NSAID-exacerbated respiratory disease: a population study

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Shareable abstract (@ERSpublications)
Population-based prevalence of N-ERD is 1.4%. N-ERD is symptomatic, with a rhinitis subgroup. The risk factors for N-ERD are older age, family history of asthma or allergic rhinitis, long-term smoking and exposure to environmental pollutants. https://bit.ly/3HxGftP

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Abstract

Background Nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate respiratory symptoms. A recent European Academy of Allergy and Clinical Immunology position paper recommended the use of an acronym, N-ERD (NSAID-exacerbated respiratory disease), for this hypersensitivity associated with asthma or chronic rhinosinusitis with or without nasal polyposis. Our aim was to estimate the prevalence of N-ERD and identify factors associated with N-ERD.

Methods In 2016, a cross-sectional questionnaire survey of a random adult population of 16 000 subjects aged 20–69 years was performed in Helsinki and Western Finland. The response rate was 51.5%.

Results The prevalence was 1.4% for N-ERD, and 0.7% for aspirin-exacerbated respiratory disease (AERD). The prevalence of N-ERD was 6.9% among subjects with asthma and 2.7% among subjects with rhinitis. The risk factors for N-ERD were older age, family history of asthma or allergic rhinitis, long-term smoking and exposure to environmental pollutants. Asthmatic subjects with N-ERD had a higher risk of respiratory symptoms, severe hypersensitivity reactions and hospitalisations than asthmatic subjects without N-ERD. The subphenotype of N-ERD with asthma was most symptomatic. Subjects with rhinitis associated with N-ERD, which would not be included in AERD, had the fewest symptoms.

Conclusion We conclude that the prevalence of N-ERD was 1.4% in a representative Finnish adult population sample. Older age, family history of asthma or allergic rhinitis, cumulative exposure to tobacco smoke, secondhand smoke, and occupational exposures increased odds of N-ERD. N-ERD was associated with significant morbidity.

Introduction

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate respiratory symptoms. Aspirin-exacerbated respiratory disease (AERD) and NSAID-exacerbated respiratory disease (N-ERD) are not interchangeable definitions, although the disease mechanisms are the same. SAMTER and BEERS [1] described AERD in 1968, and the widely used AERD definition includes a triad of aspirin-induced dyspnoea, asthma and rhinosinusitis. Besides aspirin, other NSAIDs can induce dyspnoea. Recently, a new definition of N-ERD was introduced by the European Academy of Allergy and Clinical Immunology (EAACI) [2]. According to the definition, “N-ERD is a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps (CRSwNP), whose symptoms are exacerbated by NSAIDs, including aspirin” [2]. The N-ERD definition is different to
the AERD definition, and further evidence on the clinical relevance of N-ERD compared to AERD is needed.

Patients with N-ERD react to aspirin or other NSAIDs with upper and/or lower airway symptoms usually within 30–180 min [2, 3]. These anaphylactoid reactions are cross-reactive hypersensitivity reactions to an NSAID due to the drug’s pharmacological effect, i.e. inhibition of the cyclo-oxygenase (COX)-1 enzyme [4]. NSAIDs can cause true allergies or anaphylaxis via immunologically mediated single-NSAID-induced reactions [2, 4, 5].

The prevalence of respiratory hypersensitivity reactions to NSAIDs has been 1.9% in a European multicentre study, 1.2% in Finland and 1.3% in Sweden [6–8]. Although extensive AERD research has been carried out, only a limited number of studies have been population-based [7–10]. Most previous AERD prevalence studies have been conducted in asthma or rhinitis patients [11, 12]. These prior approaches did not address the whole N-ERD group, and difficulties might arise when assumptions on prevalence or risk factors are made using earlier, narrower definitions. Interrelationships between NSAID-induced dyspnoea, asthma and rhinitis in N-ERD and subphenotypes of N-ERD are incompletely described [2]. Furthermore, uncertainty still exists regarding the risk factors for N-ERD [8, 13–15].

