

Rhinitis is associated with a greater risk of intermittent claudication in adults

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Abstract

Background: Chronic inflammatory airway disorders have been reported to be associated with vascular diseases of the heart and central nervous system, but their association with peripheral arterial disease (PAD), a high-prevalence vascular illness, has not been investigated.

Objective: To evaluate the association of asthma and rhinitis with intermittent claudication, which is a typical symptom of PAD.

Methods: The data were collected in the gene–environment interaction in respiratory disease survey, a population-based, multicase–control study. Participants underwent a standardized interview, skin prick tests and pulmonary function tests. The associations between respiratory diseases and intermittent claudication (i.e. pain in the leg during walking that disappears within 10 min when standing still) were estimated through relative risk ratios (RRR) by multinomial logistic regression models.

Results: 1174 subjects (aged 20–64 years, of which 52% were females) underwent clinical examinations and were classified into four groups: asthma only ($n = 81$), asthma–rhinitis overlap ($n = 292$), rhinitis only ($n = 299$) and controls ($n = 345$). The prevalence of intermittent claudication in these groups was, respectively, 2.5%, 3.4%, 6.4% and 2.3%. After adjusting for smoking habits and a wide range of established and potential vascular risk factors, rhinitis without asthma was associated with intermittent claudication (RRR:4.63, 95% CI:1.72–12.5), whereas no significant association was found with asthma alone (RRR:1.45, 95% CI:0.27–7.76) or asthma–rhinitis overlap (RRR:2.89, 95% CI:0.91–9.18). Atopy did not modify the observed association between intermittent claudication and rhinitis.

Conclusions: Our findings suggest that rhinitis is associated with PAD, a predictor of future cerebrovascular and cardiovascular events, independently of the presence of atopy.

During the past years, evidence has made it clear that inflammation plays a pivotal role in the pathogenesis of coronary heart disease, stroke and other clinical manifestations of atherosclerosis (1). It is therefore not surprising that

ischaemic heart disease and heart failure may frequently occur in patients with chronic inflammatory airway diseases, most notably chronic obstructive pulmonary disease (COPD) (2, 3). Asthma and rhinitis may also be associated with the atherosclerotic process (4, 5). Asthma and rhinitis are inflammatory airway disorders which primarily involve the bronchi and the nose, but the inflammation they produce could also propagate systemically (6). Moreover, inflammatory mediators and cells involved in asthma and rhinitis, such as leukotrienes and immunoglobulin E (IgE), have been linked to the pathogenesis of atherosclerosis (7, 8). Recent studies have shown an association between the presence of

Abbreviations

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CP, *Chlamydia pneumoniae*; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GEIRD, gene–environment interaction in respiratory disease; IgE, immunoglobulin E; LLN, lower limit of normality; PAD, peripheral arterial disease; RRR, relative risk ratio.

asthma and rhinitis with the risk of vascular diseases of the heart and the nervous system, such as myocardial infarction and stroke (4, 5). By contrast, to the best of our knowledge, no investigations have so far been carried out in relation to the association with peripheral arterial disease (PAD), a high-prevalence atherosclerotic process that causes stenosis and occlusion of noncerebral and noncoronary arteries (9). The study of PAD and of its association with respiratory diseases is of particular relevance, as it is a powerful predictor of future cerebrovascular and cardiovascular events (10), and, moreover, PAD is often the only evidence of atherosclerotic disease in a relevant part (9%) of patients suffering from atherosclerosis (11). The main symptom of PAD is intermittent claudication, a crampy leg pain that occurs during exercise, especially walking. The pain is due to insufficient blood flow in the legs, caused by blocked arteries.

In the present analysis, we tested whether asthma and rhinitis are associated with intermittent claudication, using the data collected in the frame of the multicentre, general population-based gene–environment interactions in respiratory disease (GEIRD) study.

