population registries for their samples. This has assumed to be a successful factor for achieving high response rates since six published studies between 1990 and 2009 presented response rates ranging from 62-89 % (4, 17, 33, 36, 38, 60). Three similar studies have been found in the rest of Europe which all presented lower response rates, ranging from 31-59 % (32, 41, 61). However, the recent two studies in this field, including the present study and Abrahamsen et al (35) which both are Nordic, used population registries and achieved inferior response rates compared to the other Nordic studies mentioned earlier, 50 % respectively 33 %. The most frequent improvement suggestion from the non-responders that would have increased the likeliness to

complete the questionnaire, was being able to answer via telephone. In this study 50 000 questionnaires were sent out and it would not be possible to conduct telephone interviews with a sample of the same size because of the increased amount of money, time and manpower to collect the answers. Also, there is no register for telephone numbers for all citizens available in Sweden. Postal questionnaires in this field of research have been proposed as a cost-effective method that if used in the step of collecting replies, the money saved can be used to pay for follow-ups of non-responders by telephone (17).

A weakness of this study was that 32 % of the subjects in the telephone interview sample did not answer the phone calls and could not be contacted. This may have been a possible factor for bias of the results of the non-responders. Also, 13 % of the subjects had a missing phone number or had moved which led to an undetectable phone number since they were collected by the addresses. The Swedish Population Registry can provide names and addresses but not the phone numbers of the citizens in Sweden and not all citizens choose to have their phone number available in commercial data bases. This problem has also been described in Norway (35). The fact that not all subjects could be contacted in first place may have increased the bias since it affected which subjects that possibly could be interviewed. However, of the subjects that could be reached by telephone, 80 % agreed to participate in the interview which shows that the attitude towards this type of research is positive. Factors that have been presented to increase the willingness to participate in telephone interviews in health research surveys are possessing personal experience of the disease being studied, governmental or charity funded studies, being a participant from previous studies, older age and female sex (62).

Future studies

Future questionnaire studies in this area are suggested to continue to address the risk of non-response bias by focus both on achieving a high response rate as well as investigating the

group of non-responders. Response rates in postal questionnaire studies are found to be continuously decreasing over time in Europe (53). Methods found to be effective to increase response rates in postal surveys, that could be applied in future studies, are for example money reward, recorded delivery (a delivery method where the recipient must sign to receive the item), a comment on the envelope stating that the subjects may benefit to open it, shorter questionnaires and providing reminders if no response (63). In this study, the most prevalent suggestions to changes in the study method were conducting the data through other forms of medias than postal questionnaire – telephone, email, Internet or some other form of digital solution. However, the alternative to respond using the Internet was available, but was only used by 10.6 % of the responders. The Internet option is therefore suggested to be marketed more clearly in future studies. A proposition is also to attach a QR code (quick response code) to the questionnaire, making it easier to answer via Internet. The problem with methods other than postal surveys is that there is no available register with email addresses or social media accounts for the whole population, as it is for addresses in Sweden. Using these types of methods may therefore lead to an unrepresentative sample since all citizens are not included in the population sampled from. Nevertheless, since the society is more and more digitalized, the population survey research might have to adjust to this trend and use digital medias instead. Digital mailboxes that are linked to social security numbers are on the rise and could possibly be an alternative to postal mailboxes. Future studies in respiratory epidemiology are recommended to compare digital questionnaires to postal and investigate the applicability of these methods.

Conclusions and Implications

In conclusion, non-responders and responders differed among several demographic characteristics. Non-responders were more prevalent younger, smokers and males compared

to responders. There were no differences in prevalence between responders and non-responders for most of the investigated respiratory symptoms and diseases, except from physician diagnosed chronic bronchitis, COPD or emphysema, longstanding cough and sputum production that were more prevalent among responders and attacks of shortness of breath that was more common among non-responders. Post-stratification weighting for non-response presented similar prevalence estimates for the weighted and unweighted data, which validates the prevalence of respiratory symptoms and diseases from the postal questionnaire study. This study reported a decreased response rate compared to the previous epidemiology study in West Sweden Asthma Study, a trend that is observed in respiratory epidemiology studies from other countries as well. Future investigations are suggested to explore how digital methods can be used instead of postal questionnaires, with the goal to maintain or raise the response rate. They are also suggested to further investigate how demographic data from registries could be used for weighting procedures regarding non-responders. This thesis contributes with valuable information about the characteristics of non-responders, both in this specific study and in epidemiological questionnaire studies in general.

