Asthma-COPD Overlap Syndrome (ACOS) among Subjects with Newly Diagnosed Adult-Onset Asthma

To the Editor:

An emerging topic in clinical research of obstructive lung diseases has been the rather recent recognition of the asthma COPD overlap syndrome, shortened as ACOS (1). There are several questions still unanswered concerning this newly recognized diagnostic entity. The clinical and functional data of ACOS patients do not seem to correspond well with the similar features in patients with asthma or COPD alone (1). In addition, the occurrence of ACOS in many parts of the world is still unknown. Furthermore, ACOS patients seem to have a different clinical evolution compared to the patients with either asthma or COPD alone (2). Thus, further research is needed to identify factors that determine the clinical characteristics as well as prognosis of ACOS.

We estimated the prevalence of ACOS among newly-diagnosed adult-onset asthma patients in Southern Finland, and assessed personal, behavioral and hereditary determinants of ACOS among asthma patients. The study population constituted 521 newly-diagnosed asthma patients from The Finnish Environmental and Asthma Study (FEAS), a population-based incident case–control study of adult-onset asthma among working-aged population (3). Information was based on an extensive questionnaire, standardized clinical examination, and spirometry. The asthma patient was defined to have ACOS if his/her spirometry showed persistent airflow obstruction with a post-bronchodilator FEV1/FVC less than 70% of predicted (see Online Supporting Information: Methods).

The prevalence of ACOS among adults with newly diagnosed asthma was 6.6% (95% confidence interval, CI 4.2-9.1%). Following the case definition, the ACOS cases had considerably lower pre- and post-bronchodilator FEV_1 and FEV_1/FVC levels than the asthma-only cases (Table 1).

In Poisson regression, adjusting for potential confounding, the ACOS cases were older (adjusted Prevalence Ratio [PR]: 3.22; 95% CI 1.39-7.47), more often men (2.63; 1.14-6.07), had lower level of education (1.36; 0.56-3.30), and were more often current (7.91; 2.25-27.81) or former smokers (3.23; 0.81-12.87) than the asthma-only cases (Table 2). Allergic diseases, especially allergic rhinitis, were less common among the ACOS cases than among the asthma-only cases (Table 2). Correspondingly, allergic diseases showed a protective effect for ACOS in the Poisson regression model. Allergic symptoms were consistently less common among the ACOS cases than among the asthma-only cases (Table 2). Having additionally other respiratory diseases was more common among the ACOS cases than among the asthma-only cases (Table 2). In unadjusted models, having these other diseases strongly increased the risk of ACOS, but in the models adjusting for age, gender, education, and smoking status, these effects were statistically non-significant. Chronic respiratory symptoms, including breathlessness, wheezing, mucus production, and cough, were slightly less common among the ACOS cases compared to the asthma-only cases, with the exception of mucus production (Table 2). Of respiratory symptoms, breathlessness, wheezing and cough associated with a lower, but statistically non-significant, risk for ACOS compared to the risk for asthma-only cases. The ACOS cases showed or reported less often any positive allergy findings in skin prick tests or in Phadiatop analysis. In contrast, we found no difference in total IgE levels between the two groups. Similarly, the allergic symptoms, positive skin prick test results or positive Phadiatop test results associated with a lower, statistically non-significant risk of ACOS compared to the asthma-only cases. Parental asthma and especially siblings having asthma, was more common among the ACOS cases than among the asthma-only cases, while parental allergy and siblings having allergy-only (i.e. they did not have asthma) were less common among the ACOS cases (Table 2). In the Poisson regression models, familial asthma was related to an increased risk of ACOS, while the tendency for a protective effect related to a relative's allergy was limited to parental allergy.