Methods

Study design and selection of the cohort

The gene–environment interaction in respiratory diseases (GEIRD) is a two-stage multicentre, multicase–control study (12). In the first stage, subjects from the general population

were cross-sectionally screened for respiratory symptoms (13). In the second stage, a sample of subjects with and without respiratory symptoms was invited for a clinical examination and laboratory measurements (14). Only the subjects recruited in the Verona centre between 2007 and 2012 were considered in this analysis.

Screening questionnaires were sent to 7415 subjects in the Verona centre. Overall, 5203 (68%) subjects answered the questionnaire, and 5014 of these subjects consented to participate in GEIRD stage 2. On the basis of the symptoms reported in the screening questionnaire, all the subjects who reported symptoms suggestive of asthma, chronic bronchitis, a random sample (30%) of subjects who reported rhinitis or hay fever and a random sample (40%) of the subjects who did not report respiratory symptoms, diagnoses or hospitalizations were invited to the clinic (Fig. 1).

Clinical measurements

The subjects' body height was measured to the nearest 0.5 cm while they stood barefoot, and the subjects were weighed to the nearest 0.1 kg with light clothing and no shoes. Body mass index (BMI) was computed dividing weight (kg) by height squared (m^2).

Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were measured using a Biomedin spirometer according to the American Thoracic Society reproducibility criteria. Lung function values were expressed as a percentage of predicted values, and the lower limit of normal LLN for

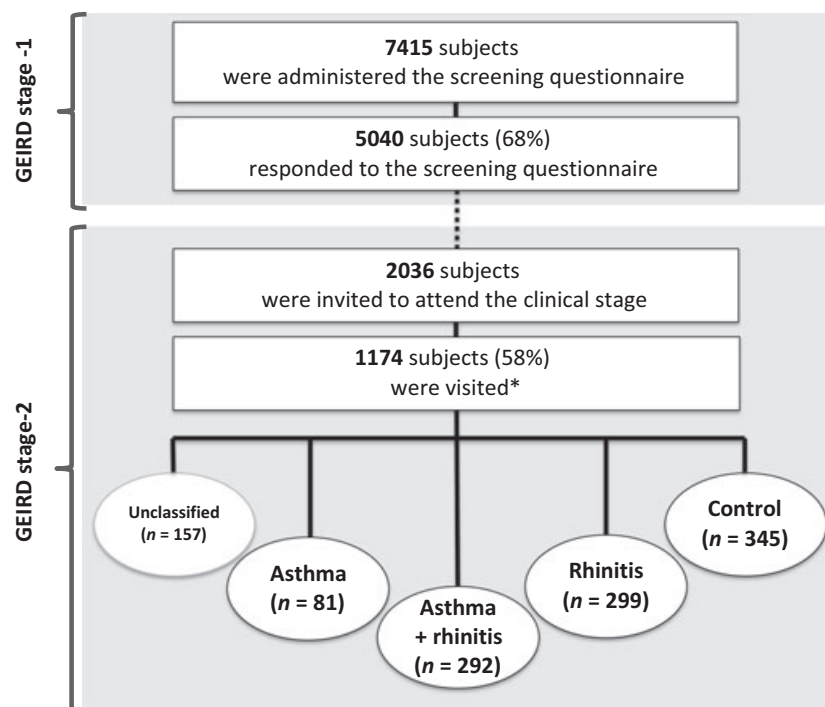


Fig. 1 Number of participants in the gene–environment interaction in respiratory disease (GEIRD) study in Verona, and classification into case–control groups. * by 31 October 2012.

the FEV1/FVC were calculated according to Quanjer (15). Spirometry was performed again 10 min after the administration of 400 µg salbutamol in subjects with FEV1/FVC <70% or <LLN. The subjects with FEV1/FVC ≥70% and ≥LLN underwent the methacholine challenge, according to a standardized protocol (16). Briefly, FEV1 was recorded 2 min after each inhalation of methacholine solutions, and in the absence of a 20% decrease in FEV1 from baseline, the next dose was administered. A subject's test was positive if FEV1 decreased by 20% at a maximum cumulative dose ≤1 mg methacholine (PD20 ≤ 1).