Populärvetenskaplig sammanfattning

Enkätstudier är ett viktigt redskap för att bland annat undersöka förekomsten av sjukdomar och symtom i nuläget samt över tid i befolkningen. Trenden av andelen som svarar på postenkäter har setts minska. Det gör samtidigt att andelen som inte svarar på enkäten ökar. Tidigare forskning har visat att icke-svarande kan skilja sig från de svarande genom till exempel högre förekomst av rökning, dödlighet, lägre socioekonomisk ställning samt sämre hälsa överlag. Om endast de svarande beaktas i en enkätstudie kan slutsatserna följaktligen bli snedfördelade. Det är därför viktigt att försöka få kontakt med en andel av de icke-svarande för att undersöka om deras svar överensstämmer med de svarandes.

Denna uppsats är en studie inom projektet West Sweden Asthma Study. År 2016 skickades det ut en postenkät till 50 000 slumpmässigt utvalda invånare i åldrarna 16-75 år i Västra Götaland. Postenkätens syfte var att kartlägga förekomsten av astma, luftvägssymtom och hösnuva i befolkningen i Västra Götaland. Svarsfrekvensen var 50 % och denna uppsats syftade till att undersöka den icke-svarande gruppen och jämföra deras svar med de svarandes.

Ett urval på 700 deltagare gjordes ur den icke-svarande gruppen som matchade ålders- och könsfördelningen av gruppen, alltså ett representativt urval. Metoden som användes var telefonintervjuer och telefonnummer till deltagarna söktes fram i två kommersiella databaser (eniro.se och hitta.se). Telefonintervjuerna utgjordes av en förkortad version av ursprungsenkäten med frågor som bland annat berörde upplevda symtom från luftvägarna, eventuella diagnostiserade sjukdomar, rökvanor samt anledning till att svar på postenkäten uteblev.

Jämförelser mellan de svarande och icke-svarande visade att de icke-svarande oftare var rökare, män, boendes i Göteborg och yngre än de svarande. De icke-svarande var oftare

anställda samt exponerade för mycket damm, gaser eller rök på arbetet, medan de svarande oftare var arbetslösa och pensionärer. Det var inga skillnader mellan grupperna i förekomst av läkardiagnostiserad astma, någonsin förekomst av astma eller bruk av astmamediciner. Läkardiagnostiserad luftrörskatarr, KOL eller emfysem (att de små lungblåsorna är skadade), långvarig hosta och slemproduktion hade högre förekomst hos de svarande. Förekomst av andnödsattacker under det senaste året var vanligare hos de icke-svarande.

Slutsatserna från uppsatsen var att grupperna skiljde sig åt vad det gäller befolkningsstatistik men inte för de flesta av de efterfrågade luftvägssymtomen och sjukdomarna. Uppsatsen bekräftar att den uppmätta förekomsten av sjukdomar och symtom från de svarande på enkäten verkar gälla för hela befolkningen i Västra Götaland. Framtida studier rekommenderas undersöka om digitala medier kan ersätta postenkäter, i syfte att höja svarsfrekvenserna. De uppmanas även titta närmare på om olika register kan användas för att få fram fakta om de icke-svarande.

Acknowledgments

I wish to thank my supervisor Linda Ekerljung for the valuable support and knowledge throughout this project. I would also like to thank Bright Nwaru for help with the post-stratification weighting. Lastly, thank you to the staff and researchers at Krefting Research Centre and within the West Sweden Asthma Study.

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