We defined ACOS cases from the asthma cases based on spirometry findings rather than self-reported history. Besides, we did not define smoking history as an inclusion criterion, nor did we exclude patients who had comorbidities. There are clearly fewer studies focusing on asthma patients having ACOS features compared to studies on COPD patients who have ACOS components (4). Another Finnish study reported the prevalence of ACOS among subjects with asthma in primary care and elaborated smoking history as a determinant of ACOS. Age of the individual and the cumulative amount of cigarette smoking were reported as determinants of ACOS (5). A cross-sectional population-based study in the US provided evidence that among adults with a history of asthma, active manifestations of asthma may play an important role in the development of COPD (6). By quitting smoking and obtaining good asthma control, asthma patients may have a lower risk of developing COPD. There are also studies suggesting that patients with ACOS generate nearly double the health care costs compared to patients with asthma without COPD, and the coexistence of features of COPD in elderly asthmatics worsen asthma control (7). COPD and asthma are heterogeneous diseases and patients may be atopic and hyperresponsive in both diseases (8). Previous studies have shown that ACOS patients defined by a self-report of asthma and COPD were two times more likely to report allergic rhinitis compared with individuals who had COPD only (9). However, there is scarce literature investigating the effect of family history of asthma and allergic diseases on ACOS among asthmatic patients. To the best of our knowledge, our research is the first population-based study, which elaborates the role of heredity of asthma and allergies for ACOS among asthmatics. Moreover, we present the role of allergic symptoms and markers of allergy for ACOS among subjects with adult-onset asthma.

There is still no generally agreed definition for ACOS. Because of this, the prevalence of ACOS is very variable in studies applying different criteria and investigating different populations. Thus, there is a need to conduct further studies to identify clinically important characteristics of the ACOS patients. Such information will help us to make progress in preventing and treating ACOS.

Furthermore, this information may be valuable when aiming at cutting the medical expenses related to asthma and ACOS. Prevention of smoking and facilitating stopping smoking protects asthmatic subjects from developing ACOS.

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Key words:
allergy; asthma; asthma-COPD overlap syndrome (ACOS); COPD; smoking

Abbreviations:

ACOS, asthma-COPD overlap syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEAS, Finnish Environment and Asthma Study; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; PR, prevalence ratio; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile

Table 1 Distribution of lung function parametes among patients with asthma only and ACOS.

Patient Characteristics	Asthma-only Median (Q1-Q3)	ACOS Median (Q1-Q3)	P value [a]
Subjects N	365	26	NA
Pre-bronchodilator			
FEV_1 L	3.01 (2.48-3.65)	1.56 (1.25-2.11)	<0.0001
FVC L	3.99 (3.37-4.79)	3.56 (3.00-3.86)	0.005
FEV_1/FVC	0.76 (0.70-0.82)	0.50 (0.42-0.55)	<0.0001
Post-bronchodilator			
FEV_1 L	3.24 (2.74-3.84)	1.87 (1.55-2.37)	<0.0001
FVC L	4.10 (3.47-4.89)	3.74 (3.20-4.49)	0.205
FEV_1/FVC	0.80 (0.74-0.85)	0.54 (0.45-0.57)	<0.0001
Reversibility [b]			
FEV_1 mL	190.0 (100.0-360.0)	250.0 (180.0-380.0)	0.153
FVC mL	70.0 (-30.0 to 210.0)	380.0 (140.0-620.0)	<0.0001

Definition of abbreviations: ACOS, Asthma-COPD overlap syndrome; FEV_1, Forced expiratory volume in 1 s; FVC, Forced vital capacity, Q1, 1st quartile; Q3, 3rd quartile

[a] Wilcoxon-Mann-Whitney test

[b] Difference between post-bronchodilator value and pre-bronchodilator value

Table 2. Determinants of ACOS among subjects with adult-onset asthma.

