

# Asthma in adults and its association with chronic rhinosinusitis: The GA<sup>2</sup>LEN survey in Europe

D. Jarvis<sup>1</sup>, R. Newson<sup>1</sup>, J. Lotvall<sup>2</sup>, D. Hastan<sup>3</sup>, P. Tomassen<sup>4</sup>, T. Keil<sup>5</sup>, M. Gjomarkaj<sup>6</sup>, B. Forsberg<sup>7</sup>, M. Gunnbjornsdottir<sup>8</sup>, J. Minov<sup>9</sup>, G. Brozek<sup>10</sup>, S. E. Dahlen<sup>11</sup>, E. Toskala<sup>12,13</sup>, M. L. Kowalski<sup>14</sup>, H. Olze<sup>15</sup>, P. Howarth<sup>16</sup>, U. Krämer<sup>17,18</sup>, J. Baelum<sup>19</sup>, C. Loureiro<sup>20</sup>, L. Kasper<sup>21</sup>, P. J. Bousquet<sup>22</sup>, J. Bousquet<sup>22,23</sup>, C. Bachert<sup>4</sup>, W. Fokkens<sup>3</sup> & P. Burney<sup>1</sup>

<sup>1</sup>Imperial College, Respiratory Epidemiology and Public Health Group and MRC-HPA Centre for Environment and Health, London, UK; <sup>2</sup>Krefting Research Institute, University of Goteburg, Goteburg, Sweden; <sup>3</sup>Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; <sup>4</sup>Department of Otorhinolaryngology, Upper Airways Research Laboratory, Ghent University, Ghent, Belgium; <sup>5</sup>Charite University Medical Centre, Institute of Social Medicine, Epidemiology and Health Economics, Berlin, Germany; <sup>6</sup>National Research Council (CNR), Institute of Biomedicine and Molecular Immunology (IBIM), Palermo, Italy; <sup>7</sup>Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine, Umea University, Umea, Sweden; <sup>8</sup>Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden; <sup>9</sup>Institute of Occupational Health of Republic of Macedonia, Skopje, Macedonia; <sup>10</sup>Department of Epidemiology, Medical University of Silesia, Katowice, Poland; <sup>11</sup>The Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; <sup>12</sup>Finnish Institute of Occupational Health, Helsinki and Helsinki University Hospital, Helsinki, Finland; <sup>13</sup>Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; <sup>14</sup>Department of Immunology, Medical University of Lodz, Rheumatology and Allergy Medical, Lodz, Poland; <sup>15</sup>Department of Otorhinolaryngology, Charité- Universitätsmedizin Berlin, Germany; <sup>16</sup>University of Southampton, Southampton, UK; <sup>17</sup>Leibniz Research Institute for Environmental Medicine, University of Düsseldorf, Düsseldorf, Germany; <sup>18</sup>Department of Dermatology and Allergy am Biederstein, Technical University Munich, Munich, Germany; <sup>19</sup>Department of Occupational and Environmental Medicine, Odense University Hospital, Odense, Denmark; <sup>20</sup>Immunology Department, Hospitais da Universidade de Coimbra, Coimbra, Portugal; <sup>21</sup>Division of Thoracoscopy and Bronchoscopy, School of Medicine, Krakow, Jagiellonian University Cracow, Cracow, Poland; <sup>22</sup>Department of Respiratory Diseases University Hospital, Hôpital Arnaud de Villeneuve, Montpellier, France; <sup>23</sup>CESP Centre for Research in Epidemiology and Population Health, Inserm, U1018, Respiratory and Epidemiology team, Villejuif, France

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## Keywords

asthma; chronic rhinosinusitis; epidemiology; GA<sup>2</sup>LEN.

## Correspondence

Dr. Deborah Jarvis, Respiratory Epidemiology and Public Health, Imperial College London, London, UK.  
Tel.: +44 207 352 8121 ext 3510  
Fax: +44 207 351 8322  
E-mail: d.jarvis@imperial.ac.uk

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## Abstract

**Background:** The prevalence of asthma and its association with chronic rhinosinusitis (CRS) have not been widely studied in population-based epidemiological surveys.

**Methods:** The Global Allergy and Asthma Network of Excellence (GA<sup>2</sup>LEN) conducted a postal questionnaire in representative samples of adults living in Europe to assess the presence of asthma and CRS defined by the European Position Paper on Rhinosinusitis and Nasal Polyps. The prevalence of self-reported current asthma by age group was determined. The association of asthma with CRS in each participating centre was assessed using logistic regression analyses, controlling for age, sex and smoking, and the effect estimates were combined using standard methods of meta-analysis.

**Results:** Over 52 000 adults aged 18–75 years and living in 19 centres in 12 countries took part. In most centres, and overall, the reported prevalence of asthma was lower in older adults (adjusted OR for 65–74 years compared with 15–24 years: 0.72; 95% CI: 0.63–0.81). In all centres, there was a strong association of asthma with CRS (adjusted OR: 3.47; 95% CI: 3.20–3.76) at all ages. The association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted OR: 11.85; 95% CI: 10.57–13.17). CRS in the absence of nasal allergies was positively associated with late-onset asthma.

