Received Date : 24-Jan-2016

Revised Date : 18-May-2016

Accepted Date : 24-May-2016

Article type : Original Article: Epidemiology and Genetics

Respiratory Hypersensitivity Reactions to NSAIDs in Europe: The Global Allergy and Asthma Network (GA^{2}LEN) Survey.

Authors

Joanna S. Makowska , Department of Immunology, Rheumatology and Allergy, Medical University of Łódź, Poland; joanna.makowska@umed.lodz.pl

Peter Burney Department of Respiratory Epidemiology and Public health, Imperial College, London, UK p.burney@imperial.ac.uk

Debbie Jarvis, Department of Respiratory Epidemiology and Public health, Imperial College, London, UK; d.jarvis@imperial.ac.uk

Thomas Keil, Institute for Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany Thomas.keil@charite.de

Peter Tomassen Upper Airways Research Laboratory, Department of Otorhinolaryngology and Logopaedic-Audiologic Science, Ghent University, Ghent, Belgium peter.tomassen@ugent.be

J. Bislimovska, Institute for Occupational Health of R. Macedonia, University "Sts Cyril and Methodius" Skopje, Skopje, Macedonia; bislimovska_j@yahoo.com

Grzegorz Brozek, Department of Epidemiology, Faculty of Medicine, Medical University of Silesia, Katowice, Poland; brozekg@poczta.onet.pl

Claus Bachert, Upper Airways Research Laboratory, Department of Otorhinolaryngology and Logopaedic-Audiologic Science, Ghent University, Ghent, Belgium; claus.bachert@ugent.be

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.12941
This article is protected by copyright. All rights reserved.

Accepted Article

Jesper Baelum Department of Otorhinolaryngology and Occupational and Environmental Medicine, Odense University Hospital, Odense, Denmark jesper.baelum@ouh.regionsyddanmark.de

Carsten Bindslev-Jensen, Department of Otorhinolaryngology and Occupational and Environmental Medicine, Odense University Hospital, Odense, Denmark; Carsten.bindslev-jensen@ouh.regionsyddanmark.de

Jean Bousquet, Department of Respiratory Medicine, Montpellier University, Montpellier, France jean.bousquet@orange.fr

Philippe J. Bousquet, Department of Respiratory Medicine, Montpellier University, Montpellier, France philippejeanbousquet@wanadoo.fr

Carlsen Kai-Håkon, Oslo, Norway, h.h.carlsen@medisin.uio.no

Sven Eric Dahlen, Department of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden sven-eric.dahlen@ki.se

Barbro Dahlen Unit of Heart and Lung Diseases, Karolinska Institutet, Stockholm, Sweden Barbro.Dahlen@ki.se

Wytske J. Fokkens, Department of Otorhinolaryngology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; w.j.fokkens@amc.uva.nl

Bertil Forsberg, Department of Public Health and Clinical Medicine, Umea University, Umea, Sweden bertil.forsberg@envmed.umu.se

Mark Gjomarkaj, Department of Respiratory Medicine, Institute of Biomedicine and Molecular Immunology, Palermo, Italy; gjomarkaj@ibim.cnr.it

Peter Howarth, E. Salagean, Department of Respiratory Cell and Molecular Biology, University of Southampton, Southampton, UK; P.H.Howarth@soton.ac.uk

Christer Janson, Department of Medical Sciences: Respiratory, Allergy and Sleep Research Uppsala University Uppsla,Sweden christer.janson@medsci.uu.se

Lukas Kasper, Department of Internal Medicine, Jagiellonian University Krakow, Krakow, Poland; lukasz.kasper@uj.edu.pl

Ursula Kraemer, Environmental Health Research Institute, Heinrich Heine University, Dusseldorf, and Department of Dermatology and Allergy, Technical University Munich, Munich, Germany; Ursula.kraemer@uni-duesseldorf.de

Carlos Louiro , Department of Immunology and Allergology, University Hospital Coimbra, Coimbra, Portugal; acnl@sapo.pt

Bo Lundback, Krefting Research Centre, University of Gothenburg, Gothenburg, Sweden; bo.lundback@gu.se

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

Jordan Minov Occupational Health of RM, University ''Sts Cyril and Methodius'' Skopje, Macedonia minovj@hotmail.com

Ewa Nizankowska-Mogilnicka, Department of Internal Medicine, Jagiellonian University Krakow, Krakow, Poland; ewan@mp.pl

***Nikos Papadopoulos**, Athens, Greece Allergy Dept, 2nd Paediatric Clinic, University of Athens, Greece* npg@allergy.gr

Alexandros G. Sakellariou, Athens, Greece, Allergy Department, University of Athens, fallen.ate@gmail.com

Ana Todo-Bom, Department of Immunology and Allergology, University Hospital Coimbra, Coimbra, Portugal; flcosta@netcabo.pt

Elina Toskala, Department of Otorhinolaryngology and Finnish Institute of Occupational Health, Helsinki University Hospital, Helsinki, Finland, now working at Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia,USA; ToskalaE@email.chop.deu

Jan E Zejda, Department of Epidemiology, Faculty of Medicine, Medical University of Silesia, Katowice, Poland jzejda@sum.edu.pl

Torsten Zuberbier, Department of Dermatology and Allergy, Charite´-Universitahtsmedizin Berlin, Berlin, Germany torsten.zuberbier@charite.de

Marek L. Kowalski, Department of Immunology, Rheumatology and Allergy, Medical University of Łódź, Poland marek.kowalski@umed.lodz.pl

Abstract (249)

Background: Non-steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most prevalent drugs inducing hypersensitivity reactions. The aim of this analysis was to estimate the prevalence of NSAIDs-induced respiratory symptoms in population across Europe and to assess its association with upper and lower respiratory tract disorders.

