Stressful life events and the onset of asthma

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Abstract

The status of stressful life events as a risk factor for asthma is unclear and may be dependent on pre-existing allergic rhinitis. This study examined whether exposure to stressful life events predicted the onset of asthma in adults.

This is a prospective, population-based cohort study of 16,881 men and women, aged 20-54 and free of diagnosed asthma at the beginning of the follow-up (January 1, 2004). Data about stressful life events were gathered with a postal survey. The onset of asthma was ascertained through national registers until December 31, 2005.

During the follow-up period, 192 incident cases of asthma were identified. High total exposure to stressful life events, as indicated by a cumulative severity score, predicted the onset of asthma (HR 1.96; 95% CI 1.22–3.13). This association was robust to adjustment for demographics, smoking, and having a cat/dog at home, and it was observed both among those with and without allergic rhinitis at the baseline. Of the 10 most stressful life events, the illness of a family member, marital problems, divorce or separation, and conflicts with a supervisor were associated with the onset of asthma.

Our study suggests that stressful life events may increase the onset of asthma.

Introduction

Introduction

Asthma is a disorder of the airways in which chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [1]. It is one of the most common chronic diseases worldwide, especially in industrialised countries. Among the adult population, the reported prevalence figures vary from 1.9% in Greece to 18.4% in Scotland [2]. In Finland, the prevalence of asthma is 4% among men and 7% among women [3] and the overall incidence rate during adulthood (i.e., 21–63 years) is 0.9 new cases per 1000 person-years [4].

A large number of studies have examined the biological risk factors for asthma. There is strong support for an increased risk of asthma that is associated with genetic factors, allergens, respiratory infections, air pollutants, tobacco smoke [5], and allergic rhinitis (AR) [6]. Recent studies suggest that AR and asthma, in fact, comprise a single syndrome known as the chronic allergic respiratory syndrome, which may affect one or two parts of the respiratory tract [7].

Recently, the role of psychosocial stress as a risk factor for asthma has gained increased attention. Stress is considered to affect the expression of asthma through multidimensional endocrine, neural, immune, and behavioural processes [8], but clinical research to date has clarified only part of the causal mechanisms that may link stress to asthma [9]. There is observational evidence that severe negative life events may increase the risk of children's asthma attacks over subsequent weeks [10] and may be associated with asthma symptoms among adolescents [11]. The association between stressful life events and an increased risk of asthma has also been reported in four retrospective studies [12, 13, 14, 15] and in at least one prospective study [16] among adults. In the latter study, which was based on 4,010 middle-aged participants in one town and its surroundings, breaking off a

life partnership predicted incident asthma, but no other stressful events were found to have an effect [16]. To our knowledge, however, no large-scale, population-based studies that explore the association between stressful life events and the onset of asthma are available.

In this study, we examine the association between stressful life events and the onset of asthma in a large population sample, taking into account pre-existing AR. We sought to determine whether (1) the total exposure to stressful life events is associated with the onset of asthma among adults; (2) specific severe life events are particularly predictive of such an onset; and (3) the association between life events and the asthma onset is dependent on pre-existing AR.

Materials and Methods

Study Population and Design

Data were drawn from the Health and Social Support (HeSSup) study, a longitudinal study on a population sample that is representative of the Finnish population in the following four age groups: 20–24, 30–34, 40–44, and 50–54 at baseline (Phase 1) [17]. Baseline characteristics were obtained from the Phase 1 postal survey conducted in 1998. Exposure to life events during a 5-year period between Phase 1 and Phase 2 was assessed with a follow-up questionnaire that was sent to all participants who were still living in Finland in 2003. Of the 25,901 respondents at baseline, 216 died before Phase 2, 234 had moved abroad, and 969 could not be reached due to unknown addresses; therefore, a total of 1,419 baseline respondents did not participate in the follow-up survey. Of all 19,629 respondents at Phase 2, which revealed an 80% response rate, 18,900 consented to the use of their recorded health information in Finnish national registers. Out of that pool, we excluded any participants with prevalent asthma or asthma history at Phase 2 (n=2,016).

