

Supplement 1.

Title: NSAID-exacerbated respiratory disease (N-ERD): a population study

Short title: Epidemiology of NSAID-exacerbated respiratory disease

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Definitions of key parameters:

Allergic rhinitis was defined as a positive response to the question "Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen (from, e.g., birch, grass, mugwort)?" or "Have you been diagnosed by a doctor as having other allergic rhinitis (caused by, e.g., cat or dog, but not caused by pollen)?"

Chronic obstructive pulmonary disease (COPD) was defined as a positive response to the question, "Have you been diagnosed as having chronic bronchitis, chronic obstructive pulmonary disease (COPD) or emphysema by a doctor?"

A family history of asthma and COPD was asked about with the following questions: "Have any of your parents, brothers or sisters now or previously had asthma or chronic bronchitis, chronic obstructive pulmonary disease (COPD) or emphysema?"

Age at asthma diagnosis was asked about with the question, "What age were you when asthma was diagnosed?"

Living on a farm during the first five years of life was evaluated by "Did you live on a farm during your first five years?"

Smoking status was divided into current smokers, ex-smokers (stopped smoking more than 12 months before), and never-smokers (neither a current smoker nor an ex-smoker).

Secondhand smoke exposure at home: "Have you been heavily exposed to tobacco smoke at home?"

Secondhand smoke exposure at work: "Have you been heavily exposed to tobacco smoke at work?"

Occupational exposure to VGDF (vapours, gases, dust, or fumes) was defined by the following question: "Does your working environment now, or has your working environment previously, had a lot of dust, gases, or fumes?"

Cumulative exposure to particulate matter was assessed using a scale of 0-3 exposures of smoking (current or ex-smoking), secondhand smoke (at home or work) and occupational exposure to VGDF.

Body mass index (BMI) was calculated based on self-reported weight and height.

Dyspnoea mMRC score ≥ 2 was defined as a positive response to the question, "Do you have to walk slower than other people of your age on the level because of breathlessness?"

Wheezing was defined as a positive response to the question, "Have you had wheezing or whistling in your chest at any time in the last 12 months?"

Longstanding cough was defined as a positive response to the question, "Have you had longstanding cough during the last 12 months?"

Tightness in the chest was defined as a positive response to the question, "Have you awakened with a feeling of tightness in your chest at any time in the last 12 months?"

Sputum production was defined as a positive response to the question, "Do you usually have phlegm when coughing, or do you have phlegm that is difficult to bring up?"

Constant nasal blocking was defined as a positive response to the question, "Have you had longstanding nasal congestion?"

Severe allergic reaction was defined as a positive response to "Have you ever had severe generalized allergic reactions (anaphylaxis)?"

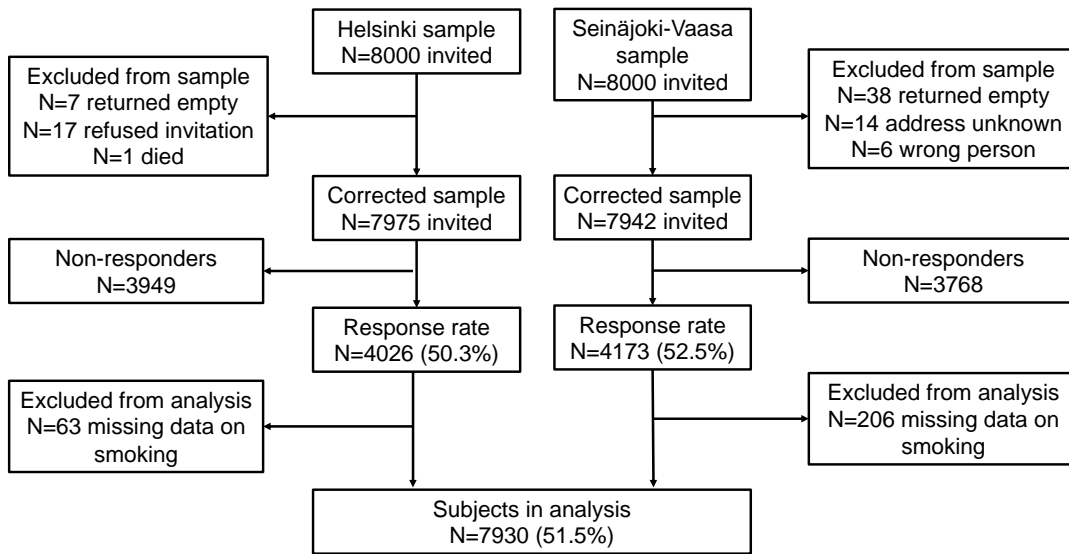


Figure S1. Flow chart of the study

Table S1. N-ERD characteristics compared to healthy controls

	N-ERD	Healthy controls	p
Total, n	110	3786	
Mean age years	52 (14)	50 (15)	0.076
Female	72 (65.5)	2025 (53.5)	0.013
Mean BMI kg/m²	27.3 (5.7)	25.9(5.4)	0.017
Family history of asthma	53 (48.2)	667 (17.6)	<0.001
Never-smoker	49 (44.5)	2110 (55.7)	0.040
Current smoker	24 (21.8)	758 (20.0)	
Ex-smoker	37 (33.6)	918 (24.2)	
Occupational exposure to VGDF	48 (45.7)	1018 (27.6)	<0.001
Childhood exposure to farming environment	43 (39.8)	1179 (32.0)	0.086

Data are n (%) or mean (SD).