The subjects were skin tested for a panel of 11 aeroallergens (14). Histamine dihydrochloride and glycerol diluents were used as positive and negative controls, respectively. A subject was considered to be atopic if positive to one or more of the tested allergens.

A sample of peripheral whole blood was collected from these subjects for a complete blood count, and the number of white blood cells, lymphocytes, monocytes, eosinophils, neutrophils and basophils was assessed.

Identification of cases and controls in clinics

Based on the symptoms reported and the results of the clinical tests, the subjects were considered to be the following:

- Cases of asthma: (1) self-reported asthma; or (2) asthma-like symptoms or use of asthma medicines in the last 12 months, plus one among (2.1) PD₂₀ ≤ 1 mg, (2.2) prebronchodilator FEV1/FVC < 70% or < LLN with a positive reversibility test (i.e. FEV1 > 12% and > 200 ml after 400 µg of salbutamol);
- Cases of rhinitis (both allergic and nonallergic): one among (1) lifetime nasal allergies, including 'hay fever'; (2) lifetime problem with sneezing, or a runny or a blocked nose (without cold/flu); (3) recurrent nasal/eye symptoms in the presence of dust, pollens or animals.

The subjects were classified into four groups: asthma only (*n* = 81) rhinitis only (*n* = 299), asthma–rhinitis overlap (*n* = 292) and controls (*n* = 345). The latter did not report any respiratory symptoms nor disease and had both (i) prebronchodilator FEV1/FVC > LLN and > 70%; and (ii) FEV1 > 80% predicted. One hundred and fifty-seven subjects were excluded from the analyses because of missing values on key information or because they did not correspond to any of the definitions above (Fig. 1).

Intermittent claudication and covariates

Using questions from the Edinburgh Claudication Questionnaire (17), a modified version of the WHO-Rose questionnaire (18), a subject was considered to have intermittent claudication if he/she answered yes to the question: 'Do you get a pain or discomfort in your legs when you walk?', plus he/she reported that it usually disappeared in 10 min or less when standing still.

Information on the following variables was collected during the clinical interview and was taken into account for the analyses: age, gender, education (no school/primary school,

secondary school, University) as a proxy of the socio-economic status, smoking habits (lifetime nonsmoker, ex-smoker, current smoker), daily alcohol intake (lifetime nonconsumer, ex-alcohol consumer, ≤15 g/day, >15 g/day), physical activity (<1 h/week, 1–3 h/week, >3 h/week) and whether the subject suffered from diabetes, hypertension or dyslipidaemia (self-reported high levels of cholesterol or triglycerides).

Statistical analysis

The subjects' characteristics were summarized as percentages or means (SD). The Pearson's chi-squared, Fisher's exact and ANOVA tests were used to test differences across cases and controls (α = 0.05). The associations between intermittent claudication and respiratory diseases were estimated through relative risk ratios (RRR) obtained by multinomial logistic regression models. Four models were fitted to the data, using the case/control indicator (0 = control, 1 = asthma only, 2 = asthma–rhinitis overlap, 3 = rhinitis only) as the dependent variable and intermittent claudication as the main independent variable: (i) unadjusted; (ii) adjusted for age, gender, smoking habits, alcohol consumption, BMI, school education and physical activity; (iii) also adjusted for the co-morbidity indicators and (iv) further adjusted for atopy.

To investigate whether the association between the case/control indicator and intermittent claudication was similar in atopic and nonatopic subjects, an interaction term between atopy and intermittent claudication was tested using the likelihood ratio test.

Sensitivity analyses were performed by evaluating the association of intermittent claudication separately in subjects with asthma (including those with overlapping rhinitis) and in subjects with rhinitis (including those with overlapping asthma), using a logistic regression model with the controls set as reference group. Statistical analyses were performed with STATA 12.1 (Stata Corp. College Station, TX, USA).

Results

In the Verona centre, 2036 subjects were invited to attend the clinical stage, and 1174 of them (58%) were examined by October 2012 (Fig. 1). The subjects who participated were similar to the subjects who did not as regards the distribution of gender, age and smoking habits.

