

Mild Asthma and Chronic Bronchitis Seem to Influence Functional Exercise Capacity: A Multi-Case Control Study

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Key Words

Asthma · Chronic bronchitis · Functional exercise capacity · Six-minute walk test

Abstract

Background: In the Genes Environment Interaction in Respiratory Diseases population-based multi-case control study, we investigated whether asthma, chronic bronchitis (CB) and rhinitis were associated with a reduced 6-minute walk distance (6MWD), and whether the 6MWD determinants were similar for subjects with/without respiratory diseases. **Methods:** Cases of asthma (n = 360), CB (n = 120), rhinitis (n = 203) and controls (no respiratory diseases: n = 302) were recruited. The variation in the 6MWD across the groups was analyzed by ANCOVA, adjusting for gender, age, height, weight and comorbidity. The 6MWD determinants were studied by linear regression, and heterogeneity across the cases and controls was investigated. **Results:** The 6MWD differed across cases and controls (p = 0.01). It was shorter for cases

of asthma (–17.1, 95% CI –28.3 to –5.8 m) and CB (–20.7, 95% CI: –36.6 to –4.8 m) than for controls (604 ± 68 m on average), but not for cases of rhinitis. The negative association between age and the 6MWD was significant for cases of CB, but not for the other groups (p = 0.001). **Conclusions:** Even at the level of severity found in the general population, asthma and CB could influence the 6MWD, which seems to reflect the functional exercise level for daily physical activities. The negative association between ageing and the 6MWD was particularly strong in subjects with CB. Our report adds to the mounting evidence that CB is not a trivial condition, especially in the ageing adult population, and it supports the importance of monitoring functional capacity and of physical reconditioning in mild asthma.

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Introduction

Asthma is the most common chronic respiratory disease in the world [1]. In the general population, about 30% of asthmatic subjects have a moderate to severe form of the disease [2]. Severe asthma can strongly limit daily life activities [3–5]. However, when asthma patients are free of symptoms, they respond to exercise in the same physiological way as other people [5]. Chronic bronchitis (CB) is markedly underdiagnosed; it has a noticeable impact on the health status, working ability and healthcare resource consumption [6, 7]. The effect of CB on functional exercise capacity has rarely been investigated. The same holds true for rhinitis, which is frequently seen as a trivial and temporary disease, but may actually seriously interfere with the physical dimension of life [4].

The 6-minute walk test (6MWT) measures the distance (6MWD) that a subject can walk quickly on a flat, hard surface for 6 min. It assesses the submaximal level of functional capacity and reflects the exercise level for daily physical activities [8].

In this study, we aimed at investigating whether cases of asthma, CB and rhinitis from the general population have a shorter 6MWD when compared with subjects without any respiratory diseases. We also investigated whether the determinants of the 6MWD were similar across cases and controls.

Methods

Study Design

The Genes Environment Interaction in Respiratory Diseases (GEIRD) project is an ongoing multicase-control study involving seven Italian centers [9]. In stage 1, new random samples or pre-existing randomly sampled cohorts from the general population (20–64 years of age, male/female = 1/1) were mailed a screening questionnaire on respiratory symptoms [10]. In stage 2, subjects reporting symptoms suggestive of CB/COPD, asthma or rhinitis, and subjects without respiratory symptoms (online suppl. table S1; for all online supplementary material, see www.karger.com/doi/10.1159/000345137) were invited to clinics, where they underwent interviews and clinical tests. All measurement protocols were in agreement with international guidelines (www.geird.org) [9]. Ethical approval was obtained in each center from the appropriate ethics committee, and written consent was obtained from each participant.

In our analysis, only the subjects recruited in the Verona center between 2007 and 2010 were considered. In this center, 5,203 (68%) out of 7,415 subjects answered the screening questionnaire; 1,032 of them attended the clinical stage (online suppl. fig. S1). Participants were similar to nonparticipating subjects in terms of gender, age and smoking (online suppl. table S2).

Lung Function and Allergologic Tests

Subjects underwent forced spirometry according to the American Thoracic Society reproducibility criteria [11]. FEV₁ % predicted and the lower limit of normal (LLN) for the FEV₁/FVC were calculated according to Quanjer et al. [12]. Subjects with an FEV₁/FVC $\geq$ 70% and $\geq$ LLN underwent a methacholine challenge test, which followed a protocol described elsewhere [13]. Subjects with an FEV₁/FVC <70% or < LLN underwent bronchodilator challenge test, and were invited (if eligible) to undergo a methacholine challenge test on a second occasion. Atopy was assessed by skin prick tests (online suppl. material).