To fill these gaps in knowledge, this study first aimed to ascertain the prevalence of N-ERD and its risk factors in a cross-sectional random adult population. Second, we explored and identified the relationship between asthma and N-ERD and its subgroups and compared the morbidity rate associated with each of them.

**Methods**

A cross-sectional survey was conducted in Helsinki and Western Finland as part of the FinEsS (Finland-Estonia-Sweden) study and in collaboration with the Nordic EpiLung study [16]. The population aged 20–69 years in the mainly urban Helsinki and the mostly rural Western Finland was included. In February 2016, the questionnaire was sent to a random sample of 16000 participants from the Finnish Population Register. Two reminders were sent to those not responding.

Previous publications have detailed the study methods as well as nonresponder data [17, 18]. The response rate was 51.5%, and nonresponders were more often younger and male, which is in line with other studies of nonresponse [19]. Responders with incomplete smoking data (n=269) were excluded (supplementary figure S1). After exclusion, 7930 responders were included in the study. We combined the data from two similar surveys to minimise bias.

**Definition of key parameters**

NSAID-induced dyspnoea was defined as a positive response to the question “Have you ever experienced difficulties breathing within 3 h of taking a pain killer?” We asked participants to name the pain killer causing difficulties breathing, and 86% named NSAIDs with certainty.

Asthma was defined as a positive response to the question “Have you been diagnosed by a doctor as having asthma?”

Rhinitis was defined as a positive response to any of the following questions: “Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (from, e.g. birch, grass, mugwort)?”; “Have you been diagnosed by a doctor as having other allergic rhinitis (caused by, e.g. cat or dog, but not caused by pollen)?”; “Do you have now, or have you had previously, allergic rhinitis (e.g. hay fever)?”; “Have you had longstanding nasal congestion?”; and “Have you had longstanding rhinitis?” Nasal polyps were not asked about by name, but nasal congestion associates to nasal polyposis. N-ERD should be considered in patients with asthma and chronic rhinosinusitis whose symptoms are exacerbated after ingestion of aspirin and other COX-1 inhibitors [2].

N-ERD was defined as NSAID-induced dyspnoea with asthma and/or rhinitis.

AERD was defined as a triad of NSAID-induced dyspnoea, asthma and rhinitis.

Definitions of other parameters are included in the supplementary material.

**Compliance with ethical standards**

General Data Protection Regulation (EU) 2016/679 was followed, and informed written consent was obtained from all individual participants. The ethics committee of the department of medicine of Helsinki
University Central Hospital approved this study (approval number 200/13/03/00/15). It was conducted according to the 1964 Helsinki declaration and its later amendments.

**Statistical analysis**

Statistical analyses were performed using SPSS Statistics software version 26 (IBM SPSS, Armonk, NY, USA). We used ANOVA to compare means, with Tukey post hoc analyses. Pearson’s Chi-squared test was used to compare categorical variables with z-tests for multiple categories. A p-value <0.05 was considered significant. With indirect standardisation, the age-standardised symptom ratio (SR) was counted as actual symptoms divided by expected symptoms. The total cohort was the standard population. Symptom rates were calculated as the sum of symptoms per 1000 people in 10-year-interval age groups.

To study risk factors for N-ERD, we performed multivariable binary logistic regression analyses to calculate odds ratios with 95% confidence intervals using N-ERD as a dependent variable. The independent variables were age, sex, family history of asthma, family history of allergic rhinitis, cumulative exposure (smoking (current or ex-smoking), secondhand smoke (at home or work) or occupational exposure to vapours, gases, dusts and fumes (VGDF)), body mass index and living on a farm during the first 5 years of life.

**Results**

The prevalence of NSAID-induced dyspnoea was 1.7% (n=132) in the study population. A significant prevalence difference was observed between centres: the prevalence was 2.0% (n=79) in rural Western Finland versus 1.3% (n=53) in urban Helsinki (p=0.023).