Thus, the final sample consisted of 16,881 participants (6,663 men and 10,218 women) who had no indication of asthma at the beginning of the follow-up (Figure 1). They were followed for a two-year period from national health registers, in order to detect the onset of new asthma cases (2004–2005) after the Phase 2 survey.

Stressful Life Events.

Life events that occurred between Phases 1 and 2 were measured by a list of 21 negative events, as in earlier studies [18, 19, 20]. For each event, the questionnaire included the following categories: never, within the previous 6 months, within the previous 5 years, and over 5 years ago. The subjects classified the severity of each event as 1 = not so burdensome, 2 = burdensome, and 3 = extremely burdensome. The events that had occurred during the previous 5 years (i.e., in the period between the questionnaires) were considered in this study. We excluded 'illness causing work disability of over 21 days' and 'retirement' because such events might be related to asthma. To assess the total exposure to life events within the 5 years of follow-up for each individual, we calculated, from the 2003 survey responses, a cumulative sum score of the severity of events that had occurred within the previous 6 months or 5 years. As weights, we used means of squared severity ratings for each event as in our earlier studies [20, 21]. Those with a zero score were defined as having no exposure. The exposed were divided into tertiles: light (cumulative sum score 2.74–5.53), moderate (6.15–12.07) and heavy (12.09–55.41). In addition to the total exposure to stressful life events, we measured the nine most burdensome categories of specific events: death of a family member (death of own child, weight [w] 7.42; death of a spouse, w 7.01); emotional, physical, or sexual violence (w 6.16), severe illness in a family member (w 5.53), death of the mother (w 5.04), a major increase in marital problems (w 4.92), divorce or separation (w 4.75), severe conflicts with a supervisor (w 4.63), severe financial difficulties (w 4.37), and death of the father (w 4.25) [20].

Case Definition for Asthma

Using the unified personal identification code system, which covers all Finnish citizens, we linked the survey responses to records from three independent and comprehensive Finnish national health registers in order to identify incident cases of asthma. The identification of the cases was based on the clinical diagnosis from two registers (i.e., the Drug Reimbursement Register and the Hospital Discharge Register) of the treating physician (for special reimbursement for medicine costs or hospitalization) or detailed information about the prescribed medication (the Drug Prescription Register). A participant was classified as having incident asthma when the caseness was verified for the first time by at least one of the three data sources between January 1, 2004, and December 31, 2005.

First, we used the Drug Reimbursement Register of the Social Insurance Institution of Finland, which contains information on persons entitled to special reimbursement for certain chronic diseases, such as asthma. Patients who apply for special reimbursement must attach a detailed medical certificate that was prepared by the treating physician, who also provides data to confirm the diagnosis. The application is then reviewed by a physician in the Social Insurance Institution to determine whether the uniformly defined requirements for the disease are met. From this register, participants were defined as incident asthma cases if they were recorded in the Central Drug Register as being eligible for asthma treatment for the first time during the follow-up.

Second, we used prescription data to assess the beginnings of medical treatment for asthma. In Finland, the National Social Insurance Scheme at the Social Insurance Institution provides basic reimbursement (currently 42%) for all filled outpatient prescriptions that are recorded in the Drug Prescription Register according to the World Health Organization's Anatomical Therapeutic

Chemical (ATC) Classification [22] and by the date of purchase. We identified all participants with two or more prescriptions for drugs for obstructive airway diseases (ATC code R03) in any year during the follow-up by using the day of the first purchase as an indicator of the onset of asthma.

Third, we obtained data from the Hospital Discharge Register of the National Institute for Health and Welfare, which includes records on all inpatient hospital admissions. This register is comprised of countrywide information on virtually all hospitalizations. We obtained the discharge dates and the corresponding main diagnoses for hospitalization due to asthma (ICD-10 J45).