Identification of Cases and Controls in Clinics

The subjects were hierarchically classified as follows (online suppl. table S3):

- 360 cases of asthma; patient reported (1) a history of asthma or (2) asthma-like symptoms/medicines in the last 12 months and had: (2.1) a positive methacholine challenge test with PD₂₀ <1 mg or (2.2) prebronchodilator FEV₁/FVC <70% or < LLN [12] with a positive reversibility test (i.e. FEV₁ >12% and >200 ml after the administration of 400 µg of salbutamol)
- 8 cases of COPD (postbronchodilator FEV₁/FVC <70% or < LLN) without asthma (not considered in the analyses because of the limited number)
- 120 cases of CB (cough and/or phlegm for at least 3 months each year for $\geq$ 2 years), with neither asthma nor COPD
- 203 cases of rhinitis (hay fever and/or nasal/eye symptoms in the presence of dust, pollens or animals) without asthma, COPD or CB
- 302 controls (subjects who were not cases and had both (1) prebronchodilator FEV₁/FVC > LLN and >70% and (2) FEV₁ >70% predicted)
- 39 subjects were unclassified due to missing data.

The 6MWT

The 6MWT protocol was developed in agreement with the American Thoracic Society guidelines (2002) [8]. Before testing, subjects were checked for contraindications. Subjects were asked to walk as far as they could without running in a 25-meter-long hallway. If a subject stopped before the 6 minutes were up (or the operator decided that he/she should not continue), the reason for stopping was recorded. The test results were expressed both as the distance walked (i.e. the 6MWD) in meters, and as the percentage of subjects who walked a distance shorter than the 5th percentile of the 6MWD distribution in controls.

Covariates

The following covariates were considered:

- Potential confounders: study cohort [9, 10], calendar period (accounting for seasonality), gender, age, height, weight, comorbidity [at least one of: hypertension or diabetes (subjects currently under medication), 'cardiovascular comorbidity' (at least one of: lifetime heart attack, ictus, angina pectoris, arrhythmia, heart or aorta surgery) or cancer]. The questions on cardiovascular comorbidities were taken from the WHO/Rose validated questionnaire [14].
- Determinants: education (low = completed before the age of 16) as a proxy of socioeconomic status, smoking habits (never smoker, past smoker i.e. not smoking in the last month or cur-

Table 1. Characteristics of cases and controls

	Asthma (n = 360)	CB (n = 120)	Rhinitis (n = 203)	Controls (n = 302)	p value
Gender, female	185 (51)	64 (53)	118 (58)	155 (51)	0.41
Age, years	42.7 ± 9.6	46.0 ± 9.7	44.1 ± 10.2	45.2 ± 9.5	0.001
Height, cm	170.4 ± 8.9	169.5 ± 9.8	168.9 ± 8.9	169.9 ± 9.1	0.25
Weight, kg	72.5 ± 14.4	71.8 ± 15.3	69.8 ± 14.3	72.5 ± 15.1	0.14
Body mass index	24.9 ± 4.4	24.8 ± 4.1	24.4 ± 4.0	25.0 ± 4.4	0.36
FEV ₁ ^a , % predicted	102.5 (14.2)	106.6 (11.2)	107.6 (13.3)	108.5 (12.3)	<0.001
FEV ₁ ^a , <80% predicted	22 (6)	1 (1)	2 (1)	1 (0)	<0.001
Atopy ^b	255 (75)	56 (49)	114 (61)	93 (32)	<0.001
Low education	41 (11)	33 (28)	23 (11)	49 (16)	<0.001
Smoking habits ^c					0.001
Nonsmoker	170 (47)	47 (39)	105 (52)	153 (51)	
Past smoker	93 (26)	28 (23)	58 (29)	95 (32)	
Current smoker	97 (27)	45 (38)	40 (20)	52 (17)	
Physical activity ^c					0.18
<1 h/week	173 (48)	66 (56)	94 (46)	149 (50)	
1–3 h/week	132 (37)	35 (30)	76 (37)	90 (30)	
>3 h/week	54 (15)	17 (14)	33 (16)	62 (21)	
Hypertension	33 (9)	20 (17)	27 (13)	32 (11)	0.11
Diabetes	3 (1)	0 (0)	3 (1)	3 (1)	0.71
Cardiovascular comorbidity ^d	20 (6)	13 (11)	19 (9)	8 (3)	0.002
Cancer	10 (3)	5 (4)	6 (3)	7 (2)	0.78
At least 1 comorbidity	58 (16)	32 (27)	45 (22)	48 (16)	0.02

Values are means ± SD or n (%)

^a Prebronchodilator spirometry.

