

## Neuroticism, extraversion, stressful life events and asthma: a cohort study of middle-aged adults

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## Original article

## Neuroticism, extraversion, stressful life events and asthma: a cohort study of middle-aged adults

**Background:** Stressful life events can trigger asthma exacerbations, but could also contribute to the development of incident asthma. However, only few studies have investigated the association between stressful life events and adult asthma prospectively. Likewise, stress-related personality traits (e.g. neuroticism and extraversion) may increase asthma risk, but this has been examined in only one prospective study. We therefore aimed to investigate the association between neuroticism, extraversion, stressful life events and incident asthma.

**Methods:** A population-based sample of 5114 middle-aged adults completed questionnaires between 1992 and 1995. Among those alive in 2002/2003, 4010 (83%) were followed-up by questionnaires. Exposures of interest included neuroticism, extraversion and three stressful life events (unemployment, having broken off a life partnership and death of a close person). Associations with incident asthma were estimated by multivariable risk ratios (RR) and 95% confidence intervals (95% CI) using Poisson regression.

**Results:** High vs low neuroticism predisposed to developing asthma (RR = 3.07, 95% CI = 1.71–5.48), but high extraversion did not (RR = 1.30, 95% CI = 0.79–2.15). Having broken off a life partnership significantly increased asthma risk (RR = 2.24, 95% CI = 1.20–4.21) in contrast to death of a close person (RR = 1.06, 95% CI = 0.64–1.75) or unemployment (RR = 1.65, 95% CI = 0.72–3.78).

**Conclusions:** High levels of neuroticism may increase the risk of asthma in middle-aged adults. Having broken off a life partnership was the only stressful event, which was associated with incident asthma. Synthesized with evidence from earlier studies, this could reflect that interpersonal conflicts may increase asthma risk, possibly along an immunological pathway.

**A. Loerbroks<sup>1,2</sup>, C. J. Apfelbacher<sup>3,4</sup>,  
J. F. Thayer<sup>2,5</sup>, D. Debling<sup>6</sup>, T. Stürmer<sup>7</sup>**

<sup>1</sup>Institute of Psychology, Heidelberg University, Heidelberg, Germany; <sup>2</sup>Mannheim Institute of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, Heidelberg University, Mannheim, Germany; <sup>3</sup>Department of Clinical Social Medicine, University Hospital Heidelberg, Heidelberg, Germany; <sup>4</sup>Division of Public Health and Primary Care, Brighton and Sussex Medical School, Falmer, UK; <sup>5</sup>The Ohio State University, Department of Psychology, Columbus, Ohio, USA; <sup>6</sup>German Childhood Cancer Registry at the Institute for Medical Biostatistics, Epidemiology and Informatics, University of Mainz, Mainz, Germany; <sup>7</sup>Division of Preventive Medicine and Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MD, USA

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Dr Adrian Loerbroks, MSc, MSc  
Mannheim Institute of Public Health  
Social and Preventive Medicine  
Mannheim Medical Faculty  
Heidelberg University  
Ludolf-Krehl-Strasse 7-11  
68167 Mannheim  
Germany

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Stress is considered to affect health outcomes and morbidity in asthma patients (1, 2) and stressful life events may trigger asthma exacerbations (3). Stress may also contribute to the development of incident asthma (1, 2) possibly along a pathway involving inflammatory processes (4–6). It is therefore conceivable that life events that are associated with considerable distress and personality traits that are related to stress susceptibility may predispose to developing asthma, too. Extraversion and in particular neuroticism can be conceptualized as such stress-related personality traits. These traits have been related to perceived stress (7, 8), to coping styles (9) and, in some studies, to physiological indicators of the stress response (i.e. cortisol) (10, 11). Apart from their potential inflammatory link to asthma aetiology, the effects of these traits on asthma genesis could be mediated by lifestyle-

related factors such as smoking (12, 13) and overweight/obesity (14, 15), which may reflect unhealthy behavioural coping with stress.