The Venn diagram in figure 1 presents the interrelationship between NSAID-induced dyspnoea, asthma and rhinitis; how the N-ERD group was defined; and how the definition and prevalence differ from those of AERD. Of the responders, 11.1% (n=879) had asthma and 49.8% (n=3952) had rhinitis. A small subgroup of persons reported NSAID-induced dyspnoea, but did not have asthma or rhinitis (0.3%, n=22); thus, they were not included in the N-ERD group.

The prevalence of N-ERD was 1.4% (n=110), and that of AERD was 0.7% (n=56). The prevalence of N-ERD was 1.1% (n=89) with longstanding nasal congestion. The prevalence of N-ERD was 6.9% (n=61) among patients with asthma and 2.7% among patients with rhinitis (n=105).

**Characteristics of N-ERD**

The patient characteristics of the N-ERD, asthma without N-ERD, rhinitis without N-ERD and NSAID-induced dyspnoea without N-ERD groups are shown in table 1. The mean age of subjects with

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**FIGURE 1** Proportional Venn diagram describing the overlap of asthma, rhinitis, nonsteroidal anti-inflammatory drug (NSAID)-induced dyspnoea, the definition of NSAID-exacerbated respiratory disease (N-ERD) and how it differs from aspirin-exacerbated respiratory disease (AERD) and NSAID-induced dyspnoea without N-ERD.
N-ERD was 52 years. The mean age of asthma diagnosis was 32 years, both being higher than in asthma without N-ERD, and the asthma diagnosis in N-ERD was made mainly after the 12th birthday (>83% of cases) and is often late-adult in onset (44% after age 40 years) (table 1). Childhood exposure to farming environment was more common in N-ERD than in asthma. Supplementary table S1 shows a comparison between N-ERD and healthy controls.

### N-ERD compared to asthma

Dyspnoea modified Medical Research Council (mMRC) score ⩾2, tightness in the chest, sputum production and constant nasal blocking were more common in N-ERD than in asthma without N-ERD. No difference in wheezing or longstanding cough was evident between the groups (figure 2, supplementary table S2). Age-standardised symptom ratios were calculated, and in them, dyspnoea mMRC score ⩾2 had an SR of 4.0 in N-ERD and 2.9 in asthma without N-ERD compared to the total cohort (supplementary table S2).

The prevalence of severe allergic reactions or anaphylaxis was higher in N-ERD than in asthma without N-ERD (13.6% versus 5.3%, p<0.001). Drug reactions, mainly to NSAIDs, were the most common cause of anaphylaxis in N-ERD. Food reactions were the most common cause in asthma without N-ERD. The prevalence of asthma hospitalisations was two times higher in the N-ERD group than in the asthma without N-ERD group (4.5% versus 1.7%, p=0.049) (supplementary table S3).

### Is the N-ERD definition valid?

To identify whether the rhinitis-only subgroup, not included in AERD, was clinically relevant, we decided to compare it to those with asthma (AERD) and those with only NSAID-induced dyspnoea. We decided to include eight patients with NSAID-induced dyspnoea with rhinitis and COPD, but without asthma in the asthma group due to their respiratory disease. Distinguishing between obstructive respiratory diseases can be challenging, both in clinical work and in surveys.

We compared the groups with NSAID-induced dyspnoea without N-ERD (n=22), rhinitis alone (n=46) and asthma (with or without rhinitis) (n=64). Figure 3 shows a clear trend of increasing respiratory symptoms, with the mildest symptoms in NSAID-induced dyspnoea without N-ERD and the most severe symptoms in the N-ERD subgroups (figure 3, supplementary table S4). The prevalence of severe allergic reactions/
FIGURE 2 The prevalence of respiratory symptoms in nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) (n=110) and asthma without N-ERD (n=818). Comparison between groups was made using Pearson’s Chi-squared test.