Methods: The GA^{2}LEN survey was conducted in 22 centers in 15 European countries. Each of 19 centers selected random samples of 5000 adults aged 15-74 from their general population, and in three centers (Athens, Munich, Oslo) a younger population was sampled. Questionnaires including questions about age, gender, presence of symptoms of asthma, allergic rhinitis, chronic rhinosinusitis, smoking status and history of NSAIDs-induced hypersensitivity reactions were sent to participants by mail. Total 62, 737 participants completed the questionnaires.

This article is protected by copyright. All rights reserved.

Results: The mean prevalence of NSAIDs-induced dyspnea was 1.9% and was highest in the three Polish centers [Katowice (4.9%), Krakow (4.8%) and Lodz (4.4%)] and lowest in Skopje, (0.9%), Amsterdam (1.1%) and Umea (1.2%). In multivariate analysis, the prevalence of respiratory reactions to NSAIDs was higher in participants with chronic rhinosinusitis symptoms (Odds Ratio 2.12; 95%CI 1.78-2.74), asthma symptoms in last 12 months (2.7; 2.18-3.35), hospitalization due to asthma (1.53; 1.22-1.99), and adults vs children (1.53; 1.24-1.89), but was not associated with allergic rhinitis.

Conclusion: Our study documented significant variation between European countries in the prevalence of NSAIDs-induced respiratory hypersensitivity reactions, and association with chronic airway diseases, but also with environmental factors.

Abbreviations: NSAIDs- non-steroidal anti-inflammatory drugs, NERD- NSAIDs Exacerbated Respiratory Disease, CRS chronic rhinosinusitis, NIRHR- NSAIDs-induced respiratory hypersensitivity reaction, EPOS-European Position Paper on Rhinosinusitis and Nasal Polyps

Introduction

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently consumed drugs and hypersensitivity to NSAIDs has been reported to be the most prevalent (1-3) or second only to antibiotics (4). According to the recent classification, five subtypes of NSAIDs hypersensitivity can be distinguished of which only the first type (NSAID-Exacerbated Respiratory Disease; NERD) is manifested by dyspnea, resulting from acute bronchial obstruction (5-7). Typically NERD patients suffer from preexisting chronic disease of lower (asthma) and upper airways (rhinosinusitis), often complicated by nasal polyps. In patients with the type II (NSAID Exacerbated Cutaneous Disease), type III (NSAIDs- Induced Urticaria/Angioedema) and type IV (Single NSAIDs- Induced Urticaria/Angioedema/Anaphylaxis), dyspnea is not common and is usually of upper airway origin, related to the occurrence of laryngioedema. It is worth noting that in some patients mixed reactions including e.g. both respiratory and skin symptoms may occur.

Most studies published earlier assessed the prevalence of aspirin/NSAIDs-induced respiratory symptoms in selected populations of asthmatics and/or patients with chronic rhinosinusitis (CRS), which is compatible with the diagnosis of type I hypersensitivity (NERD), previously called “aspirin triad” (9-13). Prevalence of respiratory type of

This article is protected by copyright. All rights reserved.

Accepted Article

hypersensitivity to NSAIDs depended on the population sampled: was higher among patients with asthma (14-16), patients with rhinosinusitis and nasal polyposis (13, 14, 17) and seemed to be more prevalent among more severe asthmatics (18-20). Only few studies analyzed prevalence of NSAIDs-induced hypersensitivity in the general population, and these recruited patients only in single countries (15, 21, 22).

In this study we aimed to assess the prevalence of respiratory symptoms after NSAIDs intake as well analyze associated conditions and risk factors in randomly selected samples of the general population from 15 European countries.

Methods

Study design and setting

The GA^{2}LEN survey was a cross-sectional study conducted in 22 centers across Europe in 2008-2009 as previously described (23). In 19 centers random samples of 5000 adults aged 15-74 were selected from the general population, whereas in three centers (Athens, Greece; Munich, Germany; Oslo, Norway) a younger population was sampled (aged 13 to 25). In all, but four centers the samples were selected by random from registries of inhabitants in certain administrative area. In two centers (Skopje, Palermo) study participants were drawn by random from the GPs registries, in two from pediatric database (Oslo, Athens) and in other center (Munich) the population was from previous study SOLAR. The sampling frame and response rates in each center were provided in the Annex (table). A questionnaire including questions about age, gender, presence of symptoms of asthma, allergic rhinitis, CRS, smoking status was written in English, and then translated to local languages. Questionnaire translation incorporated 3 stages: forward translation (from English into local language(s)), backward translation (comparison and any necessary editing) and optional local population testing (including subjects with asthma, and/or allergies, and/or sinusitis, and/or rhinitis).The questionnaire was sent to participants by mail and at least 3 attempts were made to elicit a response. Response rates varied from 25% in Krakow to 80% in Skopje. The study was approved by the relevant local ethics committees in all participating centers.

Definition of outcomes

NSAIDs-induced respiratory hypersensitivity reaction (NIRHR) was defined as a positive answer to the question “Have you ever had difficulty with breathing within 3 hours of taking a painkiller?“. Asthma was defined as a history of ever having asthma and reporting at least one of the following symptoms in the last 12 months: wheeze or whistling in the chest,

This article is protected by copyright. All rights reserved.

Accepted Article

waking with chest tightness, waking with shortness of breath and waking with an attack of coughing, as previously reported (23). CRS was defined based on EPOS criteria (24) that is on presence of at least two of the following symptoms for at least 12 weeks in past year: nasal blockage, nasal discharge, facial pain or pressure and reduction in sense of smell with at least one of the symptoms being nasal blockage or nasal discharge. Allergic rhinitis was defined based on a positive answer to the question "Do you have any nasal allergies or hay fever".