To elucidate whether stressful events or personality traits may contribute to the development of asthma, these associations need to be studied prospectively. A number of prospective studies on stressful life events and the onset of asthma have been conducted in populations of children (2), but evidence from adult populations is sparse. The association between neuroticism, extraversion and asthma has been examined in only one epidemiological study with a prospective design (16). This investigation found that neuroticism was not related to the onset of asthma, and that high levels of extraversion increased asthma risk in women, but not in men.

As a result of the marked scarcity of longitudinal data on the relation between neuroticism, extraversion, stressful life events and asthma, we aimed to explore these associations prospectively based on data from a large population-based cohort study of middle-aged adults.

## Methods

### Study population

Details on the study population can be found elsewhere (17). Briefly, at baseline (1992–1995), a population-based sample of 5114 women and men aged 40–65 years from Heidelberg and surroundings completed a questionnaire assessing lifestyles, comorbidity and personality traits. In 2002/2003, participants were followed-up for mortality and morbidity (18, 19) after a median of 8.5 years. Among those alive at follow up ( $n = 4857$ ), the response rate was 83% ( $n = 4010$ ). Study protocols were approved by the ethics committee of the Faculty of Medicine, University of Heidelberg.

### Questionnaire data

Neuroticism and extraversion were measured at baseline each by 24 closed-ended questions using the validated German version of the Eysenck Personality Inventory (20). The psychometric properties of this tool have been documented. For instance, reported split-half reliabilities for the neuroticism scale and the extraversion scale range from 0.74 to 0.78 and 0.64 to 0.75, respectively (20). One point was assigned for each affirmative answer. One point was assigned for each affirmative answer and mean neuroticism and extraversion scores were calculated.

At baseline, a total of three closed-ended questions addressed life events that were assumed to be stressful. These questions were: 'During the last 5 years, did you lose your job or fail to obtain an appropriate job?', 'During the last 5 years, did you break off a life partnership (break off the relationship with your parents or divorce from your partner)?', 'During the last 5 years, did a close person die (e.g. partner, family member, friend)?'.

At baseline, participants were asked whether they currently have or ever had asthma. Provided response categories were: 'I currently have asthma', 'I do not have asthma anymore', 'I do not know whether I still have it' and 'No, I do not have asthma/I have never had asthma'. Prevalent asthma at baseline was defined as a participant responding 'I currently have asthma', 'I do not have asthma anymore' or 'I do not know whether I still have it'. If the answer 'No, I do not have asthma/I have never had asthma' was given, the individual was considered to be free of asthma.

At follow up, respondents were asked whether they had ever been diagnosed with asthma by a physician (yes or no were the only possible answers). We defined incident asthma as self-reported asthma at follow up in participants without asthma at baseline.

### Statistical analyses

Neuroticism and extraversion may be categorized by pragmatically constructing groups of equal size based on the respective score distribution in the study population (21). Given the limited number of incident asthma cases, we sought to maximize efficiency and decided to split the study population into two cohorts of similar size. We dichotomized neuroticism and extraversion scales by splitting the study population at the median of the respective score distribution. Stressful life events were evaluated individually as it

has been suggested that different stressors have different effects on the immune system (22) and possibly also on the occurrence of asthma.

We estimated prevalence ratios (PRs) in cross-sectional analyses and risk ratios (RRs) in longitudinal analyses together with their 95% confidence intervals (95% CI) by Poisson regression using a log-link function and the empirical (robust) variance in SAS (23). Analyses were conducted for the entire sample, but were also stratified by gender in order to make our findings comparable to the only previous prospective study on neuroticism, extraversion and asthma (16). Gender differences were assessed by the Wald's test for an interaction term between gender and the corresponding exposure of interest.