The characteristics of cases and controls, as determined in the clinical interview, are reported in Table 1. The average age ranged from 42.0 years in the subjects with asthma–rhinitis overlap to 46.1 years in the subjects with asthma only (P = 0.001). The proportion of females and males was similar across groups, and there were no differences in the distribution of lifestyle variables, schooling, BMI or co-morbidities.

Table 2 shows some clinical features of cases and controls. The subjects with asthma only and asthma–rhinitis overlap had poorer lung function compared to the controls and the subjects with rhinitis only (P < 0.001). The subjects with rhinitis (especially in those with overlapping asthma) had higher blood eosinophil counts than the subjects with asthma only and the controls (P < 0.001). Similarly, the frequency of

Table 1 Characteristics of cases and controls

	Control (n = 345)	Asthma only (n = 81)	Asthma + rhinitis (n = 292)	Rhinitis only (n = 299)	P-value*
Female sex	180 (52)	46 (57)	142 (49)	160 (54)	0.503
Age (year)	45.3 ± 9.6	46.1 ± 9.0	42.0 ± 9.6	44.2 ± 10.2	<0.001
Smoking habits					
Nonsmokers	179 (52)	35 (43)	142 (49)	152 (51)	0.166
Ex-smokers	104 (30)	23 (28)	75 (26)	79 (26)	
Smokers	60 (18)	23 (28)	86 (26)	68 (23)	
Alcohol consumption					
No	198 (59)	43 (53)	156 (54)	165 (55)	0.782
≤15 g/day	100 (30)	27 (33)	84 (29)	90 (30)	
>15 g/day	35 (10)	11 (14)	45 (16)	39 (13)	
Ex-alcohol consumers	4 (1)	0 (0)	3 (1)	4 (1)	
Schooling					
Lower education	106 (31)	21 (27)	70 (25)	89 (30)	0.421
High school	157 (46)	43 (55)	146 (52)	135 (45)	
University	82 (24)	14 (18)	66 (23)	74 (25)	
Physical activity					
<1 h/week	171 (50)	43 (53)	136 (47)	140 (47)	0.342
1–3 h/week	104 (30)	27 (33)	110 (38)	108 (37)	
>3 h/week	69 (20)	11 (14)	45 (15)	48 (16)	
BMI					
<18.5 kg/m ²	8 (2)	0 (0)	4 (1)	7 (2)	0.379
18.5–25 kg/m ²	179 (52)	48 (60)	156 (53)	177 (59)	
25–30 kg/m ²	114 (33)	20 (25)	100 (34)	86 (29)	
>30 kg/m ²	44 (13)	12 (15)	32 (11)	29 (10)	
Diabetes	4 (1)	1 (1)	2 (1)	3 (1)	0.932
Hypertension	59 (17)	12 (15)	47 (16)	64 (21)	0.292
Dyslipidaemia	91 (27)	23 (29)	63 (22)	78 (26)	0.424

Values are means ± SD or n (%).

*P-values for differences among groups were calculated using chi-squared or Kruskal–Wallis test.

Table 2 Clinical characteristics of the cases and controls

	Control (n = 345)	Asthma only (n = 81)	Asthma + rhinitis (n = 292)	Rhinitis only (n = 299)	P*
Spirometry					
FEV1, % predicted	109 ± 12	105 ± 15	102 ± 14	106 ± 13	<0.001
FEV1, <80% predicted	1 (0)	4 (5)	19 (7)	6 (2)	<0.001
FEV1/FVC (%)	83.4 ± 5.9	78.8 ± 7.7	78.3 ± 7.4	81.5 ± 7.0	<0.001
Blood count					
White blood cells (×1000/μl)	6.6 ± 1.7	7.1 ± 1.5	7.0 ± 1.9	6.7 ± 1.8	0.033
Eosinophils (unit/μl)	132 ± 98	153 ± 173	221 ± 188	171 ± 153	<0.001
Neutrophils (×1000/μl)	4.1 ± 1.4	4.4 ± 1.2	4.3 ± 1.6	4.1 ± 1.6	0.110
Basophils (unit/μl)	28.1 ± 15.5	32.1 ± 17.1	33.1 ± 17.7	31.9 ± 17.2	0.003
Lymphocytes (×1000/μl)	1.91 ± 0.49	2.03 ± 0.59	1.97 ± 0.53	1.95 ± 0.57	0.204
Monocytes (unit/μl)	361 ± 113	375 ± 113	365 ± 114	361 ± 113	0.683
Atopy†	102 (31)	26 (33)	240 (87)	186 (66)	<0.001

Values are means ± SD or n (%).