Statistical analysis

Sampling probability weights were used to standardize prevalence by gender and 5-year age group (starting from 15–19) to a European Standard Population. Associations of a range of potential risk factors with NSAIDs induced respiratory hypersensitivity reaction (NIRHR) were assessed by logistic regression. First, logistic regression was used to assess the relationship between dependent variables and each of the independent variables (presented in table 2). A stepwise forward procedure was then used to select variables. Predictors with p-levels of at least 0.1 estimated in univariate models were included into multivariate regression analyses. Covariates defined in multivariate model were test for multicollinearity. The variance inflation factor (*VIF*), defined as $VIF=1/(1-R^2_i)$ in an auxiliary regression was used as regression diagnostic for multicollinearity; $VIF>10$ was arbitrary defined as evidence for multicollinearity. Finally covariates defined in multivariate model were checked for potential confounding by centers. Overall effects (ORs) were weighted for sample size per center using meta-analysis and heterogeneity estimates (Wald chi-squared tests and the I-squared). The potential influence of nonresponse on prevalence estimates was assessed as previously described (7). Chi square test was used to determine whether there was significant difference between prevalence of asthmatic, nasal symptoms and smoking in patients with and without NIRHR. For assessment of correlation Spearman Test was used. To compare NIRHR group and controls not reporting NIRHR T –student test was applied. All of the statistical analyses were performed using StatSoft Statistica for Windows, release 8.0 (StatSoft, Inc., Tulsa, USA). The null hypothesis was rejected if $p<0.05$.

Results

Prevalence of NSAIDs-induced hypersensitivity reactions

This study included data from 22 centers in 13 countries with the total number of 62,737 participants completing the questionnaires. The general characteristics of the populations studied are presented in table 1 showing the prevalence of NSAIDs-Induced hypersensitivity respiratory reactions (NIRHR), asthma, nasal allergies and CRS.

This article is protected by copyright. All rights reserved.

Accepted Article

The overall mean prevalence of dyspnea reported after NSAID ingestion was 1.94% in sampled adult populations (**Figure 1**). The prevalence varied substantially between centers and was highest in the three Polish centers: Katowice (4.9%), Krakow (4.8%) and Lodz (4.4%) and lowest in Skopje (0.9%), Amsterdam (1.1%) and Umea (1.2%). Prevalence of NIRHR was studied in three centers which included teenagers and younger adults. Although the prevalence of NIRHR in Oslo and Munich (LMU) was lower among younger population than among adults (0.5% and 0.7%), prevalence of NIRHR among children in the Greek capital Athens was 4.9%, identical with the highest observed among the adults in Katowice.

Participants reporting NIRHR were older (mean age 45.8 vs 42.9; p<0.001) and more likely to be female (67.1% vs 54.1%; p<0.001), than those not reporting NIRHR. The prevalence of NIRHR was highest in age group 45-65 years old (2.3%) although this age group did not have the highest prevalence of asthma or CRS (**Table 1**). This age group did have the highest prevalence of ever smoking (55%). An intermediate prevalence of NIRHR was observed among those above 65 years old (1.9%) and the lowest among younger participants (1.6%) (p<0.001). The prevalence of respiratory symptoms after NSAIDs ingestion in females was almost double that in males (2.4% vs 1.3%; p<0.001)(**Table 1**).

Association of NSAIDs-induced respiratory hypersensitivity reactions with smoking

The prevalence of NIRHR was higher among ever smokers compared to never smokers (2.4 vs 1.5%; p<0.001). Participants reporting NIRHR were more likely to be current smokers (28.4% vs 19.5%; p=0.005) and lifetime smokers (54.1% vs 43.3%; p<0.001). Amongst smokers the age of starting smoking was slightly higher in NIRHR group (17 vs 16; p=0.003). The median pack years of smoking were significantly higher in NIRHR group (13.9 vs 11.0; p<0.001).

Association of NSAIDs-induced respiratory hypersensitivity reactions with chronic airway disorders

Asthma

The prevalence of asthma in the NIRHR group was four-fold higher compared to participants not reporting NIRHR (29.9% vs 7.1%; p<0.001). Three times more subjects in the group of NIRHR reported that they ever had asthma (34.2% vs 10.7%; p<0.001) and five times more subjects were ever hospitalized for asthma. Asthma severity and control appeared different in participants with and without NIRHR. Participants with NIRHR were hospitalized more often for asthma (11.8% vs 2.4%; p<0.001), had current asthma symptoms (within last 12 months) more often(22% vs 3.4%; p<0.001) and were more frequently taking medications for

This article is protected by copyright. All rights reserved.

Accepted Article

asthma (26.1 vs 5.6%; p<0.001). In this group late onset asthma prevailed: the mean onset of asthmatic symptoms was 20 years in subjects with reported reaction to NSAID compared to 13 years in NSAIDs-tolerant subjects; p<0.001).

Nasal symptoms

In general, study participants with NIRHR had more often nasal symptoms suggesting more frequent chronic nasal pathologies. Problems with any nasal allergies were reported by more than half of all subjects with NIRHR but only by one third of those who reported not to have NIRHR (52.7% vs 29.3%; p <0.001), and nasal allergic symptoms occurring during the last 12 months were also more frequent (49.9% vs 25.5%) in the group with NSAID intolerance. Three times more participants from the NIRHR group fulfilled the criteria of chronic rhinosinusitis (32.7% vs 10%; p<0.001).The sense of smell, which was also included in CRS definition, was reduced in 22.8% of subjects with NIRHR as compared to 7.2% of those not reporting NIRHR (p<0.001).

Coexistence of NIRHR, asthma and chronic rhinosinusitis

Although one third of NIRHR patients had asthma or chronic rhinosinusitis, only 15% of them presented with the typical “aspirin triad” i.e. coexistence of NSAIDs hypersensitivity, asthma and chronic rhinosinusitis. Half of NIRHR subjects (52%) had neither asthma nor chronic rhinosinusitis.