All of the individuals who were identified as having an onset of asthma in any of these registers before January 1, 2004, were excluded from the analysis, as were those individuals who reported a life-time diagnosis of asthma in either survey. Of all 192 incident cases of asthma that were detected on any of the three registers, 190 (99%) cases had purchases of prescribed medication for asthma and 41 (21%) cases had a clinical diagnosis of asthma noted in hospitalisation or special reimbursement records. Of the latter, 39 (95%) cases also had purchases of prescribed medication for asthma.

Baseline Characteristics

All baseline characteristics were measured at Phase 1. The possible risk factors for the development of asthma that were considered in this study included AR, exposure to dogs or cats [5], and smoking [23]. The participants were asked whether a doctor had previously told them that they have or have had AR (yes/no). The subjects were classified as having AR vs. not having AR (baseline). AR is a risk factor for asthma, particularly for the allergic phenotype [6, 24]. Information about a pet dog/cat was obtained by asking whether the participant has a pet. The variable was dichotomised as

having a pet dog/cat at home vs. not having one. The participants reported their current and past smoking habits, smoking rate, and number of cigarettes [17]. They were classified as non-smokers, past smokers, or current smokers. Socio-demographic background variables included gender, age group, level of education (basic / vocational / college / university), and marital status (single, divorced, or widowed vs. married or cohabiting).

Statistical Analysis

All analyses were performed by using PASW Statistics for Windows software, Release 18.0.0. The associations between the baseline characteristics and the onset of asthma, as well as those between life events that occurred in between Phase 1 and Phase 2 and the onset of asthma, were analyzed via the Cox proportional hazard model. Follow-up began on January 1, 2004 (i.e. after the year of Phase 2 survey), and ended upon the first occurrence of the outcome measure, death, or December 31, 2005, whichever came first. We calculated hazard ratios (HR) and their 95% confidence intervals (95% CI).

We studied the associations of baseline characteristics and risk factors with the onset of asthma during the risk time. Then, we studied the association between the total exposure to life events and onset of asthma, first adjusting the analysis for all demographics, and finally adding the risk factors to the model. Adjusting in the same way, we analysed the association between the ten most stressful life events and asthma onset in the risk time.

The gender difference in the association of the cumulative severity score to the onset of asthma was assessed with the interaction term gender* cumulative severity score. Because no significant interaction was found (p=0.43), we analysed men and women in combination adjusting for gender.

We performed two sensitivity analyses. First, we tested whether the effect of life events on asthma were dependent on AR. This analysis was carried out among two subgroups: participants with (n= 4,029) and without AR (n= 12,726). Second, we tested whether the association between life events and the subsequent onset of asthma was dependent on case definition. This analysis was carried out in subgroups of participants whose case definition was based on the clinical diagnosis of the treating physician (i.e., special reimbursement for medicine costs or hospitalization, [n=41]), and those whose caseness was determined according to prescribed medication (n=190).

Results

During a mean follow-up of 2.0 (SD 0.12) years, 192 participants were diagnosed with asthma. Past smoking habits, older age, and the presence of AR were associated with an increased risk (Table 1).

Stressful Life Events and Asthma

Altogether, 13,050 (79%) participants in our study reported that they encountered a stressful event during the 5-year exposure window between Phase 1 and Phase 2. Of these participants, 4,659 (36%) experienced 1 event, 7,846 (47%) experienced 2 to 5 events, and 545 (3%) endured 6 to 12 events. There were 3,366 participants who report no events.

The cumulative severity rating of the events ranged from 0 to 55.41 (median 6.97). Table 2 shows that those in the highest tertile of exposure to life events had 2 times (95% CI 1.26–3.20) a greater risk of asthma during the follow-up, compared to participants who did not experience any stressful

life events. This relative risk remained unchanged after taking into account adjustments for demographics, smoking habits, and exposure to dogs or cats.