**Conclusion:** Geographical variation in the prevalence of self-reported asthma was observed across Europe, but overall, self-reported asthma was more common in young adults, women and smokers. In all age groups, men and women, and irrespective of smoking behaviour, asthma was also associated with CRS.

In the 1990s, the European Community Respiratory Health Survey (ECRHS) reported substantial geographical variation in the prevalence of asthma in young adults (1) and showed, in both cross-sectional (2) and longitudinal (3) analyses, that asthma was associated with allergic rhinitis. Other studies suggest that other nasal disorders, such as 'sinus troubles' may also be associated with asthma (4). Chronic rhinosinusitis (CRS) is an inflammatory condition of the mucosa of the nose or sinuses and includes conditions in which inflammation of the sinus may occur secondary to an inflammation of the nasal mucosa. Until recently, few epidemiological studies have collected standardized information on CRS.

The Global Allergy and Asthma Network of Excellence (GA<sup>2</sup>LEN) has developed a questionnaire to assess the presence of CRS in epidemiological studies (5), using criteria set out in The European Position Paper on Rhinosinusitis and Nasal Polyps (EP<sup>3</sup>OS) (6). This questionnaire has been included in a multicentre European study in which one of the primary aims was to assess the prevalence of asthma in adults of all ages. A report describing substantial geographical variation in CRS prevalence in Europe using the information collected has been published. (7).

In this report, we aim to (i) describe the prevalence of reported asthma in adults, including older age groups, and (ii) assess the relationship of asthma with CRS. This is important because the generations who have formed part of the 'allergy epidemic' are now ageing, and further information on the pattern of disease in these older age groups is needed for health service planning. Furthermore, there is little epidemiological data in either young or older adults on the association of asthma with CRS.

## Methods

### Survey

The core protocol for the GA<sup>2</sup>LEN survey required participating centres to identify a random sample of at least 3000 adults aged 15–74 years from an available population-based sampling frame. In 2008–2009, potential participants were sent a short questionnaire by mail, and at least three attempts were made to elicit a response. The questionnaire collected information on age, gender, smoking and the presence of symptoms of asthma (including age of onset), CRS and allergic rhinitis.

### Definition of outcomes

Asthma was defined as reporting having ever had asthma AND reporting at least one of the following symptoms in the last 12 months (i) wheeze or whistling in the chest, (ii) waking with chest tightness, (iii) waking with shortness of breath, and (iv) waking with an attack of coughing.

'Current late-onset asthma' was defined as asthma reported to have started at or after the age of 16 ('current early-onset asthma' was reported to have an onset before 16 years of age).

Chronic rhinosinusitis was defined following the EP<sup>3</sup>OS criteria, that is, the presence of at least two of the following symptoms for at least 12 weeks in the past year: (i) nasal blockage, (ii) nasal discharge, (iii) facial pain or pressure or (iv) reduction in sense of smell with *at least one* of the symptoms being nasal blockage or nasal discharge.

Allergic rhinitis was defined as a positive response to the question 'Do you have any nasal allergies or hay fever?'

### Analysis

Prevalences, odds ratios and relative risk ratios were estimated using logistic regression with Huber variances. Sampling probability weights were used to standardize prevalences by gender and 5-year age group (15–19 to 70–74) to a European Standard Population.

Odds ratios for asthma with respect to gender, 10-year age group and smoking status (current smoker, ex-smoker and lifetime nonsmoker) were assessed in each centre using two logistic regression models, one with these factors only and the other with additional information on smoking, measured as pack-years. In this latter adjustment, the odds ratios for 25 and 50 pack-years were determined, assuming the effects of other exposure levels to be interpolated quadratically, using the spline method (8).

Odds ratios for asthma with respect to CRS were estimated in all subjects, lifetime nonsmokers smokers only, men, women, and 20-year age groups (15–34, 35–54 and 55–74) with adjustments as appropriate for gender, 10-year age group, smoking status, and pack-years.

Relative risk ratios for early-onset and late-onset asthma with CRS only, nasal allergies only, or both conditions were estimated using multinomial logistic regression models, with no asthma as the baseline outcome level with adjustments similar to above.

For all analyses, centre effect estimates were averaged using geometric mean odds ratios weighted by sample number. Heterogeneity between centres was measured using Wald chi-squared tests and the I-squared (9). The potential influence of nonresponse on prevalence estimates was assessed as previously described (7). All analyses were conducted in Stata Version 11 (10).

## Results

### Response

Twenty-five centres (15 countries) took part in the survey. Centres in Munich, Oslo and Athens (all participants <30 years old) and three in Russia (not population based) were excluded as they did not follow the full protocol. This report presents information from 19 centres (12 countries).