In centers recruiting adults prevalence of NIRHR correlated with the prevalence of chronic rhinosinusitis (R=0.56; p<0.05) and with prevalence of any nasal allergies (R=0.59; p<0.01), but did not correlate with asthma prevalence (r=0.15; p=0.53) or prevalence of lifetime smoking (R=0.39, p=0.09).

Risk of NIRHR and respiratory comorbidities

To further assess associations of NIRHR with the presence of chronic inflammatory airway disorders, the association of NIHRR with asthma and chronic rhinosinusitis was examined in univariable and multivariable logistic regression analyses. Results from the univariate analysis is shown in Table 2. In univariate analysis we found the increased risk of NIRHR in patients with asthma [OR =5.50 (4.84-6.26)], chronic rhinosinusitis [OR= 4.28 (3.78-4.84)], older age (adults vs adolescents [OR=1.53 (1.24-1.89)] but also with ever smoking [OR 1.62 (1.45-1.82)], and female gender [OR 1.68 (1.49-1.90)] (**Table 2**). In multivariate analysis independent associations of NIRHR with chronic rhinosinusitis OR=2.12 (1.78-2.74), current asthma symptoms OR= 2.7 (2.18-3.35), and hospitalization due to asthma ever OR= 1.53 (1.22-1.99)(**Figure 2**) were observed. **Figure 3** presents overall effects (ORs) of: late

This article is protected by copyright. All rights reserved.

Accepted Article

asthma onset, hospitalization due to asthma ever, asthma attack in the last 12 months, presence of chronic rhino-sinusitis on NSAIDs induced respiratory hypersensitivity reaction (NIRHR) assessed in each centre.

Discussion

This is the first study describing the prevalence of perceived respiratory type of hypersensitivity to NSAIDs in the large sample (62,737 participants) of general European population, thus showing the magnitude of the problem, which may be a challenge to the health care systems across Europe. Overall 1.9% of participants in the survey reported problems with breathing after ingestion of NSAIDs, but the prevalence varied between centers. Our study confirmed previously reported associations of the occurrence of NIRHR with chronic rhinosinusitis and bronchial asthma. Furthermore, we showed a strong association with asthma severity and control and with smoking.

In most previous studies the prevalence of dyspnea induced by NSAIDs was assessed in patients with asthma, rhinosinusitis and/or nasal polyps, and those studies which assessed such prevalence in general population were performed only in a single country (1, 4, 14). In the study from Portugal 1.9% of subjects declared hypersensitivity reactions to NSAIDs (with different clinical patterns), but only 0.2% presented dyspnea and 0.3% reported symptoms from the upper respiratory tract (4). The prevalence of self-reported drug reactions among Brazilian students was as high as 12% and NSAIDs were responsible for almost half of these reactions (1). In this study respiratory symptoms after the intake of NSAIDs were reported by 2.3% of students, a prevalence very similar to that in our survey. In general Finnish population sample, prevalence of aspirin hypersensitivity causing shortness of breath was 1.2%, but in Helsinki was twice as high (2.6%). Thus, our survey confirms in large European population, significant population burden of adverse respiratory reactions to NSAIDs reported previously in epidemiological studies from single countries (14, 15, 20, 21).

Wide regional differences in the prevalence of NSAIDs hypersensitivity in Europe were reported in our study, with reactions being almost 5 times more frequent in the Polish center at Katowice (4.9%) as in Skopje in Macedonia (0.9%), however no consistent north-south or west-east gradient was observed. Three centers (Athens, Oslo and Munich) surveyed only a younger population up to 25 years of age, and in two of those centers (Oslo and Munich) the prevalence was low, which is in agreement with previous studies reporting lower prevalence of NSAIDs hypersensitivity in among children and adolescent (25, 26). However, the prevalence among young subjects in Athens was 10% of the sampled population, which requires further investigation. Although in most of the cases ENDA classification of NSAIDs hypersensitivity can be applied to children, other phenotypes of reactions were observed in

This article is protected by copyright. All rights reserved.

Accepted Article

specifically in younger population (27). Regional differences in the prevalence reported in this study may reflect true differences in the prevalence of NSAIDs hypersensitivity related to e.g. local genetic background, or environmental factors .Since we did not have access to data on the country of birth of participants we cannot comment on the effect of ethnicity. However, the effects of environmental factors or differences in the perception and/or local specificity in reporting of drug-induced respiratory symptoms could not be excluded (28). Cities in which the prevalence of NIRHR was highest – Krakow and Katowice are among the most polluted cities in Europe (28), thus, it is likely, that environmental pollution might affect the development of hypersensitive reactions to NSAIDs or alternatively the prevalence of respiratory symptoms associated with hypersensitivity

Interesting, but difficult to explain is observation that subjects from cities with highest prevalence of NIHRH also had the highest level of sensitization to Staphylococcus aureus endotoxins as reported in previous analysis of the GA^{2}LEN survey (29).
One cannot exclude that the level of consumption of NSAIDs in specific countries could also affect the prevalence of NIRHR, high consumption of NSAIDs in Macedonia (30) is associated with the lowest prevalence of NIRHR reported in our survey. Lack of data from other European countries does not allow for estimation of the real effect of NSAIDs consumption on the prevalence of hypersensitivity reactions.