FIGURE 3 The prevalence of respiratory symptoms in nonsteroidal anti-inflammatory drug (NSAID)-induced dyspnoea without co-existing disease but with rhinitis or asthma; the latter two being NSAID-exacerbated respiratory disease (N-ERD) subgroups and the last one being part of aspirin-exacerbated respiratory disease. Comparison between groups was made using Pearson’s Chi-squared test with the z-test.
Factors associated with N-ERD

We performed univariable and multivariable binary logistic regression analyses to evaluate factors associated with N-ERD. In these analyses, N-ERD was compared to a reference category of those without N-ERD. Older age, family history of asthma, allergic rhinitis and a cumulative total of two or three exposures to particulate matter had higher odds for N-ERD in adjusted analyses, whereas childhood exposure to farming environment increased odds only in unadjusted analyses (table 2). Cumulative exposure was classified as zero to three exposures calculating smoking (current or ex-smoking), secondhand smoke (smoke exposure at home or at work) and occupational exposure to vapours, gases, dusts and fumes.

Discussion

The recent EAACI position paper recommended that N-ERD is a more proper term to describe the syndrome of respiratory hypersensitivity to NSAIDs associated with asthma and/or chronic rhinosinusitis with nasal polyps. N-ERD has a broader definition than the previous AERD. This study showed that the prevalence of N-ERD in a random population sample was 1.4%. The risk factors were older age, family histories of asthma and allergic rhinitis and the dose-response to cumulative exposure to tobacco smoke, secondhand smoke and occupational particulate matter. Asthma in N-ERD mainly had an adult onset. Compared to asthma without N-ERD, participants with N-ERD were more symptomatic.

Comparison to previous prevalence studies

We found a population-based prevalence of 1.4% for N-ERD. The prevalence of AERD was 0.7%, similar to that reported by other population-based studies, 0.5% in Sweden and 0.6% in Poland, externally validating our results [8, 9]. In contrast to the previous AERD definition, the N-ERD definition includes those patients with only one disease combined with respiratory hypersensitivity reactions to NSAIDs, such as chronic rhinosinusitis with polyps. Therefore, the prevalence of AERD is only half that of N-ERD. In patients with asthma, the N-ERD definition is similar to the previous AERD definition. To illustrate, the prevalence of N-ERD was 6.9% among participants with asthma in our study, similar to a recent meta-analysis reporting a 7.2% prevalence of AERD [11]. However, the prevalence of N-ERD among participants with asthma in our study was somewhat lower than the 9.0% reported based on the oral provocation challenge test and 9.9% noted in a questionnaire-based survey among adults with asthma [12].

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**TABLE 2** Factors associated with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) determined by multivariable binary logistic regression

| Age                  | Crude OR (95% CI) | Adjusted OR (95% CI) |
|----------------------|-------------------|-----------------------|
| 20–39 years (ref.)   |                   |                       |
| 40–59 years          | 2.15 (1.25–3.68)  | 2.11 (1.19–3.76)      |
| 60–69 years          | 2.90 (1.68–4.99)  | 3.08 (1.68–5.64)      |
| Female sex           | 1.57 (1.06–2.33)  | 1.46 (0.94–2.28)      |
| Family history of asthma | 2.98 (2.04–4.34) | 2.34 (1.53–3.57)      |
| Family history of allergic rhinitis | 2.46 (1.68–3.59) | 2.47 (1.60–3.83)      |

**Cumulative exposure**

| 0 exposures (ref.) | 1.63 (0.97–2.75) | 1.49 (0.86–2.59) |
| 1 exposure         | 2.65 (1.53–4.57) | 2.41 (1.34–4.34) |
| 2 exposures        | 3.83 (1.98–7.39) | 3.68 (1.82–7.46) |

**BMI**

| <25 kg·m⁻² (ref.) | 1.75 (1.18–2.57) | 1.38 (0.90–2.12) |
| 25–29.99 kg·m⁻²   | 1.27 (0.82–1.98) | 1.02 (0.64–1.64) |
| ⩾30 kg·m⁻²         | 1.72 (1.05–2.81) | 1.14 (0.67–1.95) |