Table 1 shows the response rate and the crude prevalence of asthma, CRS and allergic rhinitis in each participating centre. Response rates varied from centre to centre with no consistent evidence that those with asthma or allergic rhinitis replied earlier than those without these conditions (Somers' D  $P > 0.05$ ). As reported earlier (7), there was limited evidence

**Table 1** Response rate and prevalence of asthma, chronic rhinosinusitis and allergic rhinitis (directly standardized to European Standard Population) in all participants by centre

| Country     | Centre      | Responded and provided information on date of birth and gender |      | Median age (IQR) | % male | % smoke | Prevalence (%) asthma | Prevalence (%) asthma (lifetime nonsmokers only) | Prevalence (%) chronic rhinosinusitis by EP3OS criteria | Prevalence (%) allergic rhinitis |
|-------------|-------------|----------------------------------------------------------------|------|------------------|--------|---------|-----------------------|--------------------------------------------------|---------------------------------------------------------|----------------------------------|
|             |             | n/N                                                            | Rate |                  |        |         |                       |                                                  |                                                         |                                  |
| Sweden      | Gothenburg  | 8619/15000                                                     | 57.5 | 42.9 (29.8–57.7) | 44.9   | 16.1    | 7.1                   | 6.3                                              | 8.2                                                     | 26.5                             |
|             | Stockholm   | 5887/10000                                                     | 58.9 | 43.1 (31.2–57.4) | 45.8   | 16.7    | 8.6                   | 7.8                                              | 9.6                                                     | 28.9                             |
|             | Umea        | 6055/10000                                                     | 60.5 | 42.6 (28.0–57.8) | 46.0   | 9.8     | 11.2                  | 10.9                                             | 8.1                                                     | 25.8                             |
| Finland     | Uppsala     | 6114/10000                                                     | 61.1 | 43.2 (29.0–58.1) | 45.0   | 13.0    | 9.5                   | 9.0                                              | 8.6                                                     | 27.6                             |
|             | Helsinki    | 1809/5510                                                      | 32.8 | 41.0 (28.5–58.5) | 47.3   | 26.4    | 7.8                   | 7.9                                              | 6.9                                                     | 39.9                             |
|             | Odense      | 3340/5000                                                      | 66.8 | 46.6 (34.0–59.2) | 46.9   | 26.2    | 8.6                   | 7.7                                              | 7.8                                                     | 26.1                             |
| Denmark     | Katowice    | 2672/6000                                                      | 44.5 | 44.8 (29.5–58.0) | 45.9   | 30.8    | 5.2                   | 3.9                                              | 17.3                                                    | 33.4                             |
|             | Krakow      | 1267/5000                                                      | 25.3 | 44.9 (29.2–58.6) | 41.4   | 23.5    | 7.1                   | 7.8                                              | 19.7                                                    | 41.6                             |
|             | Lodz        | 1772/5000                                                      | 35.4 | 48.8 (31.4–59.0) | 44.6   | 27.6    | 6.0                   | 5.0                                              | 14.4                                                    | 36.2                             |
| UK          | London      | 1825/5000                                                      | 36.5 | 45.8 (35.3–57.7) | 41.7   | 17.2    | 11.4                  | 11.4                                             | 10.0                                                    | 33.5                             |
|             | Southampton | 1191/5000                                                      | 23.8 | 50.0 (37.1–61.3) | 43.2   | 20.4    | 14.2                  | 11.8                                             | 11.2                                                    | 32.7                             |
|             | Amsterdam   | 3191/5000                                                      | 63.8 | 48.8 (37.4–59.6) | 45.3   | 20.7    | 6.4                   | 5.5                                              | 14.3                                                    | 28.4                             |
| Netherlands | Ghent       | 1851/5029                                                      | 36.8 | 44.9 (31.3–57.2) | 45.9   | 23.9    | 7.6                   | 7.5                                              | 18.8                                                    | 27.5                             |
|             | Brandenburg | 2252/5552                                                      | 40.8 | 48.2 (37.6–61.2) | 44.2   | 25.3    | 6.3                   | 6.8                                              | 6.9                                                     | 22.6                             |
|             | Duisburg    | 1158/5000                                                      | 23.2 | 47.6 (35.5–61.0) | 45.7   | 28.7    | 10.1                  | 9.6                                              | 14.1                                                    | 29.6                             |
| France      | Montpellier | 1385/5000                                                      | 27.7 | 47.9 (34.2–58.3) | 41.3   | 22.8    | 10.3                  | 8.8                                              | 13.3                                                    | 43.9                             |
|             | Skopje      | 3613/4500                                                      | 80.3 | 39.4 (25.7–52.9) | 46.0   | 37.8    | 5.1                   | 5.0                                              | 8.2                                                     | 41.3                             |
| Macedonia   | Palermo     | 965/2500                                                       | 38.6 | 39.3 (27.9–51.8) | 37.2   | 23.2    | 10.7                  | 10.8                                             | 10.9                                                    | 27.0                             |
|             | Italy       | 2162/4877                                                      | 44.3 | 43.0 (32.1–57.2) | 40.1   | 14.6    | 16.8                  | 16.8                                             | 27.1                                                    | 32.9                             |
| Portugal    | Coimbra     | 57128/118968                                                   | 48.0 | 44.4 (30.6–57.9) | 44.8   | 20.1    | 8.5                   | 8.2                                              | 10.9                                                    | 30.4                             |

that those with CRS tended to respond later than those without CRS in some centres.