^b Percentage of subjects positive for at least 1 out of 14 allergens (see suppl. material).

^c Percentages may not sum up to 100 because of rounding.

^d Lifetime heart attack, ictus, angina pectoris, arrhythmia, heart or aorta surgery.

rent smoker), physical activity (<1 h/week, 1–3 h/week or >3 h/week) and FEV₁ % predicted.

- The case/control indicator (0 = control, 1 = asthma, 2 = CB and 3 = rhinitis).

Statistics

Subject characteristics were summarized as percentages or means (SD). The χ^2 test, Fisher exact test, ANOVA and Student t test were used to test differences ($\alpha = 0.05$). To study whether the 6MWD was different across cases and controls, an ANCOVA model was used which included the 6MWD as the dependent variable and the case/control indicator and the potential confounders as independent variables. If the overall difference across cases and controls was statistically significant, pairwise comparisons between groups were tested by Student t tests with the Holm-Bonferroni correction for multiple comparisons.

The determinants of the 6MWD were studied by fitting multiple linear regression models for cases and controls separately. All the potential confounders and determinants were included in each model. To investigate whether the association between the determinants and the 6MWD was similar across the cases and controls (test for heterogeneity), the interactions between each de-

terminant and the case/control indicator were tested by the likelihood ratio test, by fitting multiple linear regression models on all the cases and controls together (one model for each interaction term being tested). These models included all the previous covariates plus the case/control indicator as independent variables.

When the interaction was not statistically significant (p value for heterogeneity >0.10), an overall estimate (i.e. pooled across the cases and controls) of the association between each determinant and the 6MWD was obtained.

Results

CB cases were the oldest (46.0 years), had the highest prevalence of low education (28%), lifetime smoking (61%) and comorbidity (27%), especially cardiovascular comorbidity (11%) (table 1). Allergen sensitization was more common among cases of asthma (75%) and rhinitis (61%) than among cases of CB (49%) or among controls (32%).

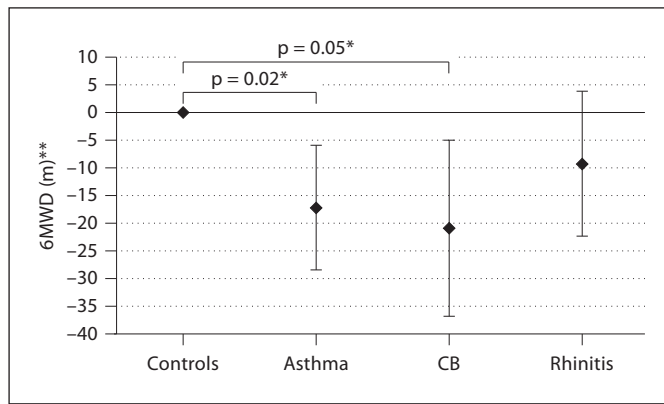


Fig. 1. Mean difference (with 95% CIs) in the 6MWD of cases versus controls, adjusted for gender, age, height, weight, comorbidity, study cohort and calendar period. * p values corrected for multiple testing. ** Difference with respect to controls.

Table 2. Characteristics of the subjects who did and did not perform the 6MWT

	6MWT		p value
	yes	no	
Number	871 (88)	114 (12)	
Gender, female	468 (54)	54 (47)	0.17
Age, years	43.3 ± 9.5	50.8 ± 9.1	<0.001
Body mass index	24.4 ± 3.9	27.9 ± 5.6	<0.001
Low education	115 (13)	31 (27)	<0.001
Smoking habits			0.002
Nonsmoker	423 (49)	52 (46)	
Past smoker	228 (26)	46 (40)	
Current smoker	218 (25)	16 (14)	
Physical activity			0.02
<1 h/week	413 (48)	69 (61)	
1–3 h/week	306 (35)	27 (24)	
>3 h/week	148 (17)	18 (16)	
Comorbidity	116 (13)	67 (59)	<0.001

Values are means ± SD or n (%).

Participation in the 6MWT

The 6MWT was completed by 871 (88%) subjects. One hundred and ten were excluded because they had *claudicatio intermittens*, were disabled from walking for a condition different from lung/heart disease or due to other exclusion criteria [8] (online suppl. material). One subject refused and three were excluded because they did not

complete the test. When compared to subjects who did the test, subjects who did not do the test were older and weighed more, had a lower education level, were more frequently past smokers, sedentary and more likely to report comorbidities (table 2). The test participation rate ranged from 85% (rhinitis and CB) to 92% (controls) (online suppl. table S3).