Analyses of specific life events showed that 7 of the 9 categories of the most severe events were associated with a 1.5–1.7-fold risk of asthma during the follow-up period (Table 3). Statistically, a significantly increased risk of asthma onset was observed after a divorce or separation, major increase in marital problems, severe illness in a family member, severe conflicts with a supervisor, and severe financial difficulties. These associations were robust to all adjustments with one exception; the category 'severe financial difficulties' was not associated with asthma risk in the fully adjusted model. The only categories that showed no association with asthma onset were 'death of a family member' and 'death of own father.'

Figure 2 illustrates the cumulative hazard curves of asthma onset by exposure to stressful life events. The expected dispersion of hazard curves between categories of cumulative severity scores was observed across the entire follow-up period (p for log-rank test=0.006).

Sensitivity Analyses

To test the robustness of our findings, we excluded the participants with AR. This analysis replicated the findings for all participants. The hazard of asthma onset for those who were most severely exposed to life events was 1.9 times higher (95% CI, 1.04–3.43) than that for the non-exposed (Table 3). In an analysis that included the participants with AR only, the risk estimate was practically the same. However, it failed to reach statistical significance due to lower numbers. The non-significant interaction (p=0.46) between AR and life events is consistent with these findings.

A further sensitivity analysis testing whether the association between life events and a subsequent onset of asthma was dependent on case definition also replicated findings from the main analysis. Determining incident asthma on the basis of drug prescriptions (in analysis n=187), the hazard ratio for high exposure was 2.09 (95% CI 1.33–3.33, a test for trend <0.001). If incident asthma was determined solely on the basis clinical diagnosis (i.e., special reimbursement for asthma or hospitalization, n=41), the hazard ratio after a high level of exposure to stressful life events remained practically the same (HR 2.41) but did not reach statistical significance (95% CI 0.88–6.63, test for trend p=0.07). These associations were adjusted for age and gender; light and moderate exposure scores were combined due to the small number of cases. (data not shown).

Discussion

In this population-based prospective cohort study of almost 17,000 participants who had no indication of asthma at the beginning of the follow-up period, a high exposure to stressful life events was associated with a 2-fold increased risk of the subsequent onset of asthma as measured by reliable national health registers. The elevated risk was not accounted for by baseline characteristics, such as demographics, smoking habits or exposure to dogs or cats, and it was of the same magnitude both among those with and without AR. We also found that specific severe events (i.e., a divorce or separation, a major increase in marital problems, severely illness in a family member, and severe conflicts with a supervisor) were predictive of the onset of asthma.

Our findings support the biopsychosocial model of stress [25], which suggests that stressful life events may alter the psychological, immunological, and endocrine systems and contribute to the onset of asthma. To the best of our knowledge, the relationship between total exposure to negative life events and the onset of asthma has not been previously reported. The findings of this study are

in agreement with prior studies that suggest an association of stressful life events with various health problems ranging from sleep disturbances and sickness absence to depression and breast cancer [19, 20, 26, 27].

To date, only a few studies have prospectively investigated the association between stressful life events and adult asthma. The only longitudinal cohort study of which we are aware followed a population-based sample of 4,010 middle-aged adults from Germany via questionnaire surveys at baseline (1992–1995) and follow-up (2002/2003) [16]. Exposure to three stressful life events was measured (i.e., unemployment, having broken off a life partnership, and death of someone close). Having broken off a life partnership was associated with a risk of incident asthma that is 2.2-times higher, while no excess risk was found for the other two life events. However, this study was based on a self-report of asthma. In addition, some earlier clinical and retrospective studies [12, 14] noted that adults with acute asthma report that they have experienced a divorce or marital problems before the onset of the disease more often than the non-asthmatic controls. In our study, based on a follow-up of a population sample with no indication of asthma at baseline, individuals who had interpersonal conflicts indicated by divorce or separation, a major increase in marital problems, and severe conflicts with a supervisor experienced a risk of incident asthma that was 1.6–1.7 times higher in the future. In agreement with previous studies [15, 16], the death of someone close, such as a family member or one's own mother or father, was not associated with increased risk of asthma. The fact that the case definition was based on objective indicators of asthma increased the credibility of our findings.