### Prevalence of asthma

Standardized to a European population, the prevalence of asthma varied substantially between centres (5.2% in Katowice, Poland to 16.8% in Coimbra, Portugal) (Fig. 1). The median prevalence of asthma in the 19 centres was 8.6% in Stockholm, Sweden. Centres that had a 'high' prevalence of asthma (the lower limit of the 95% confidence interval excluded 8.6%) were Umea, Uppsala, London, Southampton, Palermo and Coimbra. Centres with a 'low' prevalence of asthma (the upper limit of the 95% confidence interval excluded 8.6%) were Gothenburg, Katowice, Lodz, Amsterdam, Brandenburg and Skopje. A similar pattern of geographical variation was seen when the sample was restricted to lifetime nonsmokers (Table 1).

Overall, asthma was less common in older age groups than younger age groups (Table 2), but this was not seen in all centres (Fig. 2). In the oldest age group (65–74 years), the prevalence of asthma was 7.6%, with substantial variation between countries (Gothenburg, Sweden: 4.7%, 95% CI: 3.6%–6.2%; Coimbra, Portugal 13.8%, 95% CI: 10.3–18.3%; Southampton, UK 13.8%, 95% CI: 9.6%–19.4%). Of note, asthma was more common in older than younger subjects in Skopje, Macedonia, the three Polish centres and in Helsinki, Finland (Fig. 2). The prevalence of asthma was consistently higher in females than males in all centres within the study (Table 2).

Asthma was reported more frequently by current smokers than nonsmokers (Table 2) and was associated with cumulative tobacco use (adjusted OR for asthma comparing 50 pack-years of smoking with none: 1.22; 95% CI: 1.01–1.48).

There was substantial variation in the direction and strength of this association between centres largely because of the low number of heavy smokers in some centres. Ex-smokers had more asthma than lifetime nonsmokers (OR 1.25 95% 1.15–1.36).

### Asthma and CRS

In all centres, asthma was strongly and consistently associated with CRS (Fig. S1 – shows country-specific estimates of the association), with some variation in the strength of these positive associations (overall OR: 3.48; 95% CI: 3.21–3.77; test for heterogeneity  $P = 0.001$ ). Asthma was associated with CRS in men, in women and in all age groups (Table 3), even in analyses restricted to lifetime nonsmokers. In lifetime nonsmokers, the strength of the association was greater in men than women (difference in association by gender  $P = 0.001$ ), there was no evidence that the association varied by age (difference in association by age group  $P = 0.72$ ).

### Asthma and CRS and nasal allergies

Overall, 56.7% of those reporting symptoms that fulfilled the EP<sup>3</sup>OS criteria for CRS also reported 'hay fever or nasal allergies'.

Compared with those who had neither CRS nor allergic rhinitis, asthma was more common in those with CRS only (adjusted OR: 2.71; 95% CI: 2.30–3.20) and nasal allergies only (adjusted OR: 5.72; 95% CI: 5.27–6.21). However, participants who reported both CRS and nasal allergies were even more likely to report asthma (adjusted OR: 11.85; 95% CI: 10.57–13.17). This overall pattern was seen in all centres, although there was variation in the strength of the estimates.