Determinant	Asthma-only n (%)	ACOS n (%)	Unadjusted model PR (95% CI)	Adjusted model [a] PR (95% CI)
Subjects N	365	26	NA	NA
Age, years				
Median (Q1-Q3)	42.0 (30.0-51.0)	53.0 (48.0-60.0)	NA	NA
20-29 years	87 (23.8%)	0 (0.0%)	ref	ref
30-39 years	80 (21.9%)	2 (7.7%)		
40-49 years	85 (23.3%)	7 (26.9%)		
≥50 years	113 (31.0%)	17 (65.4%)	3.79 (1.69-8.51)	3.22 (1.39-7.47)
Male sex	121 (33.2%)	17 (65.4%)	3.46 (1.54-7.77)	2.63 (1.14-6.07)
Education				
University or college	127 (34.8%)	7 (26.9%)	ref	ref
Vocational institution	109 (29.9%)	1 (3.9%)	0.17 (0.02-1.41)	0.12 (0.01-0.98)
Other	129 (35.3%)	18 (69.2%)	2.34 (0.98-5.61)	1.36 (0.56-3.30)
Smoking [b]				
Never	180 (49.6%)	3 (11.5%)	ref	ref
Former	83 (22.9%)	7 (26.9%)	4.74 (1.23-18.35)	3.23 (0.81-12.87)
Current	100 (27.6%)	16 (61.5%)	8.41 (2.45-28.88)	7.91 (2.25-27.81)
Allergic diseases				
Allergic rhinitis including Hay fever [c]	148 (40.6%)	5 (19.2%)	0.37 (0.14-0.98)	0.70 (0.25-1.96)
Allergic conjunctivitis [c]	90 (24.7%)	4 (15.4%)	0.57 (0.20-1.67)	0.75 (0.26-2.23)
Allergic dermatitis [c]	151 (41.4%)	7 (26.9%)	0.54 (0.23-1.29)	0.71 (0.29-1.72)
Any of the previous three allergic diseases [c]	225 (61.6%)	9 (34.6%)	0.36 (0.16-0.80)	0.53 (0.23-1.21)
Diagnosed hypersensitivity to painkillers	39 (10.7%)	1 (3.9%)	0.35 (0.05-2.59)	0.50 (0.06-3.83)
Other respiratory diseases				
Chronic bronchitis ever	103 (28.2%)	15 (57.7%)	3.15 (1.45-6.87)	1.71 (0.73-4.02)
Pulmonary emphysema	7 (1.9%)	5 (19.2%)	7.52 (2.84-19.94)	2.50 (0.89-7.05)
Bronchiectasis	5 (1.4%)	4 (15.4%)	7.72 (2.66-22.39)	2.70 (0.85-8.54)

Chronic respiratory symptoms [d]				
Breathlessness	328 (89.9%)	21 (80.8%)	0.51 (0.19-1.34)	0.48 (0.17-1.31)
Wheezing	310 (84.9%)	20 (76.9%)	0.62 (0.25-1.53)	0.71 (0.28-1.79)
Mucus production [e]	267 (73.2%)	19 (73.1%)	1.00 (0.42-2.37)	0.96 (0.40-2.30)
Cough [e]	252 (69.0%)	15 (57.7%)	0.63 (0.29-1.38)	0.58 (0.26-1.30)
Skin symptoms [e]	176 (48.2%)	10 (38.5%)	0.69 (0.31-1.52)	0.68 (0.29-1.51)
Nasal symptoms [e]	285 (78.1%)	17 (65.4%)	0.56 (0.25-1.25)	0.83 (0.35-1.97)
Eye symptoms [e]	178 (48.8%)	9 (34.6%)	0.58 (0.26-1.30)	0.68 (0.29-1.55)
Throat symptoms [e]	242 (66.3%)	15 (57.7%)	0.71 (0.33-1.55)	0.96 (0.42-2.20)
Self-reported allergy test results				
All negative	182 (49.9%)	17 (65.4%)	ref	ref
1-2 positive	88 (24.1%)	5 (19.2%)	0.63 (0.23-1.71)	0.88 (0.32-2.41)
≥ 3 positive	95 (26.0%)	4 (15.4%)	0.47 (0.16 to 1.41)	0.84 (0.26-2.66)
any positive	183 (50.1%)	9 (34.6%)	0.55 (0.24-1.23)	0.86 (0.37-1.99)
Skin prick tests [f]				
All negative	126 (46.0%)	9 (69.2%)	ref	ref
1-2 positive	58 (21.2%)	3 (23.1%)	0.74 (0.20-2.72)	1.16 (0.31-4.39)
≥ 3 positive	90 (32.9%)	1 (7.7%)	0.16 (0.02-1.30)	0.30 (0.04-2.50)
any positive	148 (54.0%)	4 (30.8%)	0.39 (0.12-1.28)	0.70 (0.21-2.33)
Phadiatop [g]				
Negative	187 (54.5%)	16 (72.7%)	ref	ref
1-2 positive	54 (15.7%)	4 (18.2%)	0.88 (0.29-2.62)	0.98 (0.32-2.98)
≥ 3 positive	102 (29.7%)	2 (9.1%)	0.24 (0.06-1.06)	0.45 (0.10-2.06)
any positive	156 (45.5%)	6 (27.3%)	0.47 (0.18-1.20)	0.71 (0.27-1.87)
Total IgE [h, i]				
Median (Q1-Q3), kU/L	77.1 (29.3-213.0)	70.9 (22.5-207.0)	NA	NA
Q1 (≤16 kU/L)	43 (12.5%)	3 (13.6%)	ref	ref
Q2 (16-39.1 kU/L)	62 (18.1%)	6 (27.3%)	1.35 (0.33-5.41)	2.07 (0.51-8.39)
Q3 (>39.1 to <107 kU/L)	100 (29.2%)	4 (18.2%)	0.59 (0.13-2.64)	0.81 (0.18-3.65)
Q4 (≥ 107 kU/L)	138 (40.2%)	9 (40.9%)	0.94 (0.25-3.47)	1.25 (0.33-4.67)
Parental asthma [j]	81 (24.4%)	8 (34.8%)	1.59 (0.68-3.76)	2.12 (0.86-5.22)
Parental allergy [j]	85 (25.6%)	3 (13.0%)	0.46 (0.14-1.53)	0.77 (0.22-2.69)