Because of potential or reported associations with personality and asthma, we decided *a priori* to control for the following possible confounders: age, age<sup>2</sup>, education, smoking status, alcohol consumption, body mass index, physical exercise, family history of asthma and, if applicable, gender in multivariable analyses. We used conventional methods of confounder adjustment in cross-sectional analyses. In longitudinal analyses, however, we used propensity scores to control for confounding (24, 25) because of the limited number of incident cases in our study and because of the high proportion of exposed individuals based on the median split of neuroticism and extraversion. Propensity score adjustment was performed by first estimating the propensity for each study participant to be exposed to each dichotomized potential asthma risk factor (i.e. high neuroticism, high extraversion, unemployment, breaking off a life partnership and death of a close person). We estimated the individual probability of exposure by logistic regression employing the potential asthma risk factors as dependent variable and the confounders as independent variables. In a second step, participants who had a propensity score outside of the range common to exposed and unexposed individuals were excluded from the analyses. Third, the continuous propensity scores were divided into quintiles. These quintiles were then used as dummy variables in the multivariable outcome models for asthma incidence. In addition to using personality scales as dichotomized exposures, we used *z*-transformed extraversion and neuroticism scores as continuous exposures in both cross-sectional and longitudinal analyses.

## Results

As illustrated by Table 1, increasing age was associated with a decrease in extraversion, but not with neuroticism. Women were more likely to have high neuroticism scores than men. There were no gender differences with respect to extraversion. Higher educational levels were related to both lower neuroticism and lower extraversion. Smoking status was not associated with neuroticism, but was strongly related to extraversion, which was the lowest in never-smokers and the highest in current smokers. Both increasing alcohol intake and increasing levels of physical exercise were associated with lower neuroticism and higher extraversion. Body mass index levels and a positive family history of asthma were associated with higher neuroticism, but were unrelated to extraversion.

Of the 4854 baseline participants with complete information on asthma, 334 (6.9%) reported prevalent asthma. Among baseline participants with complete information on the respective item, 7.8% ( $n = 394$ ) lost their job or failed to find a new job within a period of

Table 1. Participants [*n* (%)] with a high or low neuroticism score or extraversion score according to baseline characteristics

| Characteristic                       | Neuroticism* |             | Extraversion* |             |
|--------------------------------------|--------------|-------------|---------------|-------------|
|                                      | Low          | High        | Low           | High        |
| <i>n</i>                             | 2511         | 2602        | 2783          | 2330        |
| Age (years)                          |              |             |               |             |
| <50                                  | 867 (51.6)   | 815 (48.5)  | 852 (50.7)    | 830 (49.4)  |
| 50 to <60                            | 1086 (47.8)  | 1186 (52.2) | 1236 (54.4)   | 1036 (45.6) |
| ≥60                                  | 558 (48.1)   | 601 (51.9)  | 695 (60.0)    | 464 (40.0)  |
| Gender                               |              |             |               |             |
| Women                                | 1075 (40.3)  | 1594 (59.7) | 1483 (55.6)   | 1186 (44.4) |
| Men                                  | 1436 (58.8)  | 1008 (41.2) | 1300 (53.2)   | 1144 (46.8) |
| Education (years)                    |              |             |               |             |
| <10                                  | 1154 (45.6)  | 1379 (54.4) | 1341 (52.9)   | 1192 (47.1) |
| 10                                   | 481 (47.7)   | 528 (52.3)  | 550 (54.5)    | 459 (45.5)  |
| >10                                  | 845 (56.3)   | 657 (43.7)  | 858 (57.1)    | 644 (42.9)  |
| Smoking status                       |              |             |               |             |
| Never                                | 1025 (47.4)  | 1138 (52.6) | 1298 (60.0)   | 865 (40.0)  |
| Former                               | 918 (50.8)   | 890 (49.2)  | 944 (52.2)    | 864 (47.8)  |
| Current                              | 556 (50.1)   | 555 (50.0)  | 528 (47.5)    | 583 (52.5)  |
| Alcohol consumption (g/day)          |              |             |               |             |
| None                                 | 385 (44.1)   | 489 (56.0)  | 549 (62.8)    | 325 (37.2)  |
| 0.1 to 15.0                          | 1016 (47.3)  | 1131 (52.7) | 1180 (55.0)   | 967 (45.0)  |
| 15.1 to 30.0                         | 581 (52.1)   | 534 (47.9)  | 573 (51.4)    | 542 (48.6)  |
| >30.0                                | 496 (55.3)   | 401 (44.7)  | 436 (48.6)    | 461 (51.4)  |
| Physical exercise, (h/week)          |              |             |               |             |
| None                                 | 624 (43.7)   | 804 (56.3)  | 883 (61.8)    | 545 (38.2)  |
| >0 to 2                              | 1248 (48.5)  | 1323 (51.5) | 1397 (54.3)   | 1174 (45.7) |
| >2                                   | 621 (57.9)   | 452 (42.1)  | 478 (44.6)    | 595 (55.5)  |
| Body mass index (kg/m <sup>2</sup> ) |              |             |               |             |
| <25                                  | 1282 (49.4)  | 1315 (50.6) | 1439 (55.4)   | 1158 (44.6) |
| 25 to <30                            | 976 (50.3)   | 963 (49.7)  | 1036 (53.4)   | 903 (46.6)  |
| ≥30                                  | 219 (43.8)   | 281 (56.2)  | 265 (53.0)    | 235 (47.0)  |
| Family history of asthma             |              |             |               |             |
| No                                   | 2262 (50.7)  | 2200 (49.3) | 2421 (54.3)   | 2041 (45.7) |
| Yes                                  | 221 (39.3)   | 342 (60.8)  | 319 (56.7)    | 244 (43.3)  |