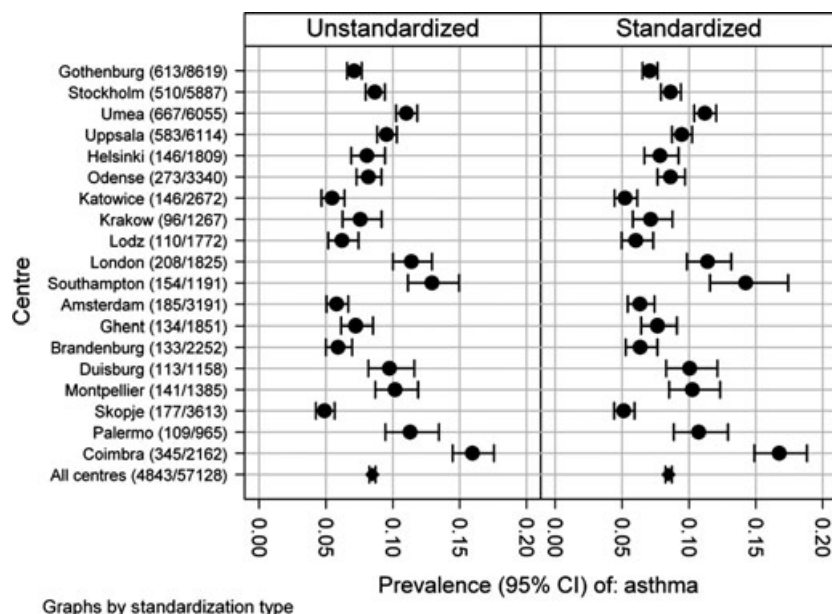
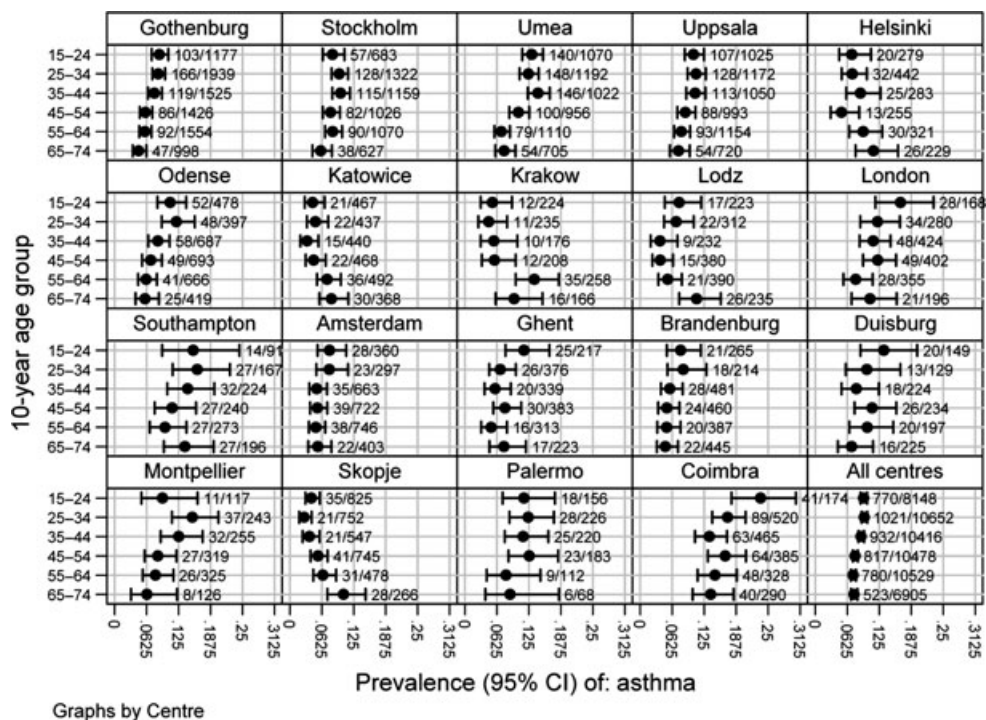


**Figure 1** The prevalence of asthma in each centre unstandardized and standardized to the European population (95% confidence intervals).

**Table 2** The mutually adjusted weighted geometric mean odds ratios of asthma for gender, age and smoking

|                               |             |                                                            | Model 2 (adjusted as for Model 1 plus pack-years of smoking) |                                         |        |
|-------------------------------|-------------|------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------|--------|
|                               |             | Model 1 (adjusted for age, gender and smoking status only) |                                                              | Tests for heterogeneity of associations |        |
| Risk factor                   | Cases/total | OR (95% CI)                                                | OR (95% CI)                                                  | $\chi^2$                                | $P$    |
| Gender                        |             |                                                            |                                                              |                                         |        |
| Male                          | 1780/23701  | 1.00                                                       | 1.00                                                         |                                         |        |
| Female                        | 2780/29484  | 1.26 (1.18, 1.34)                                          | 1.28 (1.20, 1.37)                                            | 0                                       | 0.77   |
| 10-year age group             |             |                                                            |                                                              |                                         |        |
| 15–24                         | 749/7910    | 1.00                                                       | 1.00                                                         |                                         |        |
| 25–34                         | 975/10161   | 0.93 (0.84, 1.04)                                          | 0.93 (0.83, 1.03)                                            | 0                                       | 0.69   |
| 35–44                         | 882/9786    | 0.84 (0.75, 0.94)                                          | 0.82 (0.73, 0.92)                                            | 40.9                                    | 0.033  |
| 45–54                         | 764/9604    | 0.73 (0.66, 0.82)                                          | 0.71 (0.63, 0.80)                                            | 0                                       | 0.79   |
| 55–64                         | 713/9509    | 0.70 (0.62, 0.78)                                          | 0.66 (0.59, 0.75)                                            | 40.3                                    | 0.036  |
| 65–74                         | 477/6215    | 0.72 (0.63, 0.81)                                          | 0.68 (0.60, 0.78)                                            | 29.6                                    | 0.11   |
| Smoking status                |             |                                                            |                                                              |                                         |        |
| Never                         | 2652/31556  | 1.00 (ref)                                                 | 1.00                                                         |                                         |        |
| Ex                            | 998/10758   | 1.25 (1.15, 1.36)                                          | 1.17 (1.05, 1.31)                                            | 30.4                                    | 0.1    |
| Current                       | 910/10871   | 1.16 (1.07, 1.26)                                          | 1.04 (0.93, 1.16)                                            | 35.9                                    | 0.061  |
| Smoking exposure (pack-years) |             |                                                            |                                                              |                                         |        |
|                               | 25          | NI                                                         | 1.18 (1.04, 1.33)                                            | 35.6                                    | 0.063  |
|                               | 50          | NI                                                         | 1.22 (1.01, 1.48)                                            | 69.1                                    | <0.001 |

NI, not included in the analysis.