Since the assessment of adverse respiratory reaction to NSAID was based on a single question asking for difficulties in breathing we could not precisely distinguish the type of reported hypersensitivity reaction. Difficulties in breathing following NSAIDs could be caused by bronchial obstruction or may result from developing laryngeal angioedema, thus potentially might represent one of the two subtypes of acute NSAIDs hypersensitivity reactions as listed by the most recent classification (5): either NSAIDs Exacerbated Respiratory Disease (NERD), or Single NSAIDs Induced Urticaria/Angioedema (SINUA). Respiratory symptoms are less likely to be associated with other types of NSAIDs hypersensitivity. Our study confirmed that NSAIDs induced respiratory reactions are more prevalent among patients with asthma (9-11, 14, 21) and/or chronic rhinosinusitis (12, 13) suggesting that NERD type of hypersensitivity could be most likely diagnosed in these patients. Although respiratory symptoms of NSAIDs hypersensitivity are usually considered to be a component of the “aspirin triad”, in our study only 15% of the patients complaining of breathing difficulties after NSAIDs had coexisting asthma and rhinosinusitis and more than half have not reported neither upper nor lower respiratory tract disorders. It is likely that these patients suffered from other than NERD type of NSAIDs hypersensitivity, where no underlying respiratory diseases were present.

This article is protected by copyright. All rights reserved.

Accepted Article

Our study suggests that presence of asthma symptoms or hospitalizations due to asthma during last 12 months, presence of rhinosinusitis and older age are the risk factors, which may predispose to development of respiratory type of NSAIDs hypersensitivity. In both univariate and in multivariate analysis chronic rhinosinusitis and current asthma symptoms were found to be associated with NIHRH. The prevalence of CRS among our survey participants with NIHRH was 32%, and nasal allergies were reported by half of patients, both figures are lower than reported in European (31) and American cohorts (32) of patients with Aspirin Exacerbated Respiratory Disease (AERD). However, previous studies comprised mostly asthmatic subjects who were referred to specialized clinics for diagnosis or management of AERD. On the other hand the majority of the GA^{2}LEN survey participants reporting adverse respiratory symptoms after a painkiller did not have any underlying respiratory disease. Clinical characteristics of these subjects could not be revealed based on the GA^{2}LEN questionnaire, and should be elucidated in future studies involving clinical examination.

Patients with NIRHR were more often ever smokers or current smokers and had a higher number of packyears; the odds ratio for lifetime smokers to have NIHRH was 1.6. Our data which are in line with earlier American study, suggest that environmental factors like exposure to cigarette smoke may increase the risk of having NSAIDs hypersensitivity (33). Whether other environmental factors like inhaled pollutants could have a similar effect remains unclear. NIRHRs were also more commonly reported in women compared with men by a ratio of 2:1 and was most frequently reported by people between 45-65 years old, which is consistent with previously published data from Europe (14, 31).

We are aware that our study has several potential limitations. Assessment of hypersensitivity prevalence was based on answer to a single question, on at least single drug evoked reaction thus the relation of reported symptoms to the drug intake may be questioned. It cannot be ruled out that in some patients respiratory symptoms associated with drug intake resulted from e.g. acute infection, and were not related to concomitant NSAID intake for a cold symptoms. It has been documented in several studies (34, 35) that patients with history of NSAIDs hypersensitivity may tolerate NSAIDs on challenge tests with culprit NSAID, which might result in the overestimation of the prevalence. Nevertheless, even if the true prevalence of drug hypersensitivity cannot be precisely estimated by this type of study, the survey definitely reflects perception of the problem in the population, thus should prompt further investigations. Since the patients were asked only about respiratory symptoms of hypersensitivity the study do not provide data on the prevalence of other e.g. cutaneous or anaphylactic type of NSAIDs hypersensitivity. In most of the centers patients were sampled randomly from general population, but in one center patients were selected from previously

This article is protected by copyright. All rights reserved.

Accepted Article

carried survey (Munich) and in 2 centers the GPs registries were sampled (Skopje, Palermo). Thus we cannot exclude that the sampling method could influence the results from those three centers, although apparently have not affect the overall results of the survey.

In conclusion, our study shows for the first time, the magnitude of the problem in Europe, namely relatively high prevalence of perceived hypersensitivity to NSAIDs in the general population. While showing variation in the prevalence of NIRHR among European countries the survey documented clear association between the presence of chronic airway diseases (asthma and rhinosinusitis) and NSAIDs- induced respiratory symptoms, but also points at possible relation of NSAIDs hypersensitivity to environmental pollution (specifically to smoking).

Funding

This study was conducted as a part of Workpackage 1.2.1 of the Global Allergy and Asthma European Network (GA^{2}LEN) funded by the 6th Framework program of the European Union.

List of tables and figures

Table 1. Prevalence of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) hypersensitivity reactions in the GA²LEN survey in 13 countries across Europe including 62,737 participants.

Table 2. Characteristics of subjects reporting and non-reporting NIRHR. Data are presented with number/percentage of observation and odds ratios (OR) with 95% of confidence intervals as a results of univariate logistic regression analysis.

Figure 1. The prevalence of NSAIDs induced respiratory hypersensitivity reaction (NIRHR) in each center standardized (by gender and age) to the European population (95% confidence intervals). Centers that had a 'high' prevalence NIRHR (the lower limit of the 95% confidence interval excluded 1.86%) were presented with red column. Centers with a 'low' prevalence of NIRHR (the upper limit of the 95% confidence interval excluded 1.86%) were presented with green column.

Figure 2. Association between NSAIDs induced respiratory symptoms and selected independent variables presented as odds ratios (OR) with 95% of confidence intervals (95%CI) from multivariable logistic regression analysis adjusted for study center.

Figure 3. Overall effects (ORs) of: late asthma onset (A), hospitalization due to asthma ever (B), asthma attack in the last 12 months (C), presence of chronic rhino-sinusitis (D) on NSAIDs induced respiratory hypersensitivity reaction (NIRHR) were weighted for sample size per center using meta-analysis and heterogeneity estimates (Wald chi-squared tests and the I-squared).

This article is protected by copyright. All rights reserved.

Accepted Article

Table 1.

Table 1 Prevalence of NSAIDs-induced respiratory reactions in various populations.