*P-values for differences across groups were calculated using chi-squared or Kruskal–Wallis test.

†Subjects positive for at least one of the 11 allergens tested.

atopy was higher in the cases of rhinitis (87% and 66% in those with or without overlapping asthma, respectively) compared to the controls (31%) and to the cases with asthma only (33%) ($P < 0.001$).

Thirty-nine subjects reported symptoms of intermittent claudication (Table 3). The frequency of intermittent claudication was significantly higher in the subjects with rhinitis only (6.4%), but not in the cases of asthma (2.5%) or

Table 3 Prevalence of intermittent claudication in cases and controls

	n/N	%	95% CI
Control	8/344	2.3	1.2–4.6
Asthma	2/80	2.5	0.6–9.4
Asthma + rhinitis	10/292	3.4	1.9–6.2
Rhinitis	19/299	6.4	4.1–9.7

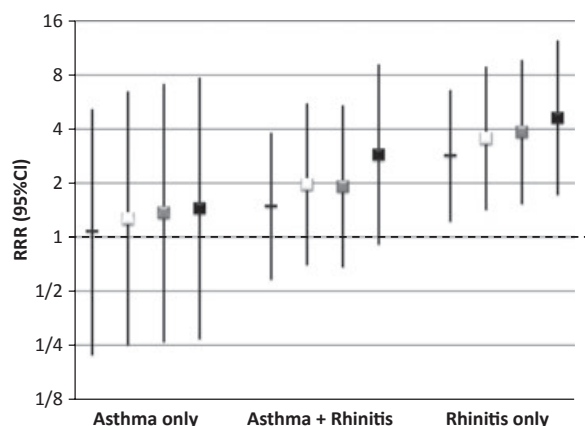


Fig. 2 Relative risk ratio (RRR, with 95% CI) for the association of intermittent claudication with asthma and rhinitis. Model A (horizontal bar): unadjusted; Model B (white square): adjusted for age, gender, body mass index (BMI), schooling, smoking habits, alcohol consumption and physical activity; Model C (grey square): adjusted for variables in B plus: diabetes, hypertension, dyslipidaemia; Model D (black square): adjusted for variables in C plus atopy.

asthma–rhinitis overlap (3.4%), compared to the control group (2.3%). After adjusting for potential confounders, the subjects with rhinitis only (RRR:3.77, 95% CI:1.50–9.48), but not asthma only (RRR:1.35, 95% CI:0.26–6.99) or asthma–rhinitis overlap (RRR:1.86, 95% CI:0.66–5.27), had a significantly higher risk of having intermittent claudication compared to the controls (Fig. 2). The association between rhinitis and intermittent claudication was even stronger when atopy was included in the model (Model D). Moreover, atopy did not significantly modify the association between respiratory diseases and intermittent claudication ($P = 0.362$).

When rhinitis was considered disregarding the presence of asthma, its association with intermittent claudication was confirmed (Table S1).

Discussion

The primary finding of this study is that subjects with a history of rhinitis had a greater risk of suffering from intermittent claudication, a symptom related to obstructive arterial diseases of the lower limbs. The greater risk of intermittent claudication with respect to controls was statistically significant for subjects with rhinitis alone, and there was an

indication of risk also for subjects with asthma–rhinitis overlap. These results were confirmed after controlling for factors that might confound the relationship, including age, sex, smoking status, body mass index, alcohol use, diabetes, hypertension and dyslipidaemia. Of importance is also the finding that the association between rhinitis and PAD was not modified by the presence of atopy.