**Figure 2** The prevalence of asthma by 10-year age group and centre.

About 49.5% of those with asthma reported that their disease began after the age of 16. CRS was strongly associated with both early-onset and late-onset asthma (RRR: 2.93;

95% CI: 2.59–3.32 and RRR: 3.85; 95% CI: 3.45–4.30, respectively). In Fig. 3(a,b), we show the results from the multinomial regression in which we examine the association

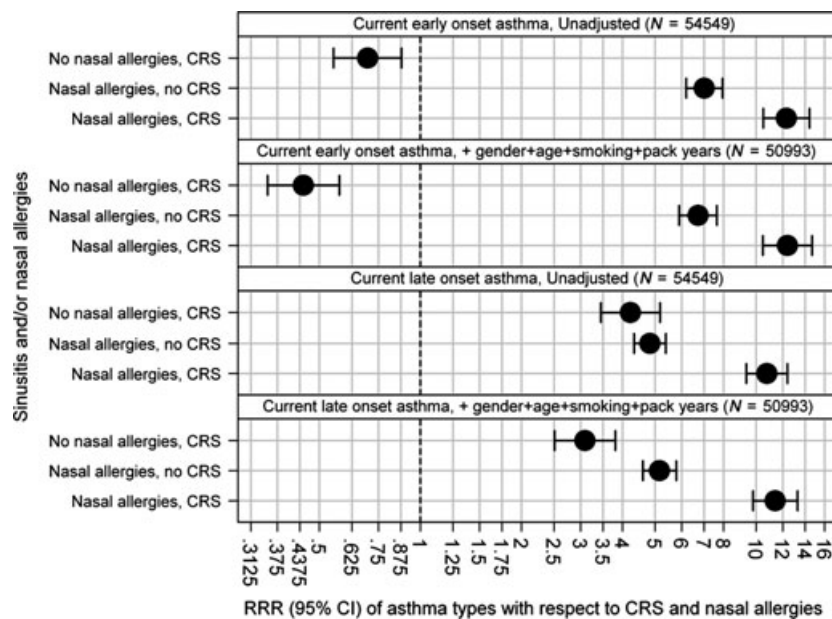
**Table 3** The adjusted odds ratio for asthma with chronic rhinosinusitis by gender and age in whole sample and restricted to lifetime non-smokers

|              | Whole sample unadjusted | Whole sample (adjusted*) | Test for heterogeneity |       | Lifetime nonsmokers only (adjusted†) | Test for heterogeneity |          |
|--------------|-------------------------|--------------------------|------------------------|-------|--------------------------------------|------------------------|----------|
|              |                         |                          | $\chi^2$               | P     |                                      | $\chi^2$               | P        |
| All subjects | 3.54                    | 3.48 (3.21–3.77)         | 57.4                   | 0.001 | 3.62 (3.24–4.04)                     | 52.0                   | 0.005    |
| Males        | 4.02                    | 4.12 (3.63–4.67)         | 39.4                   | 0.04  | 4.53 (3.81–5.38)                     | 28.6                   | 0.12     |
| Females      | 3.23                    | 3.12 (2.81–3.47)         | 37.0                   | 0.054 | 3.10 (2.68–3.59)                     | 19.8                   | 0.21     |
| 15–34        | 3.01                    | 2.91 (2.53–3.35)         | 0                      | 0.59  | 3.14 (2.64–3.74)                     | 0                      | 0.58     |
| 35–54        | 3.60                    | 3.58 (3.13–4.09)         | 16.0                   | 0.26  | 3.49 (2.86–4.25)                     | 21.9                   | 0.19     |
| 55+          | 4.04                    | 4.08 (3.47–4.79)         | 41.8                   | 0.029 | 3.41 (2.64–4.42)                     | 74.6                   | <0.0001‡ |

\*Adjusted age, gender, smoking and pack-years of smoking as appropriate.

†Adjusted for age and gender only.

‡Heterogeneity largely explained by OR of 0 in Palermo related to low sample size.

**Figure 3** The association (relative risk ratio with 95% confidence interval) of early- and late-onset asthma with chronic rhinosinusitis

only, nasal allergies only and CRS with nasal allergies.

of CRS only, nasal allergies only and CRS and nasal allergies with both early-onset asthma and late-onset asthma. Those with CRS only (compared with those who have neither CRS nor nasal allergies) report less early-onset asthma (RRR: 0.45; 95% CI: 0.35–0.57) but more late-onset asthma (RRR: 3.09; 95% CI: 2.51–3.81). The other combinations (nasal allergies only, nasal allergies plus CRS) are both positively associated with both early- and late-onset asthma.

## Discussion

This large multicentre European survey conducted in young, middle-aged and older adults shows wide variations in the prevalence of asthma. As in previous studies, the prevalence was high in the UK (1) and low in areas of the former Soviet

Block (11), which in this survey included sites in Poland, Macedonia and the former East Germany (Brandenburg). Unlike previous studies (1), the prevalence of asthma in Southern Europe (Italy and Portugal) was not lower than in other parts of Europe.