	Total number of subjects	Number of reactions (prevalence %)	P value
Age of subjects			
Age<20 years	5664	90 (1,6)	
Age 20-44 years	26817	416 (1,6)	
Age 45-65 years	22114	514 (2,32)	p<0,001
Age >65 years	7494	145 (1,9)	
Gender			
Female	33269	798 (2,4)	p<0,001
Male	29468	391 (1,3)	
Comorbidities			
Asthma	4697	355 (7,6)	p<0,001*
Chronic rhinosinusitis	6562	389 (5,9)	p<0,01*
Smoking status			
Ever smoked cigarretes	26366	643 (2,4)	p<0,001
Never smoked	36371	546 (1,5)	

* as compared to population not having asthma and not having chronic rhinosinusitis

Accepted Article

This article is protected by copyright. All rights reserved.

Table 2.

Groups of variables study variables	NSAIDs induced respiratory hypersensitivity reaction N(%) N=1189	Other N(%) N=61548	OR[a]	-95%CI	+95%CI	P
Demographic data						
Age of subject *	45,8	42,9	1,01	1,01	1,01	<0,0001
Female gender	798 (**67,1**)	33269 (**54,1**)	1,68	1,49	1,9	<0,0001
Data concerning asthma						
Ever had asthma	407 (**34,2**)	6604 (**10,7**)	4,65	4,1	5,27	<0,0001
Age of first asthma attack *	20	13	1,02	1,01	1,02	<0,0001
Ever hospitalised with asthma	140 (**11,8**)	1484 (**2,4**)	1,92	1,57	2,36	<0,0001
Attack of asthma in the last 12 months	262 (**22**)	2086 **(3,4**)	3,58	2,97	4,33	<0,0001
Currently taking any medication for asthma	311 (**26,1**)	3425 (**5,6**)	2,63	2,16	3,2	<0,0001
Derived variable based on ever having asthma and current symptoms	355 **(29,9**)	4342 (**7,1**)	5,5	4,84	6,26	<0,0001
Data concerning nasal allergy						
Any nasal allergies including hay fever	627 **(52,7**)	17098 (**27,7**)	3,02	2,68	3,4	<0,0001
Troubled by nasal allergies the last 12 months	593 **(49,9)**	15669 (**25,5**)	1,65	1,28	2,12	0,0001
Sense of smell reduced or absent for more than 12 weeks during last 12 months	271 (**22,8**)	4444 (**7,2**)	3,79	3,29	4,35	<0,0001
Doctor diagnosed chronic sinusitis	204 **(17,2**)	2951 **(4,8)**	4,11	3,52	4,8	<0,0001
Chronic rhino-sinusitis definition used to select CRS cases	389 **(32,7)**	6173 **(10**)	4,28	3,78	4,84	<0,0001
Data on smoking						
Smoked for as long as a year	643 **(54,1)**	25723 **(43,4**)	1,62	1,45	1,82	<0,0001
Age when started smoking *	17	16	1,02	1,01	1,04	<0,01
Current smoking	338 **(28,4)**	12020 **(19.5)**	1,25	1,07	1,46	<0,01
Amount of cigarettes smoked per day *	15	10	1,03	1,02	1,03	<0,0001
Pack years of smoking*	13,9	11	1,005	1,009	1,013	<0,0001

[a] dependent variable: NSAIDs induced dyspnoe

*continues variables presented as mean (for age of subject) or median value (other continuous variables)

References

1. Ensina LF, Amigo MH, Koch T, Guzman E, Paoli R, Nunes IC. Drug hypersensitivity in students from Sao Paulo, Brazil. *Clinics (Sao Paulo)* 2010;**65**:1009-1011.
2. Dona I, Blanca-Lopez N, Cornejo-Garcia JA, Torres MJ, Laguna JJ, Fernandez J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011;**41**:86-95.
3. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;**140**:1001-1006.
4. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;**34**:1597-1601.
5. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013;**68**:1219-1232.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

6. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. *Allergy* 2011;**66**:818-829.
7. Demir S, Olgac M, Unal D, Gelincik A, Colakoglu B, Buyukozturk S. Evaluation of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs according to the latest classification. *Allergy* 2015;**70**:1461-1467.
8. Stevenson DD. Aspirin and NSAID sensitivity. *Immunol Allergy Clin North Am* 2004;**24**:491-505, vii.
9. Moon JY, Kim SH, Kim TB, Kim SH, Chang YS, Lee JH, et al. Aspirin-intolerant asthma in the Korean population: prevalence and characteristics based on a questionnaire survey. *Respir Med* 2013;**107**:202-208.
10. Sabry EY. The prevalence of aspirin-induced asthma in Saudian asthmatic patients. *Allergol Immunopathol (Madr)* 2010;**38**:181-186.
11. Bavbek S, Yilmaz I, Celik G, Aydin O, Erkekol FO, Orman A, et al. Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: a cross-sectional survey. *Allergol Immunopathol (Madr)* 2012;**40**:225-230.
12. Fan Y, Feng S, Xia W, Qu L, Li X, Chen S, et al. Aspirin-exacerbated respiratory disease in China: a cohort investigation and literature review. *Am J Rhinol Allergy* 2012;**26**:e20-22.
13. Bavbek S, Dursun B, Dursun E, Korkmaz H, Sertkaya Karasoy D. The prevalence of aspirin hypersensitivity in patients with nasal polyposis and contributing factors. *Am J Rhinol Allergy* 2011;**25**:411-415.
14. Hedman J, Kaprio J, Poussa T. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;**28**:717-722.
15. Kasper L, Sladek K, Duplaga M, Bochenek G, Liebhart J, Gladysz U, et al. Prevalence of asthma with aspirin hypersensitivity in the adult population of Poland. *Allergy* 2003;**58**:1064-1066.
16. Kasper L, Sladek K, Bochenek G, Duplaga M, Szczeklik A. [The frequency of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) in the population of adult asthmatics in Poland based on an epidemiological questionnaire]. *Pneumonol Alergol Pol* 2009;**77**:431-439.
17. Kim JE, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. *Ear Nose Throat J* 2007;**86**:396-399.
18. Kowalski ML, Cieslak M, Perez-Novo CA, Makowska JS, Bachert C. Clinical and immunological determinants of severe/refractory asthma (SRA): association with Staphylococcal superantigen-specific IgE antibodies. *Allergy* 2011;**66**:32-38.
19. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J* 2003;**22**:470-477.
20. Yoshimine F, Hasegawa T, Suzuki E, Terada M, Koya T, Kondoh A, et al. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. *Respirology* 2005;**10**:477-484.
21. Vally H, Taylor ML, Thompson PJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002;**57**:569-574.
22. Yang CC, Lee JY, Chen WC. Acute generalized exanthematous pustulosis caused by celecoxib. *J Formos Med Assoc* 2004;**103**:555-557.
23. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy* 2012;**67**:91-98.
24. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007:1-136.
25. Settipane RA, Constantine HP, Settipane GA. Aspirin intolerance and recurrent urticaria in normal adults and children. Epidemiology and review. *Allergy* 1980;**35**:149-154.
26. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004;**328**:434.