Parental asthma or allergy [j]				
no	204 (61.5%)	14 (60.9%)	ref	ref
asthma only	43 (13.0%)	6 (26.1%)	1.91 (0.73-4.96)	2.72 (0.95-7.74)
allergy only	47 (14.2%)	1 (4.4%)	0.32 (0.04-2.47)	0.74 (0.09-5.91)
both	38 (11.5%)	2 (8.7%)	0.77 (0.18-3.43)	1.21 (0.26-5.56)
Sibling history of asthma [k]	47 (19.3%)	9 (60.0%)	5.44 (1.94-15.28)	2.81 (0.94-8.39)
Sibling allergy [k]	103 (42.2%)	8 (53.3%)	1.52 (0.55-4.20)	1.55 (0.56-4.34)
Sibling asthma or allergy [k]				
no	127 (52.1%)	4 (26.7%)	ref	ref
asthma only	14 (5.7%)	3 (20.0%)	5.78 (1.29-25.82)	2.67 (0.56-12.79)
allergy only	70 (28.7%)	2 (13.3%)	0.91 (0.17-4.97)	1.13 (0.20-6.31)
both	33 (13.5%)	6 (40.0%)	5.04 (1.42-17.85)	3.04 (0.82-11.23)

Definition of abbreviations: ACOS, Asthma-COPD overlap syndrome; CI, Confidence interval; kU, kilo Units; PR, prevalence ratio; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile

[a] Adjusted for age, sex, education and smoking

[b] Smoking missing for 2 cases with asthma-only

[c] Either during the past 12 months or over 12 months ago

[d] During past 12 months

[e] Prolonged or recurrent

[f] Skin prick tests missing for 91 cases with asthma-only and for 13 cases with ACOS. Those with test missing were included in the Poisson regression as their own category

[g] Phadiatop missing for 22 cases with asthma-only and for 4 cases with ACOS. Those with test missing were not included in the X^2-test of distribution but were included in the Poisson regression as their own category

[h] Quartiles are based on Jaakkola et al. 2006 [15]

[i] Total IgE missing for 22 cases with asthma only and for 4 cases with ACOS. Those with test missing were not included in the X^2-test of distribution but were included in the Poisson regression as their own category

[j] Parental asthma and allergy missing for 33 cases with asthma only and for 3 cases with ACOS

[k] Includes 244 cases with-asthma only and 15 cases with ACOS, that have reported having siblings

Online Supporting Information: Asthma-COPD Overlap Syndrome (ACOS) among Subjects with Newly Diagnosed Adult-Onset Asthma

Online methods

Study design

The design of the original study was a population-based incident case–control study of adult-onset asthma (1). We recruited all the new cases of asthma and population-based controls aged 21–63 years living in a geographically defined area, the Pirkanmaa Hospital District in Southwest Finland (2-11). The study was approved by the ethics committees of the Finnish Institute of Occupational Health and the Tampere University Hospital. All participants gave an informed consent for the study.

Study population

From September 1997 to March 2000, a total of 521 new cases (response rate 86%) of adult-onset asthma were recruited. Their diagnosis was based on extensive lung function measurements in combination with reporting of asthma symptoms. We checked through the medical records of the Pirkanmaa Hospital District to verify that these subjects had not had any previous diagnosis of asthma. We also checked with the help of their Social Insurance card (i.e. the KELA card) that they had not previously received the reimbursement right for asthma medication. These new cases of asthma were recruited through all health care facilities diagnosing asthma in the study area. In addition, The Social Insurance Institute of Finland (KELA) invited to our study those new asthmatics who had not yet been identified by our above-mentioned extensive recruitment system, but who were identified in a computer search of the KELA files listing new reimbursement rights for asthma medications in the study area. Only those with no previously diagnosed asthma or long-term use of any asthma medication were included in the study. In the current phase of this study, we defined the ACOS utilizing original spirometry results of these newly diagnosed asthma patients.