\*For each scale, low and high scores were defined based on the median split.

5 years prior to baseline interviews, 9.0% (*n* = 458) broke off a life partnership and 48.6% (*n* = 2471) experienced the death of a close person.

In cross-sectional analyses (Table 2), neuroticism showed a strong positive association with prevalent asthma in men, but not in women (PR = 2.06, 95% CI = 1.53–2.78, and PR = 1.13, 95% CI = 0.80–1.59, respectively). This interaction was statistically significant (*P*-value = 0.01). When we used neuroticism *z*-scores, we again observed a stronger association between neuroticism and asthma in men than in women (PR for 1 SD increase = 1.39, 95% CI = 1.22–1.58 and PR = 1.19, 95% CI = 1.00–1.42, respectively). We observed no meaningful association between extraversion and asthma in either gender. Unemployment was associated with an elevated prevalence of asthma in both women and men (PR = 1.56, 95% CI = 0.96–2.54 and PR = 1.54, 95% CI = 1.01–2.36, respectively). Having broken off a life

partnership was positively related to asthma in women (PR = 1.60, 95% CI = 0.99–2.59), but not in men (PR = 0.99, 95% CI = 0.58–1.69). Death of a close person was not associated with the prevalence of asthma, neither in women nor in men.

A total of 4520 individuals reported to be free of asthma at baseline and are thus the cohort for our longitudinal analyses. Of these, 200 (4.4%) died between baseline and follow-up in 2002/2003 (mortality follow up was 99.5% complete). Of those alive at follow up (*n* = 4320), 3588 (83.1%) participated in the follow-up assessments and 3572 (99.6%) of the participants provided information on asthma at follow up. Among this group used for the longitudinal analyses, 63 individuals (1.8%) developed asthma over a median follow up of 8.5 years.

Compared to those with low neuroticism, adults with high neuroticism had a threefold elevated risk of developing asthma (RR = 3.07, 95% CI = 1.71–5.48) (Table 3). Extraversion was not associated with incident asthma. Breaking off a life partnership increased the risk of asthma development (RR = 2.24, 95% CI = 1.20–4.21). In contrast, unemployment and death of a close person were not significantly related to incident asthma (RR = 1.65, 95% CI = 0.72–3.78 and RR = 1.06, 95% CI = 0.64–1.75, respectively). High neuroticism (*vs* low neuroticism) and having broken off a life partnership were associated at baseline (PR = 1.80, 95% CI = 1.49–2.18) and could therefore confound each other's relation with incident asthma. When we additionally controlled the multivariable models for these exposures, the estimates were not altered substantially; the RR for high *vs* low neuroticism was 2.92 (95% CI = 1.64–5.22) and RR for having broken off a life partnership was 2.39 (95% CI = 1.16–4.90). Because of the low number of incident cases, confidence intervals were wide when analyses was stratified by gender, particularly for dichotomized exposures. High *vs* low neuroticism predisposed both women and men to develop asthma (RR = 4.06, 95% CI = 1.60–10.30 and RR = 2.48, 95% CI = 1.11–5.56, respectively). High *vs* low extraversion was neither associated with an increased risk of asthma in women (RR = 1.60, 95% CI = 0.82–3.12), nor in men (RR = 1.01, 95% CI = 0.49–2.10), both with wide confidence intervals. With regard to stressful life events, breaking off a life partnership increased asthma risk only in women. Stratified analyses of life events by neuroticism, again based on a limited number of cases, suggested a trend towards increased asthma risk in those with high neuroticism.