We also noted a robust association between the severe disease of a family member and incident asthma. In line with this result, Salminen [14] observed that a severe disease of a family member was more common among acute asthma patients than among non-asthmatic controls. A smaller-

scale analysis found, in contrast, no association between family death or illness and diagnosed asthma [15]. It is noteworthy that there are some differences between the studies in life event variables in the analyses and in the study populations. We are not aware of any other studies on violence or financial difficulties as predictors of the onset of asthma and, in this study, no robust association between these events and asthma onset was found.

The strengths of this study include data from a large sample of working-age adults, a study design that allowed the determination of temporary order between exposure to stressful life events and the onset of the disease, and the measurement of asthma from national health registers rather than relying on self-reporting. In Finland, the validity of the national registers has been found to be high [28], reasonably accurate, and highly reliable for epidemiological study purposes [29]. We were also able to control a number of socio-demographic elements and asthma risk factors. At Phase 1, the response rate was relatively low (40%), and there may have been differences between respondents and non-respondents regarding the frequency of asthma and stressful life events. However, more than 80% of these individuals participated in the Phase 2 survey and, of them, 96% consented to the linking of data from national health registers. Thus, it is unlikely that the longitudinal associations between life events and incident asthma would be spurious, due to the low participation at Phase 1.

Conclusions

This is apparently the first epidemiological study of a working-age population that investigates the association between stressful life events and the onset of asthma from reliable health registers. We found that the severity of all stressful life events was associated with the onset of asthma and observed associations with a divorce or separation, a major increase in marital problems, a severe

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illness in a family member, and severe conflicts with a supervisor. Taking into account asthma's nature as a multifactorial disease, the finding of this study that some life events may trigger the onset of asthma in adults deepens the understanding of the disease's psychosocial risk factors.

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Table 1 Characteristics of study participants (N=16,881) and hazard ratios for incident asthma (all variables in the same model).

	Number of participants (%)	Number of cases (%)	HR (95% CI)*
All			
Gender			
Men	6,663 (40)	61 (0.9)	1.00
Women	10,218 (60)	131 (1.3)	1.33 (0.96-1.85)
Age group			
20 – 24 years	4,268 (25)	39 (0.9)	1.00
30 – 34 years	3,814 (23)	42 (1.1)	1.38 (0.85-2.24)
40 – 44 years	4,200 (25)	52 (1.2)	1.43 (0.89-2.29)
50 – 54 years	4,599 (27)	58 (1.3)	1.60 (1.01-2.51)
Marital status			
Single	5,303 (31)	61 (1.2)	1.00
Married	11,560 (69)	130 (1.1)	0.90 (0.64-1.27)
Level of education			
University	2,824 (17)	28 (1.0)	1.00
College	4,954 (30)	55 (1.1)	1.12 (0.68-1.81)
Vocational	4,024 (24)	38 (0.9)	0.95 (0.56-1.62)
Basic	4,902 (29)	65 (1.3)	1.39 (0.86-2.27)
Smoking			
Non smoker	7,298 (47)	64 (0.9)	1.00
Past smoker	4,301 (28)	67 (1.6)	1.66 (1.16-2.37)
Current smoker	3,904 (25)	50 (1.3)	1.35 (0.93-2.02)
Dog /cat at home			
No	10,556 (63)	111 (1.1)	1.00
Yes	6189 (37)	77 (1.2)	1.23 (0.91-1.99)
Allergic rhinitis			
No	12,726	112 (0.9)	1.00
Yes	4,029	76 (1.9)	2.21 (1.62-3.01)

* Data are presented as hazard ratio (95% confidence interval).