Questionnaire

Symptoms were inquired applying the following questions: “Have you had recurrent or prolonged (for over a month) cough during the past year (12 months)?”, “Have you had prolonged or recurrent mucus production from the lungs during the past year (12 months)? (Mucus from the nose is not included here.)”, “Has your breathing wheezed during the past year (12 months)? (We mean wheezing that comes from the bronchi, not the nose.)”, “Have you had breathlessness during the past year (12 months)?” “Have you had, during the past year (12 months), recurrent or prolonged nasal symptoms at times other than in connection with a common cold?”, “Have you had, during the past year (12 months), recurrent or prolonged eye symptoms at times other than in connection with a common cold?”, “Have you had, during the past year (12 months), recurrent or prolonged throat symptoms at times other than in connection with a common cold or tonsillitis?”, “Have you had prolonged or recurrent skin symptoms during the past year (12 months)?”, “Have you had recurrent or prolonged headache during the past year (12 months)?”, “Have you had recurrent or prolonged fatigue (nonspecific tiredness) during the past year (12 months)?”. For these questions, the participants could answer either “yes” or “no”. For inquiring allergies and doctor-diagnosed diseases, we used the following questions: “Have you ever had allergic rhinitis (for example hay fever) diagnosed by a doctor?”, “Have you ever had conjunctivitis (allergic eye inflammation) diagnosed by a doctor?”, “Have you ever had allergic dermatitis (skin problems) diagnosed by a doctor?”, “Have you ever had chronic bronchitis diagnosed by a doctor?”, “Do you have pulmonary emphysema diagnosed by a doctor?”, “Do you have

bronchiectasis diagnosed by a doctor?", "Do you have heart disease diagnosed by a doctor?", and "Do you have a diagnosed hypersensitivity to painkillers?". For the questions regarding allergic rhinitis, conjunctivitis, allergic dermatitis, and chronic bronchitis, the participants were asked to choose one of the following options: "yes, during the past 12 months", "yes, over 12 months ago only", and "no, never". For the questions regarding pulmonary emphysema, bronchiectasis, heart disease and hypersensitivity to painkillers, the participants could answer either "yes" or "no".

Measurement methods

At the time of recruitment, the study subjects answered a self-administered questionnaire, modified from the Helsinki Office Environment Study questionnaire (12, 13), for use in a general population (2-11). The questionnaire inquired about personal characteristics, health information (including respiratory symptoms and previous respiratory and allergic diseases), smoking status, and information on several exposures. The questions related to smoking and family history of asthma and allergies have been described elsewhere (5-7). The questions that inquired about symptoms and doctor-diagnosed diseases are presented above. Measurement of total IgE and Phadiatop (i.e. specific IgE antibodies) have been described previously (14). Phadiatop tested potential sensitivity to birch, timothy-grass, ragweed, cat, dog, horse, *Dermatophagoides pteronyssinus* and *Aspergillus fumigatus*. In addition, specific IgE antibodies were measured to test potential sensitivity to mites *Dermatophagoides pteronyssinus* and *Acarus Siro* and to molds *Aspergillus fumigatus*, *Cladosporium cladosporioides*, *Mucor racemosus*, *Penicillium notatum*, *Phoma betae* and *Strachybotrus Atra*. In addition, we used results from routine skin Prick tests to characterize sensitivity to various other allergens from food, animals, plants, yeasts, molds, mites and chemicals.

Lung function measurements

The diagnostic protocol for asthma, applied to all patients with potential asthma, included (i) reporting of occurrence of at least one asthmatic symptom, and (ii) demonstration of reversibility in airways obstruction in lung function measurements. The criteria has been displayed in previous reports (2-3). The spirometry and bronchodilation test were performed with a Medicro pneumotachygraph spirometer connected to a computer (Medikro 905; Medikro, Kuopio, Finland) according to the standards of the American Thoracic Society (15). Altogether 487 cases performed spirometry, and post-bronchodilator measurements were available for 391 (80.3%) of them.