## Discussion

In this study involving middle-aged adults, neuroticism and breaking off a life partnership were associated with an increased risk of asthma. In contrast, extraversion, unemployment and death of a close person did not show statistically significant associations with incident asthma.

Table 2. Prevalence ratios (PRs) and 95% confidence intervals (95% CI) of asthma at baseline according to personality traits and stressful life events

| Exposures                         | N    | N with prevalent asthma (%) | Age- and sex adjusted* |           |       |           |      |           | Multivariable† |           |       |           |      |           |
|-----------------------------------|------|-----------------------------|------------------------|-----------|-------|-----------|------|-----------|----------------|-----------|-------|-----------|------|-----------|
|                                   |      |                             | Women and men          |           | Women |           | Men  |           | Women and men  |           | Women |           | Men  |           |
|                                   |      |                             | PR                     | 95% CI    | PR    | 95% CI    | PR   | 95% CI    | PR             | 95% CI    | PR    | 95% CI    | PR   | 95% CI    |
| Stress-related personality traits |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| Neuroticism                       |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| Low                               | 2415 | 122 (5.1)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref       | 1.00 | ref       |
| High                              | 2438 | 212 (8.7)                   | 1.80                   | 1.44–2.24 | 1.30  | 0.95–1.79 | 2.31 | 1.72–3.09 | 1.63           | 1.29–2.06 | 1.13  | 0.80–1.59 | 2.06 | 1.53–2.78 |
| Per 1 SD increase                 | –    | –                           | 1.39                   | 1.26–1.54 | 1.29  | 1.10–1.52 | 1.48 | 1.31–1.67 | 1.30           | 1.17–1.45 | 1.19  | 1.00–1.42 | 1.39 | 1.22–1.58 |
| Extraversion                      |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| Low                               | 2640 | 178 (6.7)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref       | 1.00 | ref       |
| High                              | 2213 | 156 (7.1)                   | 1.07                   | 0.87–1.32 | 0.93  | 0.69–1.27 | 1.21 | 0.91–1.60 | 1.12           | 0.90–1.40 | 1.03  | 0.74–1.45 | 1.21 | 0.90–1.63 |
| Per 1 SD increase                 | –    | –                           | 1.05                   | 0.95–1.16 | 0.98  | 0.84–1.14 | 1.12 | 0.98–1.28 | 1.09           | 0.98–1.21 | 1.02  | 0.86–1.22 | 1.14 | 0.99–1.32 |
| Stressful life events‡            |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| Unemployment                      |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| No                                | 4446 | 291 (6.6)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref       | 1.00 | ref       |
| Yes                               | 379  | 43 (11.4)                   | 1.71                   | 1.27–2.32 | 1.84  | 1.17–2.91 | 1.62 | 1.08–2.42 | 1.57           | 1.15–2.16 | 1.56  | 0.96–2.54 | 1.54 | 1.01–2.36 |
| Broke off life partnership        |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| No                                | 4396 | 300 (6.8)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref       | 1.00 | ref       |
| Yes                               | 441  | 34 (7.7)                    | 1.26                   | 0.90–1.78 | 1.41  | 0.89–2.23 | 1.11 | 0.66–1.86 | 1.26           | 0.88–1.80 | 1.60  | 0.99–2.59 | 0.99 | 0.58–1.69 |
| Death of a close person           |      |                             |                        |           |       |           |      |           |                |           |       |           |      |           |
| No                                | 2483 | 162 (6.5)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref       | 1.00 | ref       |
| Yes                               | 2354 | 171 (7.3)                   | 1.10                   | 0.90–1.36 | 1.03  | 0.76–1.40 | 1.17 | 0.88–1.55 | 1.04           | 0.83–1.29 | 0.87  | 0.63–1.19 | 1.19 | 0.89–1.60 |