Table S2. The prevalence of respiratory symptoms in N-ERD (n=110) and asthma without N-ERD (n=818) (results also shown in Figure 3).

	N-ERD	Asthma without N-ERD	p
Total, n	110	818	
Dyspnoea mMRC ≥ 2	43 (39.1) 4.0	205 (25.1) 2.9	0.002
Wheeze	60 (54.5) 2.9	425 (52.0) 2.8	0.610
Longstanding cough	41 (37.3) 2.0	273 (33.4) 2.1	0.417
Tightness in the chest	60 (54.5) 2.8	311 (38.0) 2.1	0.001
Sputum production	67 (60.9) 3.0	400 (48.9) 2.3	0.018
Constant nasal blocking	73 (66.4) 2.5	384 (46.9) 1.7	<0.001

Data are n (%) **SR**. SR is the age-standardized symptom ratio, actual symptoms/expected symptoms, reference to the whole cohort.

Table S3. The prevalence of severe allergic reactions or anaphylaxis, emergency department visits, and hospitalization during the last year in N-ERD (n=110) and asthma without N-ERD (n=818).

	N-ERD	Asthma without N-ERD	p
Total, n	110	818	
Severe allergic reaction or anaphylaxis during the last year	15 (13.6)	43 (5.3)	<0.001
Severe allergic reaction or anaphylaxis ever	49 (44.5)	157 (19.2)	<0.001
Reason to severe allergic reaction or anaphylaxis ever			
Drug	36 (73.5)	43 (27.4)	<0.001*
Food	7 (14.3)	65 (41.4)	
Insect bite	6 (12.2)	15 (9.6)	
Other	6 (12.2)	37 (23.6)	
Visit to emergency department due to asthma attack during the last year	9 (8.2)	34 (4.2)	0.059
Hospitalization due to asthma exacerbation during the last year	5 (4.5)	14 (1.7)	0.049

Data are n (%), *significant crossover, one person having more than one cause ever, overall p-value between groups.

Table S4. The prevalence of respiratory symptoms in NSAID-induced dyspnoea without co-existing disease, with only rhinitis or asthma (including 8 patients with NSAID-induced dyspnoea with rhinitis and COPD but without asthma) (results also shown in Figure 3).

NSAID-induced dyspnoea				
Co-existing disease	no	Rhinitis	Asthma	
Total, n	22	46	64	p
Dyspnoea mMRC ≥ 2	3(13.6)	12(26.1)	31(48.4)	0.004
	1.6	3.5	4.4	
Wheeze	7(31.8)	15(32.6)	45(70.3)	<0.001
	1.2	1.7	4.0	
Longstanding cough	4(18.2)	7(15.2)	34(53.1)	<0.001
	0.9	1.0	2.6	
Tightness in the chest	3(13.6)	15(32.6)	45(70.3)	<0.001
	0.6	1.7	3.7	
Breathlessness	2(9.1)	14(30.4)	56(87.5)	<0.001
	0.2	2.1	4.8	
Sputum production	3(13.6)	17(37.0)	50(78.1)	<0.001
	0.6	2.1	3.6	
Constant nasal blocking	0(0.0)	25(54.3)	48(75.0)	<0.001
	0	2.0	2.8	

Data are n (%) **SR**. SR is the age-standardized symptom ratio, actual symptoms/expected symptoms, reference to the whole cohort.

Table S5. The prevalence of anaphylaxis, emergency department visits, and hospitalization during the last year in NSAID-induced dyspnoea without N-ERD, N-ERD with co-existing rhinitis, and asthma (including 8 NSAID-induced dyspnoea with rhinitis and COPD but without asthma).

Co-existing disease	NSAID-induced dyspnoea			p
	No.	Rhinitis	Asthma	
Total, n	22	46	64	
Anaphylaxis during the last year	3(13.6)	6(13.0)	9(14.1)	0.988
Visit to emergency department due to asthma attack during the last year	0(0.0)	0(0.0)	9(14.1)	0.006
Hospitalization due to asthma exacerbation during the last year	0(0.0)	0(0.0)	5(7.8)	0.063

Data are n (%).

Table S6. Tobacco smoke, secondhand smoke and occupational exposure associated with N-ERD as determined by univariable and multivariable binary logistic regression adjusted for age and sex.

	Crude		Adjusted for age and sex	
	OR	95% CI	OR	95% CI
Non-smoker (ref.)
Current smoker	1.22	0.74-1.99	1.37	0.84-2.26
Ex-smoker	1.64	1.07-2.53	1.61	1.04-2.50
Smoke exposure at home	2.99	1.92-4.66	2.79	1.78-4.37
Smoke exposure at work	2.33	1.44-3.78	2.35	1.43-3.86
Occupational exposure to VGDF	1.83	1.24-2.70	1.96	1.32-2.92