Differences between Cases and Controls in the 6MWD

The mean 6MWD for controls was 604 (SD 68, 5th percentile 505) m, while cases of asthma, CB and rhinitis walked 594 m (SD 70), 589 m (SD 79) and 600 m (SD 69), respectively. The percentage of cases with a 6MWD <505 m was 8, 14 and 7% for asthma, CB and rhinitis, respectively.

When adjusted for the potential confounders, the 6MWD showed a statistically significant variation across cases and controls ($p = 0.01$), which means that the variability of the 6MWD across groups (cases and controls) was greater than the variability of the 6MWD among subjects within groups. With respect to controls, the 6MWD was shorter for cases of asthma (–17.1 m) and CB (–20.7 m) (p corrected for multiple testing = 0.02 and 0.05, respectively), but not for cases of rhinitis (fig. 1).

Determinants of the 6MWD

None of the determinants investigated across the cases and controls, with the exception of age, showed a statistically significant heterogeneity ($p = 0.001$) (table 3). The association between age and the 6MWD was negative (–2.8 m per year of age) and statistically significant ($p = 0.002$) only for subjects with CB. A low education was consistently associated with the 6MWD. Overall, current smokers walked a shorter distance than nonsmokers. Intense physical activity and greater FEV₁ % predicted were associated with a longer 6MWD. Comorbidity was not associated with the test performance. Not even cardiovascular comorbidity was associated with the 6MWD when it was considered instead of overall comorbidity in a sensitivity analysis, and the associations of the other determinants with the 6MWD were virtually unchanged (data not shown).

Discussion

The 6MWD of cases of asthma, CB and rhinitis was compared to that of controls in the GEIRD population-based multicase-control study. Since most activities of daily living are performed at submaximal levels of exer-

Table 3. Mutually adjusted^a estimates (with 95% CIs) of the association between subject characteristics and the 6MWD, stratified by case/control status

	Controls (n = 271) ^c	Asthma cases (n = 318) ^c	CB cases (n = 98) ^c	Rhinitis cases (n = 170) ^c	p value (heterogeneity)	Pooled estimate ^{a, b} all (n = 857) ^c
Gender, female	-9.5 (-35.2; 16.1)	-17.2 (-38.5; 4.1)	-58.5 (-105.6; -11.4)	-19.0 (-51.6; 13.7)	0.19	-17.3 (-30.7; -3.9)
Age, years	-0.2 (-1.2; 0.8)	-0.6 (-1.6; 0.3)	-2.8 (-4.4; -1.2)	-0.3 (-1.5; 0.8)	0.002	-
Low education	-17.8 (-40.0; 4.5)	-29.4 (-56.4; -2.4)	-39.1 (-71.7; -6.5)	-27.4 (-62.2; 7.3)	0.63	-24.8 (-38.3; -11.3)
Smoking habits					0.42	
Nonsmoker	0	0	0	0		0
Past smoker	-6.9 (-25.2; 11.4)	0.1 (-18.7; 18.9)	15.5 (-22.9; 53.8)	-18.7 (-43.5; 6.0)		-5.8 (-16.5; 4.8)
Current smoker	-19.0 (-40.5; 2.4)	0.7 (-17.0; 18.4)	-15.7 (-47.7; 16.3)	-16.6 (-43.4; 10.2)		-11.8 (-22.8; -0.8)
Physical activity					0.33	
<1 h/week	0	0	0	0		0
1–3 h/week	10.4 (-7.5; 28.3)	3.8 (-12.2; 19.9)	14.1 (-17.4; 45.6)	1.0 (-21.3; 23.3)		6.3 (-3.4; 16.0)
>3 h/week	38.3 (17.1; 59.6)	23.3 (1.1; 45.6)	-8.0 (-48.7; 32.8)	2.0 (-28.2; 32.3)		21.7 (9.1; 34.3)
FEV ₁ , % predicted	0.5 (-0.2; 1.2)	0.4 (-0.2; 0.9)	-0.1 (-1.3; 1.1)	0.4 (-0.3; 1.2)	0.66	0.4 (0.1; 0.8)
Comorbidity	-5.7 (-31.6; 20.2)	-2.9 (-27.6; 21.8)	-18.3 (-53.7; 17.1)	3.8 (-26.4; 34.1)	0.29	-3.5 (-17.1; 10.0)

Estimates that are statistically significant (p < 0.05) are reported in bold.

^a Also adjusted for height, weight, study cohort and calendar period.