\*Analyses in the entire sample were adjusted for age (continuous and squared) and gender. Gender-stratified analyses were only adjusted for age (continuous and squared).

†Analyses in the entire sample were adjusted for age (continuous and squared), gender, education (<10, 10, >10 years), smoking status (never, former, current), alcohol consumption (0, 0.1–15.0, 15.1–30.0, >30.0 g/day), physical exercise (0, >0–2, >2 h/week), body mass index (<25, 25 to <30, ≥30 kg/m<sup>2</sup>), family history of asthma (yes, no). Gender-stratified analyses were adjusted for the same confounders except for gender.

‡During a period of 5 years prior to the baseline interview.

Strengths of our study include its large population-based sample and high participation rates. We were able to conduct longitudinal analyses thereby minimizing selection bias and information bias. Personality traits were measured by validated scales. Moreover, we adjusted for many important confounders at baseline in multivariable analyses.

We relied on self-reports of asthma, which is a pragmatic and efficient option of data collection for large epidemiological studies. Certainly, the possibility that nonreversible airway obstruction is labelled 'asthma' cannot be ruled out. There is, however, no generally accepted gold standard for the diagnosis of asthma (26). Using self-reported asthma or self-reported physician-diagnosed asthma is therefore acceptable in analytical epidemiological studies (26). Another potential drawback is that stress-related personality characteristics could be differentially related to the reporting of asthma (e.g. those with high neuroticism may be more likely to report asthma). This might produce artefact associations. It seems unlikely that this would have introduced meaningful bias in our longitudinal analyses if we assume that personality traits are fairly stable, because false-positive cases of asthma would have been excluded from longitudinal analyses because of asthma at baseline. Another issue is that the items assessing stressful life events were rather unspecific. We only asked whether a particular

event had occurred or not within a period of 5 years before baseline. We had information neither on the exact timing of the stressful life events nor on how stressful the reported events have been perceived. Such factors might determine the actual stress response (27).

A further limitation of the study is the limited number of incident asthma cases. This resulted in wide confidence intervals for some exposures (i.e. unemployment) and for gender-specific estimates. Because of the low number of incident cases, personality traits were dichotomized at the median. This dichotomy is relatively crude and tertiles or quartiles of personality scores might have revealed more specific patterns of association. To avoid the necessity of choosing a cut-off and to increase statistical power, we also used personality scores as a continuous variable. Analyses with these variables produced similar results as analyses with dichotomized exposures.

Selective survival during follow up can never be ruled out and may affect exposure-disease associations in longitudinal studies with long intervals between questionnaires (as in our study). Neither extraversion nor any stressful life events were significantly associated with all-cause mortality in our study (data not shown). In accordance with earlier studies (28, 29), we, however, observed a positive association between neuroticism and mortality during follow up: 1 SD increase of the neuroticism score was related to a 22% increase of the age-and

Table 3. Risk ratios (RRs) and 95% confidence intervals (95% CI) of incident asthma according to personality traits and stressful life events