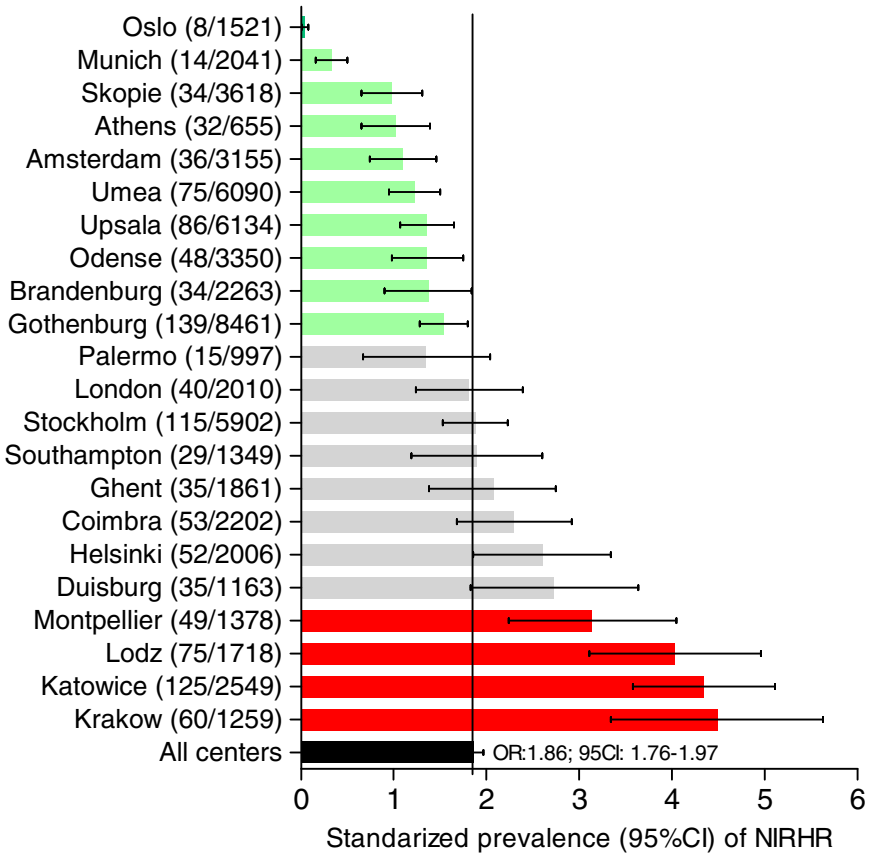
This article is protected by copyright. All rights reserved.

27. Cavkaytar O, Arik Yilmaz E, Karaatmaca B, Buyuktiryaki B, Sackesen C, Sekerel BE, et al. Different Phenotypes of Non-Steroidal Anti-Inflammatory Drug Hypersensitivity during Childhood. *Int Arch Allergy Immunol* 2015;**167**:211-221.
28. WHO database of outdoor polution http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/).
29. Tomassen P, Jarvis D, Newson R, Van Ree R, Forsberg B, Howarth P, et al. Staphylococcus aureus enterotoxin-specific IgE is associated with asthma in the general population: a GA(2)LEN study. *Allergy* 2013;**68**:1289-1297.
30. Health Fund of R. Macedonia. Annual Report 2013: Drug consumption. www.fzo.org.mk. 2006.
31. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000;**16**:432-436.
32. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002;**89**:474-478.
33. Chang JE, Ding D, Martin-Lazaro J, White A, Stevenson DD. Smoking, environmental tobacco smoke, and aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2012;**108**:14-19.
34. Viola M, Rumi G, Valluzzi RL, Gaeta F, Caruso C, Romano A. Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity. *Clin Exp Allergy* 2011;**41**:96-103.
35. Blanca-Lopez N, M JT, Dona I, Campo P, Rondon C, Seoane Reula ME, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. *Clin Exp Allergy* 2013;**43**:85-91.