Table 2 Exposure to stressful life events (cumulative severity score) as a predictor of incident asthma

Life event severity score	Number [a]	Model 1 HR (95% CI)*	Model 2 HR (95% CI)*	Model 3 HR (95% CI)*
All participants				
0o	3,023	1.00	1.00	1.00
>0–5.53	4,136	1.35 (0.83–2.19)	1.35 (0.83–2.20)	1.35 (0.83–2.19)
6.15–12.07	3,835	1.20 (0.72–1.99)	1.20 (0.73–2.00)	1.19 (0.72–1.98)
>12.09	3,837	**1.96 (1.23–3.12)**	**2.01 (1.26–3.20)**	**1.96 (1.22–3.13)**
Without allergic rhinitis				
0o	2,381	1.00	1.00	1.00
>0–5.53	3,154	1.42 (0.77–2.60)	1.42 (0.77–2.61)	1.41 (0.77–2.60)
6.15–12.07	2,911	1.02 (0.53–1.97)	1.03 (0.53–1.99)	1.02 (0.53–1.97)
>12.09	2,772	**1.83 (1.01–3.31)**	**1.88 (1.04–3.43)**	**1.84 (1.01–3.35)**
With allergic rhinitis				
0o	622	1.00	1.00	1.00
>0–5.53	955	1.08 (0.47–2.47)	1.13 (0.49–2.58)	1.13 (0.49–2.59)
6.15–12.05	907	1.29 (0.58–2.91)	1.31 (0.58–2.95)	1.31 (0.58–2.95)
>12.11	1,048	1.79 (0.84–3.82)	1.90 (0.89–4.05)	1.83 (0.85–3.94)

*Cox regression models were used, results shown by hazard ratios (HR) with 95% confidence intervals (CI). Statistically significant hazard ratios are shown in bold.

Model 1: Crude
Model 2: Adjusted for sociodemographic factors (age, gender, marital status and education)
Model 3: Model 2+ asthma risk factors (smoking and cat/dog at home)

[a] Calculated from model 3

Table 3 Most severe specific life events as predictors of incident asthma.

Life event during five years	No. of subjects in the analysis [a]	No. of subjects with the event	Model 1 HR (95% CI)*	Model 2 HR (95% CI)*	Model 3 HR (95% CI)*
Death of a family member*	203	155	0.85 (0.21–3.42)	0.71 (0.17–2.88)	0.72 (0.18–2.93)
Violence	792	149	1.48 (0.84–2.61)	1.44 (0.81–2.56)	1.39 (0.78–2.47)
Severe illness in a family member	2652	133	**1.52 (1.06–2.19)**	**1.47 (1.01–2.12)**	**1.47 (1.01–2.12)**
Death of mother	1106	134	1.57 (0.97–2.56)	1.41 (0.83–2.41)	1.40 (0.82–2.39)
Major increase in marital problems	2773	135	**1.62 (1.12–2.33)**	**1.47 (1.01–2.12)**	**1.47 (1.01–2.12)**
Divorce or separation	1822	115	**1.65 (1.08–2.55)**	**1.75 (1.13–2.73)**	**1.67 (1.07–2.62)**
Severe conflicts with supervisor	1381	152	**1.61 (1.04–2.49)**	**1.65 (1.07–2.56)**	**1.63 (1.05–2.52)**
Severe financial difficulties	2500	142	**1.47 (1.01–2.13)**	1.41 (0.97–2.06)	1.40 (0.95–2.05)
Death of father	1387	100	0.85 (0.48–1.53)	0.76 (0.41–1.43)	0.77 (0.41–1.43)