Asthma was more common among younger participants. This is likely to reflect the increase in atopy and asthma that has occurred between generations (12–14) and is notably absent from the countries of Eastern Europe where the prevalence of asthma is still relatively low. However, asthma was not more common among the younger participants in Finland, a country in which generational increases in atopy and asthma have been well documented (15, 16) over the last twenty years.

We found strong and independent associations between asthma and both allergic rhinitis and chronic rhinosinusitis.

These associations were consistent across all centres. An association between asthma and 'nasal allergies or hay fever'(3) and 'hay fever' (17, 18) has been found in longitudinal studies, but this is not entirely explained by a common association with atopy as it also occurs in those with no sensitization to common aeroallergens (3, 19).

Our study is the first general population survey that has shown the association of asthma with chronic rhinosinusitis using symptoms proposed by EP<sup>3</sup>OS to define the nasal disorder rather than reported diagnoses. Compared with asking about diagnosed sinusitis, this approach has been shown to give at least as valid an indication of the presence of rhinosinusitis as confirmed by nasal endoscopy (5). Reported symptoms have the advantage of not being dependent on local health service practice and local use of diagnostic terms and are more appropriate for surveys, particularly when these are multicentre or, as in this case, multinational. Of the studies that have used physician diagnosis of disease, the Tucson longitudinal study has shown that chronic cough with wheeze is associated with doctor-diagnosed 'sinus trouble' (20) in children, and has shown a greater incidence of adult-onset asthma among those who reported 'blocked or stuffy nose in the absence of a cold' with physician diagnosed 'sinus troubles'(4).

We recognize that allergic rhinitis and CRS coexist, that the former may lead to the latter and that 'chronic rhinosinusitis', like 'asthma' reflects several phenotypes. Even though both rhinitis and sinus disease are associated with asthma, a review of patients with asthma taking part in trials of asthma therapy suggested that it was the co-existence of chronic rhinosinusitis, not allergic rhinitis, that was associated with lower asthma-related quality of life (21).

We found that chronic rhinosinusitis without allergic rhinitis was associated positively with adult-onset asthma and negatively with childhood-onset asthma. As with all studies that rely on recall there may be misclassification of the reported age at which asthma first began with a proportion classifying their disease as adult-onset when, in fact, they had symptoms in childhood (22). This could result in overestimation of the association of adult-onset disease with CRS and underestimation for childhood-onset disease. Our results are compatible with a small clinical study of adults with asthma in which all those who recalled their asthma beginning before the age of 16 (but not those with adult-onset asthma) reported they had asthma before they developed sinusitis (23) Chronic rhinosinusitis with polyps has been specifically associated with asthma (24, 25). We have no direct information on polyps, but we did ask about loss of smell, a symptom strongly associated with polyposis (26). We found a much stronger association of asthma with 'CRS with loss of smell' (OR: 4.25; 95% CI: 3.74–4.71) than of asthma with 'CRS without a loss of a sense of smell' (OR: 2.88; 95% CI: 2.59–3.21) (*P*-value for the difference < 0.0001).

Response to the survey varied between centres and is only modest in some sites. Response bias is more likely to affect

estimates of prevalence than estimates of association, but we found little evidence that nonresponse influenced the prevalence of CRS (7) and no evidence that late responders to the survey were more or less likely to report a history of nasal allergies or asthma. It is unlikely that the strong associations of asthma with chronic rhinosinusitis arose as a result of low response rates.

The associations we have observed are supported by clinical studies demonstrating that CRS is prevalent in those with severe asthma (27, 28) and a Swedish community-based study in which nasal blockage and rhinorrhea were more common in asthmatics with multiple respiratory symptoms than in those who reported few symptoms (29). These associations have been interpreted as chronic rhinosinusitis causing asthma because of the release of inflammatory mediators and cytokines from the diseased sinus tissue into the circulation (30) and recruitment of eosinophils into both upper and lower airways from the bone marrow and circulation (31). It has also been shown that Th2-biased eosinophilic inflammation within the sinuses may be amplified by the presence of Staphylococcal superantigens inducing polyclonal T-cell activation and local IgE formation (25, 32).

In summary, this large international survey has shown a wide variation in the prevalence of asthma across Europe and has shown a lower prevalence in the older age group, except in the former Soviet states and Finland. It has shown strong and independent associations between asthma and both rhinitis and chronic rhino-sinusitis. Better understanding of these conditions and their interdependence may lead to better management.

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### Author contributions

PB, WF, CB and J Bousquet developed the overall study design and the instruments that were used. RN conducted the statistical analysis. DJ wrote the manuscript. All authors were directly involved in the study design, data collection and data quality checks in their local centre. All authors contributed to the final manuscript.

### Conflict of interests

All authors have declared no conflict of interests.

## Supporting Information

Additional Supporting Information may be found in the online version of this article found at: <http://www.wileyonlinelibrary.com>

**Figure S1.** The adjusted association (OR plus 95% CI) of asthma with chronic rhinosinusitis in each participating centre.