Accepted Article

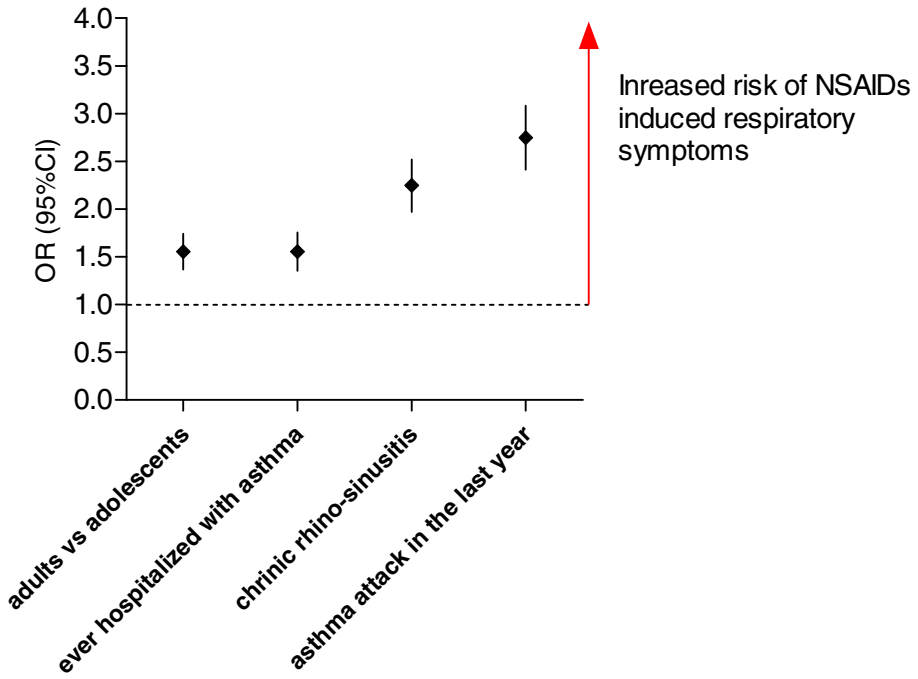
This article is protected by copyright. All rights reserved.

Accepted Article



This article is protected by copyright. All rights reserved.

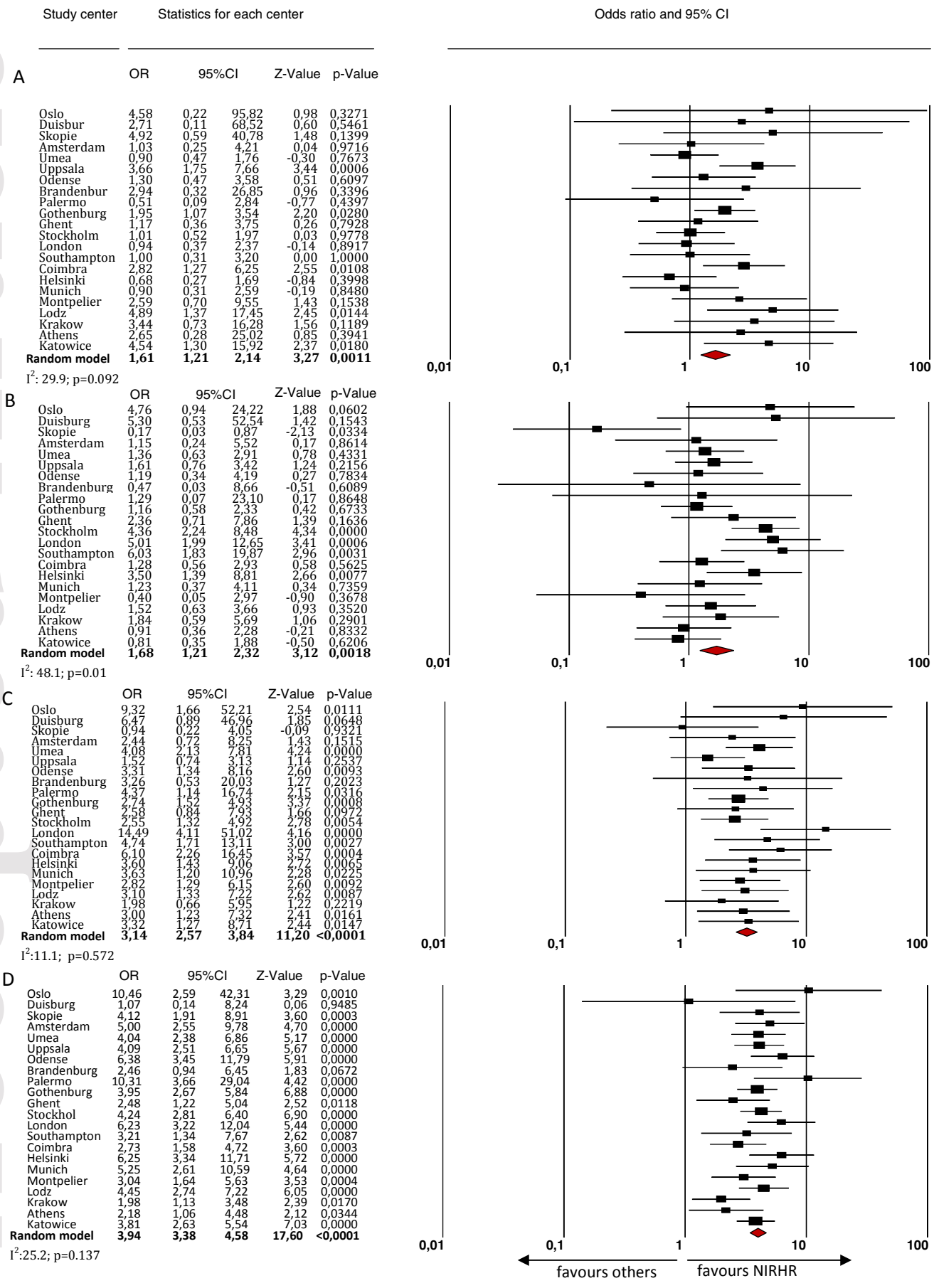
Figure 2



Accepted Article

This article is protected by copyright. All rights reserved.

Figure 3



Accepted Article

This article is protected by copyright. All rights reserved.