Cox regression models were used, results shown by hazard ratios (HR) with 95% confidence intervals (CI). Statistically significant hazard ratios are shown in bold.
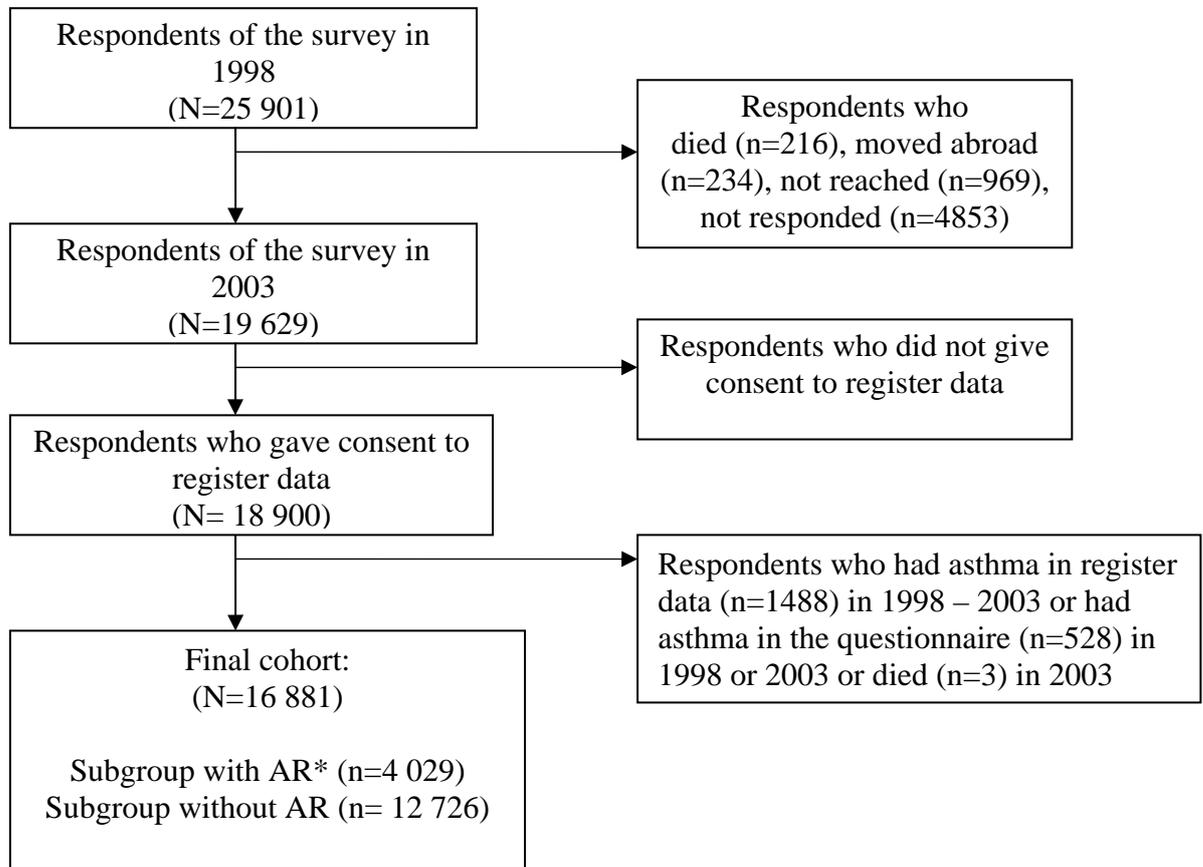
*Death of own child or death of spouse

Model 1: Crude
Model 2: Adjusted for sociodemographic factors (age, gender, marital status and education)
Model 3: Model 2+ asthma risk factors (smoking and cat/dog at home)

[a] Calculated from model 3

Figure 1 Flow chart of the sample selection procedure

Respondents of the survey in 1998
(N=25 901)

Respondents who died (n=216), moved abroad (n=234), not reached (n=969), not responded (n=4853)

Respondents of the survey in 2003
(N=19 629)

Respondents who did not give consent to register data

Respondents who gave consent to register data
(N= 18 900)

Respondents who had asthma in register data (n=1488) in 1998 – 2003 or had asthma in the questionnaire (n=528) in 1998 or 2003 or died (n=3) in 2003

Final cohort:
(N=16 881)

Subgroup with AR* (n=4 029)
Subgroup without AR (n= 12 726)

*Allergic rhinitis

Figure 2 Cumulative hazard of asthma onset by exposure to stressful life events

All participans and onset of asthma