FEV_1/FVC models and definition of ACOS

There is still no generally agreed definition for ACOS. ACOS criteria or definition utilized varied in different studies. It is generally accepted that ACOS patients who demonstrate both an asthma component and a COPD component. In this study, the asthma patient was defined to have ACOS if his/her spirometry showed persistent airflow obstruction with a post-bronchodilator FEV1/FVC less than 70% of predicted (16, 17-19). We used our own definition of ACOS, because it was meaningful for elaborating how asthmatics subjects with and without the main feature of COPD (chronic irreversible airflow limitation) differ. The purpose was neither to challenge nor endorse the GINA/GOLD description nor to create new diagnostic criteria for ACO overlap/ACOS.

To calculate the predicted FEV_1/FVC values, we fitted two separate reference models, one based on pre-bronchodilator FEV_1/FVC values and the other on post-bronchodilator FEV_1/FVC values. Pre-bronchodilator values have commonly used to define the presences of COPD and ACOS in studies that did not conduct bronchodilator tests and therefor did not have post-bronchodilator

values (20, 21).

Although post-bronchodilator values are more appropriate for the assessment of irreversible bronchial obstruction, we fitted both values in order to compare the results. We used never-smoking controls of the FEAS study to calculate the reference values, since they best represent the source population for the asthma-only and the ACOS cases. Separate linear regression models were fitted for men (n=49) and women (n=89). The models included age and height as covariates. Based on these reference models, we then calculated the predicted FEV_1/FVC values for both the asthma-only and the ACOS cases as follows:

1. predicted FEV_1/FVC based on **pre-**bronchodilator values:

   a. predicted FEV_1/FVC for men = 1.34631 - 0.00003273 * AGE (years) - 0.00292 * Height (cm)

   b. predicted FEV_1/FVC for women = 1.13360 - 0.00093847 * AGE (years) - 0.00144 * Height (cm).

2. predicted FEV_1/FVC based on **post-**bronchodilator values:

   a. predicted FEV_1/FVC for men = 1.09745 + 0.00025350 * AGE (years) - 0.00147* Height (cm)

   b. predicted FEV_1/FVC for women = 1.10826 - 0.00117 * AGE (years) - 0.00110 * Height (cm)

We then calculated the percent predicted FEV_1/FVC for each subject as the ratio of the **measured post-**bronchodilator FEV_1/FVC to the predicted (either based on pre-bronchodilator values or post-bronchodilator values) FEV_1/FVC *100.

We then defined ACOS as having the FEV_1/FVC < 70% of the predicted. Using the prediction model based on the post-bronchodilator values of the never-smoking controls resulted in altogether 26 cases with ACOS and 365 cases with asthma-only. This definition was selected as the primary one since COPD is usually defined in clinical practice based on post-bronchodilator values, as pre-bronchodilator values cannot distinguish between reversible (typical for asthma) and irreversible (typical for COPD) obstruction. Using the prediction model based on pre-bronchodilator values among the never-smoking controls resulted in 21 cases with ACOS and 370 cases with asthma-only, data not shown.

Statistical methods

The aims of the analyses were to estimate the occurrence of ACOS among newly diagnosed adult-onset asthma cases, to characterize and compare the ACOS and asthma only patients, and to assess the determinants of ACOS. First, we estimated the prevalence rate of ACOS and its 95% confidence interval from the binomial distribution. Second, we compared differences in the characteristics of ACOS and asthma-only patients applying the Mann-Whitney U test and the chi square test. Third, we assessed the determinants of ACOS using the prevalence ratio (PR) as a measure of effect and association. PRs were estimated by fitting unadjusted and adjusted Poisson regressions applying SAS procedure GENMOD, with logarithmic link function. We applied LSMEANS-statement to obtain the relative risk estimates and their 95% confidence intervals (CI). If a PR could not be estimated using the GENMOD-procedure, because of a small number of individuals in a category, we used 2 x 2 tabulation with logit estimation and a correction of 0.5 for the cell containing zero to obtain the crude relative risk and its 95% CI. We adjusted for gender, age, education (as an indicator for socioeconomic status), and personal smoking status (never, former, or current) in the multivariate analyses. We applied SAS statistical package v.9.4 (SAS Institute Inc., Cary, NC, USA) for statistical analyses.

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