| Exposures                         | N    | N with incident asthma (%) | Age- and sex adjusted* |           |       |           |      |           | Multivariable† |           |       |            |      |           |
|-----------------------------------|------|----------------------------|------------------------|-----------|-------|-----------|------|-----------|----------------|-----------|-------|------------|------|-----------|
|                                   |      |                            | Women and men          |           | Women |           | Men  |           | Women and men  |           | Women |            | Men  |           |
|                                   |      |                            | RR                     | 95% CI    | RR    | 95% CI    | RR   | 95% CI    | RR             | 95% CI    | RR    | 95% CI     | RR   | 95% CI    |
| Stress-related personality traits |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| Neuroticism                       |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| Low                               | 1809 | 17 (0.9)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref        | 1.00 | ref       |
| High                              | 1763 | 46 (2.6)                   | 2.86                   | 1.64–4.98 | 3.38  | 1.41–8.09 | 2.50 | 1.18–5.33 | 3.07           | 1.71–5.48 | 4.06  | 1.60–10.30 | 2.48 | 1.11–5.56 |
| Per 1 SD increase                 | –    | –                          | 1.56                   | 1.26–1.95 | 1.55  | 1.18–2.04 | 1.58 | 1.12–2.24 | 1.60           | 1.28–1.99 | 1.61  | 1.23–2.11  | 1.59 | 1.09–2.32 |
| Extraversion                      |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| Low                               | 1975 | 30 (1.5)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref        | 1.00 | ref       |
| High                              | 1596 | 33 (2.1)                   | 1.32                   | 0.81–2.15 | 1.65  | 0.85–3.22 | 1.00 | 0.48–2.07 | 1.30           | 0.79–2.15 | 1.60  | 0.82–3.12  | 1.01 | 0.49–2.10 |
| Per 1 SD increase                 | –    | –                          | 1.07                   | 0.85–1.36 | 1.20  | 0.89–1.63 | 0.94 | 0.65–1.36 | 1.11           | 0.87–1.41 | 1.21  | 0.88–1.68  | 0.99 | 0.68–1.42 |
| Stressful life events‡            |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| Unemployment                      |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| No                                | 3303 | 56 (1.7)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref        | 1.00 | ref       |
| Yes                               | 249  | 7 (2.8)                    | 1.69                   | 0.78–3.67 | 1.38  | 0.42–4.50 | 2.05 | 0.72–5.78 | 1.65           | 0.72–3.78 | 1.54  | 0.49–4.79  | 1.60 | 0.49–5.21 |
| Broke off life partnership        |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| No                                | 3252 | 52 (1.6)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref        | 1.00 | ref       |
| Yes                               | 308  | 11 (3.6)                   | 2.04                   | 1.08–3.86 | 2.48  | 1.14–5.40 | 1.42 | 0.44–4.63 | 2.24           | 1.20–4.21 | 2.63  | 1.27–5.48  | 1.65 | 0.50–5.44 |
| Death of a close person           |      |                            |                        |           |       |           |      |           |                |           |       |            |      |           |
| No                                | 1839 | 33 (1.8)                   | 1.00                   | ref       | 1.00  | ref       | 1.00 | ref       | 1.00           | ref       | 1.00  | ref        | 1.00 | ref       |
| Yes                               | 1720 | 30 (1.7)                   | 0.99                   | 0.60–1.61 | 0.87  | 0.45–1.68 | 1.16 | 0.56–2.39 | 1.06           | 0.64–1.75 | 0.85  | 0.43–1.70  | 1.36 | 0.66–2.80 |

\*Analyses in the entire sample were adjusted for age (continuous and squared) and gender. Gender-stratified analyses were only adjusted for age (continuous and squared). Conventional multivariable outcome models were used to adjust for confounders.

†Analyses in the entire sample were adjusted for age (continuous and squared), gender, education (< 10; 10; > 10 years), smoking status (never, former, current), alcohol consumption (0; 0.1–15.0; 15.1–30.0; >30.0 g/day), physical exercise (0, >0 to 2, >2 h/week), body mass index (< 25, 25 to < 30, ≥ 30 kg/m<sup>2</sup>), family history of asthma (yes, no). Gender-stratified analyses were adjusted for the same confounders except for gender. Multivariable RRs for dichotomized exposures were adjusted using propensity score quintiles. RRs for 1 SD increase in neuroticism or extraversion were adjusted using conventional multivariable outcome models.

‡During a period of 5 years prior to the baseline interview.

sex-adjusted mortality risk. Thus, we might possibly have underestimated the magnitude of the true association between neuroticism and incident asthma because of selective survival.