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## References

- European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;**9**:687–695.
- Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;**113**:86–93.
- Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008;**372**:1049–1057.
- Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;**109**:419–425.
- Tomassen P, Newson R, Hoffmans R, Lotvall J, Cardell L, Gunnbjørndottir M et al. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis – a GA<sup>2</sup>LEN study. *Allergy* 2010;**66**:556–561.
- Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007;**20**:1–136.
- Hastan D, Fokkens W, Bachert C, Newson R, Bislimovska J, Bockelbrink A et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA<sup>2</sup>LEN study. *Allergy* 2011. in press (doi:10.1111/j.1398-9995.2011.02646.x).
- Newson R. B-splines and splines parameterized by their values at reference points on the x axis. *Stata Technical Bulletin* 2000;**57**:20–27.
- Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558.
- StataCorp. Stata [Computer Program]. College Station, Texas: StataCorp, 2009.
- von Mutius E, Martinez FD, Fritsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149**:358–364.
- Sunyer J, Anto JM, Tobias A, Burney P. Generational increase of self-reported first attack of asthma in fifteen industrialized countries. European Community Respiratory Health Study (ECRHS). *Eur Respir J* 1999;**14**:885–891.
- Law M, Morris JK, Wald N, Luczynska C, Burney P. Changes in atopy over a quarter of a century, based on cross sectional data at three time periods. *BMJ* 2005;**330**:1187–1188.
- Jarvis D, Luczynska C, Chinn S, Potts J, Sunyer J, Janson C et al. Change in prevalence of IgE sensitisation and mean total IgE by age and cohort. *J Allergy Clin Immunol* 2005;**116**:675–682.
- Haahtela T, Lindholm H, Bjorksten F, Koskenvuo K, Laitinen LA. Prevalence of asthma in Finnish young men. *BMJ* 1990;**301**:266–268.
- Kosunen TU, Hook-Nikanne J, Salomaa A, Sarna S, Aromaa A, Haahtela T. Increase of allergen-specific immunoglobulin E antibodies from 1973 to 1994 in a Finnish population and a possible relationship to *Helicobacter pylori* infections. *Clin Exp Allergy* 2002;**32**:373–378.
- Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax* 1992;**47**:537–542.
- Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women in the Finnish Twin Cohort from 1975 to 1990, and their relation to hayfever and chronic bronchitis. *Chest* 1999;**115**:928–936.
- Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects. *J Allergy Clin Immunol* 1999;**104**:301–304.
- Sherrill DL, Guerra S, Cristina Minervini M, Wright AL, Martinez FD. The relation of rhinitis to recurrent cough and wheezing: a longitudinal study. *Respir Med* 2005;**99**:1377–1385.
- Dixon A, Kaminsky D, Holbrook J, Wise R, Shade D, Irvin C. Allergic rhinitis and sinusitis in asthma. *Chest* 2006;**130**:429–435.
- Burgess J, Walters EH, Byrnes G, Wharton C, Jenkins M, Abramson M et al. Who remembers whether they had asthma as children? *J Asthma* 2006;**43**:727–730.
- Matsuno O, Ono E, Takenaka R, Okubo T, Takatani K, Ueno T et al. Asthma and sinusitis: association and implication. *Int Arch Allergy Immunol* 2008;**147**:52–58.
- Litvack J, Fing K, Mace J, James K, Smith T. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. *Laryngoscope* 2008;**118**:2225–2230.
- Bachert C, Zhang N, Holtappels G, De Lobel L, van Cauwenberge P, Liu S et al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with co-morbid asthma. *J Allergy Clin Immunol* 2010;**126**:962–968.
- Vento S, Ertama L, Hytonen M, Wolff C, Malmberg C. Nasal polyposis: clinical course during 20 years. *Ann Allergy Asthma Immunol* 2000;**65**:209–214.
- ten Brinke A, Grootendorst S, Schmidt J, de Bruine F, van Buchem N, Sterk P et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;**109**:621–626.
- ten Brinke A, Sterk P, Masclee A, Spinhoven P, Schmidt J, Zwiderman AH et al. Risk factors of frequent exacerbations in difficult to treat asthma. *Eur Respir J* 2005;**26**:812–818.
- Lotvall J, Ekerljung L, Lundback B. Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis – evidence from the West Sweden Asthma Study. *Respir Res* 2010;**11**:163.
- Braunstaal G, Fokkens W. Nasal involvement in allergic asthma. *Allergy* 2003;**58**:1235–1243.
- Wolley M, Denburg J, Ellis R, Dahlback M, O'Byrne P. Allergen-induced changes in bone marrow progenitors and airway responsiveness in dogs and the effect of inhaled budesonide on these parameters. *Am J Resp Cell Mol Biol* 1994;**11**:600–606.
- Tomassen P, van Zele T, Zhang N, Perez-Novo C, van Bruaene N, Gevaert P. Pathophysiology of chronic rhinosinusitis. *Proc Am Thorac Soc* 2011;**8**:115–120.

## On-line repository

**Figure E1. The adjusted association (OR plus 95% CI) of asthma with chronic rhinosinusitis in each participating centre.**

Note: Positive association in all centres, with variation in the strength of the association (overall OR 3.48 95% CI 3.21-3.77; test for heterogeneity  $p=0.001$ )