**Childhood exposure to farming environment**

| Ref.: reference category (without N-ERD); BMI: body mass index. | Adjusted OR (95% CI) |
|----------------------------------------------------------------|-----------------------|

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The prevalence of respiratory hypersensitivity reactions to NSAIDs found in our study, 1.7%, was similar to that previously reported [6–8]. The prevalence of NSAID-induced dyspnoea showed variation between rural and urban centres in our research. These results corroborate the findings of a study comparing the prevalence of NSAID-induced dyspnoea between 15 countries, where it was reported to be lowest, at 0.9%, in the city of Skopje and highest, at 4.9%, in the city of Katowice [6]. These and our results support a possible role for environmental factors in N-ERD pathogenesis.

The natural history of N-ERD

N-ERD is a new disease definition, so much of our knowledge on the risk factors and pathogenesis comes from studies on AERD. Pathological changes in N-ERD and/or AERD have been proposed to involve chronic immune dysregulation, T2 immunity with eosinophils, mast cells, group 2 innate lymphoid cell infiltration and genetic variation in diverse molecular pathways of arachidonic acid metabolism [2, 3, 20]. In a previous study, a family history of AERD was a risk factor for AERD [13], and a family history of asthma and allergic rhinitis were risk factors for N-ERD in our study, confirming that hereditary and/or genetic factors play a role in the pathogenesis of N-ERD.

Our study strengthens previous evidence derived from studies on AERD on the role of occupational exposure to VGDF and smoke exposure as risk factors [8, 15]. We found an increased risk of N-ERD with cumulative exposure, in concordance with a previous study where the risk of AERD was higher for those with smoking exposure both as a child and as an adult [15]. One possible pathway mediating this is that tobacco smoke and other environmental exposures are drivers of microbial dysbiosis in the airways [21]. For example, IgE antibodies to *Staphylococcus aureus* enterotoxin were significantly increased in patients with CRSwNP and AERD compared with controls and CRSwNP without AERD [22]. Much uncertainty still exists about the accumulation of factors sufficient for the disease process to begin. Still, our study supports the idea that the risk is and possibly dose-dependent with cumulative exposure to particulate matter. Childhood exposure to farming environment was significantly more common in N-ERD than asthma without N-ERD, whereas a nonsignificant trend was seen compared to healthy controls. In our recent study, childhood exposure to farming environment had lower odds of early-diagnosed asthma and higher odds of late-diagnosed asthma [23].

The latency period of N-ERD might be decades. According to a previous study, NSAID hypersensitivity may occur before the onset of apparent respiratory disease, usually marking the beginning of asthma/CRSwNP [2]. The group with NSAID-induced dyspnoea without N-ERD in our survey conceivably represents subclinical disease. This group had a similar age to the N-ERD group, but less family history of asthma. Upper airway symptoms might precede asthma by 1–5 years in N-ERD [24], upper airway disease in N-ERD is usually CRSwNP and upper respiratory symptoms are on average worse than in NSAID-tolerant patients [25]. In line with previous reports, the onset of symptoms and the usual time of diagnosis are in the third or fourth decades of life in subjects with AERD [26]. In our study, the mean age of the asthma diagnosis was higher in N-ERD than in asthma without N-ERD. The prevalence of N-ERD increased with age, similar to previous findings on AERD [8].

The majority of N-ERD participants were female and overweight, parallel to previous findings [8, 14]. Our results reflect other studies showing that upper airway disease in N-ERD patients was dominated by nasal blockage and/or nasal congestion [27]. In contrast to results from another cohort [27], most of the rhinitis was nonallergic in the current study. In our study, dyspnoea mMRC score ≥2, tightness in the chest, sputum production and constant nasal blockage were more common in N-ERD than in asthma without N-ERD. In agreement with previous data on AERD, asthma morbidity was increased considerably in N-ERD compared with asthma without AERD [8, 12].