Little research has addressed the relationship between rhinitis and cardiovascular diseases. Previous studies reported that rhinosinusitis may be associated with ischaemic stroke and myocardial infarction (19). The present study is the first of its kind that shows an association between rhinitis and intermittent claudication, a typical symptom of lower extremity PAD.

The precise nature of the association between rhinitis and atherosclerotic vascular disease remains speculative. Rhinitis may constitute a true risk factor and predisposition to PAD through specific pathophysiologic pathways. There is evidence that rhinitis can produce a systemic inflammation mediated by cytokines and vasoactive peptides released into the circulation (20) and that inflammation may promote atherosclerotic diseases (1).

Previous studies reporting an association between allergic rhinitis and cardiovascular diseases have suggested that leukotrienes and IgE, two pivotal mediators associated to atopy, might be involved in the pathogenesis of atherosclerosis (7, 8, 21). In our study, atopy did not modify the association between rhinitis and claudication, indicating that mechanisms other than those related to atopy are likely to be involved in PAD.

Our study showed that patients with rhinitis (with or without asthma) had the highest count of peripheral eosinophils, and subjects with intermittent claudication had a higher eosinophil count than subjects without claudication in both the control and rhinitis groups (Table S2). This finding suggests that eosinophils may play a direct role in the atherosclerotic process, in agreement with previous studies (22). However, when the number of eosinophils was adjusted for in the analysis (data not shown), the relationship between rhinitis and PAD was confirmed, further supporting an independent role of rhinitis.

Several studies suggest that viral or bacterial infections can contribute to atherosclerosis either via the direct infection of vascular cells or via the indirect effects of cytokines or acute phase proteins induced by infection at nonvascular sites (23). Acute exacerbations of rhinosinusitis are often precipitated by infections (24). In particular, *Chlamydia pneumoniae* (CP), an obligate intracellular human pathogen, can cause infections both of the lower and the upper respiratory tract, including pneumonia, bronchitis, pharyngitis and sinusitis (25). CP components have been detected in the atherosclerotic plaque (26), and a recent study demonstrated that CP-specific IgG levels are elevated among patients with coronary artery diseases and are associated with disease development (27).

Furthermore, the association between rhinitis and atherosclerosis may be caused by an inherent joint susceptibility to both diseases through shared inflammatory

pathways. Previous studies have shown that patients with rhinosinusitis had higher levels of C-reactive protein (CRP) than controls and that CRP levels were associated with the severity of nasal symptoms (28). CRP levels in turn predict cardiovascular events and are associated with increased mortality in patients with peripheral vascular diseases (29). There is also evidence of a direct role of CRP in the pathogenesis of atherosclerosis, as indicated by the detection of CRP deposition in the arterial intima at the site of atherogenesis (30).

Finally, reversed causation cannot be excluded. Some cardiovascular diseases, potentially associated to PAD such as myocardial infarction, may impair host immunity, render the host susceptible to bacterial infection (31) and more prone to sinusitis. Furthermore, some drugs used in the treatment of cardiovascular diseases (particularly hypertension), such as angiotensin-converting enzyme inhibitors, β -blockers and prazosin, can cause chronic rhinitis (32). However, the association between rhinitis and PAD did not change after controlling for hypertension and for antihypertensive treatment (data not shown).

In our sample, we did not find a statistically significant association between asthma and PAD, even though the low number of cases with intermittent claudication and of subjects with asthma did not provide a definitive conclusion. The studies so far conducted on the relationship between atherosclerosis and asthma have produced conflicting results. Depending on the clinical outcome considered, different studies reported positive, null and even negative associations between asthma and cardiovascular diseases (4, 33, 34). It should also be noted that the studies providing evidence of a positive association between asthma and cardiovascular disease did not separately consider cases with and without rhinitis, failing to take the confounding effect of rhinitis into account. The reason why asthma, differently from rhinitis, seems not to be associated with claudication is not clear. It is possible that some drugs used in the treatment of bronchial disease, such as the leukotriene receptor antagonist montelukast or inhaled corticosteroids, may have a protective role for cardiovascular diseases (35, 36). Unfortunately, one limitation of our study is that it did not have enough cases and controls to investigate these hypotheses, and therefore, we were not able to analyse specific disease phenotypes or risk subgroups.