High levels of neuroticism emerged from our analyses as a strong determinant of incident asthma in women and men in both age-adjusted and multivariable analyses. Only one study has previously examined neuroticism and asthma prospectively (16). In age-adjusted, sex-stratified, prospective analyses, Huovinen et al. (16) observed an increased odds ratio (OR) for self-reported asthma for men with high neuroticism vs men with low neuroticism, but the corresponding OR was not increased in women. After adjustment for respiratory symptoms, diseases and hay fever, the positive association observed in men was attenuated.

We observed inconsistent and weak associations between extraversion and asthma. The study by Huovinen et al. (16) suggested that high extraversion increased the odds of incident asthma in women, but not in men. The authors hypothesized that extraversion levels are associated with lifestyle differences in women and that smoking may partly explain the impact of extraversion on incident asthma in women. In our study, many lifestyle-related factors were associated with both extraversion

and neuroticism as well as with asthma suggesting that lifestyles might indeed be intermediate or confounding factors. In sensitivity analyses, we therefore excluded smoking status, alcohol consumption, physical exercise and body mass index from all multivariable models using the same population. However, we obtained very similar results for all exposures indicating that lifestyles are unlikely to explain the associations observed in our study (data not shown).

To our knowledge, only one previous study has examined stressful life events in relation to subsequent onset of asthma in adults who were initially free of asthma: a very large study conducted among individuals involved in the events on 9/11 suggested that those having experienced particularly stressful events had a higher asthma incidence (30). This association was, however, not controlled for potentially confounding variables (e.g. exposure to dust). Further, participants were asked to report new asthma 2–3 years after their exposure; thus, recall bias is possible. Another population-based prospective study revealed that hospital admissions for asthma were not predicted by the number of recent adverse events in adulthood, but by the impact of these life events (31). Our study suggested specific associations between stressful events and the onset of asthma; breaking off a life partnership significantly

increased the risk of asthma in contrast to the death of a close person and job loss. A cross-sectional study among Finnish university students (32) suggested that parental or personal conflicts (including parental divorce, separation from the spouse or severe conflicts in long-term close relationships) tend to increase the odds of asthma irrespective of their timing (before, concurrently or after the diagnosis of asthma). In line with our findings, there was no association between asthma and death or severe disease of a family member experienced prior or concurrently to the diagnosis of asthma. Likewise, a cross-sectional study among Australian men did not observe associations between asthma and unemployment or widowhood, but found a positive relationship between asthma and separation/divorce (33). The authors discussed increases of unhealthy behaviours and the removal of spousal support as a potential explanation. It remains, however, unclear to what extent unhealthy behavioural changes and removal of the partner's support can account for specific patterns of associations (e.g. for the lack of association between the death of a close person and asthma).

The physiological mechanisms by which personality, stress and emotions might influence the development or course of asthma are still not well known. Asthma is now considered to be largely a chronic inflammatory disease of the airways and many studies have linked stress and emotions to inflammatory processes (4, 5). Neuroticism is associated with emotional instability and a predisposition to experience distress (7). As such, persons high on neuroticism may be more exposed to stressful situations and their concomitant alteration of

inflammatory processes. However, evidence exists that the immune consequences differ for acute *vs* chronic stress (34) leading to some studies showing that certain types of stress lead to increases, whereas others lead to decreases in airway inflammation (35). Therefore, additional research is needed to clarify the exact nature of the stressors that are associated with asthma and how personality factors like neuroticism might factor into the equation.

Furthermore, victim-blaming must be avoided. Personality profiles might reflect certain genotypes and might not be modifiable or amenable to intervention. Finally, one should keep in mind that the absolute risk of asthma was very small in our cohort, even if a high susceptibility to stress and certain stressful events predisposed individuals to asthma.

In conclusion, our main findings are that high levels of neuroticism and breaking off a life partnership are independent risk factors for developing asthma. These observations might add to the understanding of the multifactorial aetiology of asthma, which remains to be elucidated.

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