N-ERD was associated with morbidity in our study. The rate of hospitalisation due to asthma exacerbation during the past year was twice as high in N-ERD as in asthma without N-ERD. No statistically significant trend was observed in emergency department visits. These results are consistent with results from a multicentre population study in which the risk of uncontrolled asthma in N-ERD patients was increased twofold and asthma-related hospitalisations increased by 40% [12]. Self-reported severe allergic reactions during the past year were more common in N-ERD than in asthma without N-ERD.

In a recent study, the clinical phenotypes of AERD were characterised by genetic variation within multiple pathways for arachidonic acid metabolism, inflammation and immune responses [20]. Asthma in AERD is heterogeneous, as it might be mild, severe or uncontrolled [28]. To evaluate if the N-ERD rhinitis subgroup had undiagnosed asthma, we compared this subgroup to those with asthma and they had milder symptoms but were symptomatic compared to those with only NSAID-induced dyspnoea. Our grouping
might be helpful for clinicians planning treatment together with endotyping different IgE levels, eosinophil counts, plasma tryptase, urinary leukotriene E4 and mast cell-derived prostaglandin D2 [28–31].

**Strengths and limitations**

This study’s strengths were its large general population-based random sample and its validated questionnaire to evaluate the prevalence and risk factors of N-ERD [17, 18, 32]. Although the sample was large, participants with N-ERD were limited in number (n=110). N-ERD subgroups were slightly small for making comparisons, and we could not examine factors associated with different N-ERD phenotypes.

The present study is based on a self-reported diagnosis; thus, the absence of clinical data can be considered a limitation. We consider self-reported physician asthma diagnosis reliable due to reimbursement policies ensuring objective diagnosis. Rhinitis also included allergic rhinitis and was assessed with four questions. Questions regarding nasal polypsis, hyposmia or anosmia were not asked, but longstanding nasal congestion is a symptom of nasal polyposis. With that criterion, the N-ERD prevalence estimate would be slightly lower, at 1.1%. In addition, self-reported reactions probably include milder allergic reactions and might include other mechanisms causing dyspnoea. Compared to the reported frequency of severe allergic reactions, 0.001% annually in Finland [33], the prevalence of severe allergic reactions in our study was high and was most prevalent in the NSAID-induced dyspnoea without N-ERD group. As a possible explanation to the high prevalence of allergic reactions, anaphylaxis has been linked to mast cell activation [33, 34], and recently, mast cell-derived prostaglandin D2 was considered a central pathogenic mediator in N-ERD [29].

Like other recent surveys, this one found that younger individuals and males may be under-represented due to lower participation rates in these subgroups [19, 35]. We combined data from two study centres to minimise bias and increase the sample size due to the moderate response rate. The effect of nonresponder bias may be limited, since the N-ERD patients’ mean age and age of asthma onset were higher. Therefore, we consider the results reliable. Despite limitations, this study offers new, clinically important insight into the prevalence and clinical significance of N-ERD.

**Clinical implications**

A better understanding of pathogenesis may lead to new treatments, and secondary preventive therapies for those with N-ERD rhinitis might stop progression of the disease to asthma in the future. The most common cause of severe allergic reaction in N-ERD was drug reactions, mainly to NSAIDs, so further efforts in patient education about anaphylaxis and public awareness about the avoidance of COX-1 inhibitors might be required.

**Conclusions**

The prevalence of N-ERD was 1.4% in the Finnish adult population. Risk factors for N-ERD were older age, family histories of asthma and allergic rhinitis and cumulative exposure to tobacco smoke, secondhand smoke and occupational exposures. N-ERD was associated with significant morbidity compared to asthma without N-ERD, although it includes patients with rhinitis. The prevalence of anaphylaxis was higher in N-ERD than in asthma without N-ERD, raising concerns that need further research.

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