The subjects with rhinitis combined with asthma did not have a statistically significant increased risk of intermittent claudication. However, the relative risk for asthma–rhinitis overlap, although not significantly different from the control group, was much greater than that for asthma alone (Fig. 2). This result is probably due to the low number of cases, and further studies on a larger sample are needed to clarify this point.

A limitation of the study is that for the determination of obstructive arteriopathy of the lower limbs, the patients were identified by symptoms rather than specific vascular tests, such as the measurement of the ankle-brachial index. Another limit of the study is that the definition of rhinitis adopted may overdiagnose the disease. However, this fact (i.e. including some subjects without rhinitis in the rhinitis

group) is likely to result in a dilution rather than an overestimation of the strength of the association between rhinitis and intermittent claudication.

In conclusion, the present study provides new evidence that rhinitis, which has previously been viewed as a benign condition, may be a contributor to intermittent claudication, a symptom associated to lower limb arteriopathy, after adjustment for major cardiovascular risk factors. Because the epidemic of rhinitis is still on the increase and over 20% of the European adult population suffers from the disease (13, 37), these findings may have broad public health implications.

If this association was confirmed by appropriate longitudinal studies, it would add to the significant burden that is imposed by rhinitis, a highly prevalent condition in the general population. The biological mechanisms by which subjects with rhinitis may have an excess risk of intermittent claudication require further study.

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Author contributions

Dr Ferrari supervised the clinical data collection, co-conceived and designed the present study, drafted the initial manuscript and approved the final manuscript as submitted. Dr Pesce participated in the design of the present study, carried out the statistical analyses, critically reviewed the manuscript and approved the final manuscript as submitted. Dr Marcon participated in the design of the present study, critically reviewed the manuscript and approved the final manuscript as submitted. Dr Vallerio, Dr Fratta-Pasini collected the clinical data, critically reviewed the manuscript and approved the final manuscript as submitted. Prof de Marco is the coordinator of the GEIRD Study, supervised the data collection, co-conceived and designed the present study, critically reviewed the manuscript and approved the final manuscript as submitted.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Odds ratios (OR, with 95% CI) for the association of asthma (with or without rhinitis) and rhinitis (with or without asthma) with intermittent claudication.

Table S2. Blood concentration of eosinophils (unit/ μ l) in the subjects with and without intermittent claudication.

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1 **SUPPLEMENTARY MATERIAL**

2 **Table S1:** Odds ratios (OR, with 95%CI) for the association of asthma (with or without rhinitis) and rhinitis
 3 (with or without asthma) with intermittent claudication .

	Model A[†]	Model B[†]	Model C[†]	Model D[†]
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Asthma	1.40 (0.57-3.47)	1.81 (0.67-4.95)	1.88 (0.68-5.21)	2.79 (0.91-8.62)
Rhinitis	2.17 (0.98-4.80)	2.79 (1.16-6.67)	2.84 (1.19-6.83)	4.05 (1.54-10.6)

[†]Model A: crude association; Model B adjusted for age, gender, smoking habits, alcohol consumption, schooling and physical activity; Model C adjusted for variables in B plus body mass index, diabetes, hypertension, dyslipidemia; Model D adjusted for variables in C plus atopy.

4

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Table S2: Blood concentration of eosinophils (unit/ μ L) in the subjects with and without intermittent claudication.

	Intermittent claudication? (n)	Eosinophil count	
		Mean (SD)	Median [IQR]
Control group	No (309)	131 (96)	107 [61-163]
	Yes (8)	177 (135)	182 [62-209]
Rhinitis[†]	No (522)	194 (167)	153 [91-238]
	Yes (23)	237 (272)	192 [102-235]
†including subjects with rhinitis-asthma overlap			