^b Obtained by a multiple linear regression model including all the covariates, plus the case/control indicator and its interaction term with age; appropriate when p (heterogeneity) > 0.10.

^c Number of subjects in the complete case analysis.

tion, the 6MWD may reflect the functional exercise level for daily physical activities [8]. Therefore, our results may be useful to understand the degree of physical limitation associated with several mild respiratory diseases that are common in the general population.

Our main findings are:

- Mild asthma and CB without asthma were associated with a reduced 6MWD.
- Rhinitis was not significantly associated with the test performance.
- The detrimental effect of ageing was particularly strong for subjects with CB.

The 6MWT is simple, valid and reliable [8, 15]. It is generally used in clinical settings to measure the functional status and the response to medical interventions of patients with moderate to severe heart or lung disease [3, 8], and very few data exist on subjects with milder conditions. To our knowledge, this is the first population-based study that compared the 6MWD of cases of asthma, CB and rhinitis to that of healthy subjects. As the GEIRD study screened random samples of the general population, the cases that were identified in the study were affected by a relatively mild form of respiratory diseases.

Respiratory Diseases and the 6MWD

The mean 6MWD of controls in our study (604 m) was inside the range reported in the literature of reference equations for healthy subjects, i.e. from 527 to 698 months [16–20]. Differences in the populations studied and test protocols may explain this large between-study variability [21].

Patients with moderate to severe COPD or asthma frequently describe limitations in their physical fitness [5, 22, 23]. In our study, cases of asthma had a decreased test performance with respect to controls. A low level of fitness in asthmatics may be due to inactivity and sedentary habits [8]. However, airflow obstruction, decreased ventilatory capacity, dyspnea and exercise-induced bronchospasm may in themselves lead to a sedentary lifestyle [8, 24]. Subjects with a respiratory disease may (more or less consciously) self-limit their test performance because they are worried about triggering symptoms [25, 26]. In asthmatics with fixed airflow obstruction, poor mechanical efficiency and the high oxygen demand of the respiratory muscles [22], depression [27], anxiety [26] and impaired cognition and balance [28] may also contribute to poor functional capacity.

Nonasthmatic subjects with CB had a reduction in the 6MWD, with respect to controls, that was similar to that of asthma cases (-20.7 vs. -17.1 m, respectively). Several

studies have reported worse health outcomes for subjects with CB and normal lung function than for healthy subjects, including a greater risk of COPD, hospitalization and death [7, 29]. Subjects with CB may also have poorer physical fitness, and they may be limited in their daily activities and exercise [30]. Self-limitation of physical activity and a sedentary lifestyle could at least in part explain our findings also in this group.

Cases of rhinitis also had a reduced test performance with respect to controls, but this difference was slight and it was not statistically significant.

All the analyses were adjusted for an indicator of cardiovascular diseases, hypertension, diabetes or cancer. Moreover, the subjects disabled from walking or affected by *claudicatio intermittens* were excluded from testing. Therefore, it is very unlikely that these comorbidities could have confounded the observed associations.

Clinical Relevance of the Case-Control Differences in the 6MWD

There is an ongoing debate about what constitutes a change in the 6MWD that is clinically relevant [31–34], and yet no study has proposed a minimal distance that is relevant to subjects with mild respiratory diseases. The most recent estimate of a minimal important difference in (severe) COPD is approximately 26 m [34]. In our view, this threshold was not appropriate for our study, where subjects with different (and milder) conditions with respect to COPD were compared to healthy controls. Nonetheless, it is interesting to observe that, in our study, the differences in the distance walked by cases of asthma or CB with respect to controls (–17.1 and –20.7 m, respectively), were close to the difference associated with gender (18.3 m). We speculate, therefore, that the differences observed are not negligible.

Determinants of the 6MWD

In general, older subjects walked shorter distances than younger subjects [16–20], but the negative association between age and the 6MWD was significant only for cases of CB ($p = 0.001$). This finding may be, at least in part, related to the slightly older age of this group with respect to the others, and it may reflect a more rapid deterioration of physical fitness along with aging for subjects with a history of smoking and symptoms of CB [7, 29, 35]. The association of the other determinants with the 6MWD was similar across the cases and controls. Subjects with a lower education walked a shorter distance than subjects with a higher education. Similarly, a low socioeconomic status has been associated with re-

duced sport performance,[36] as well as with obesity and sedentary habits [37]. Chronic exposure to cigarette smoking may explain the shorter 6MWD of current smokers with respect to nonsmokers, but recent smoking may also have contributed [38]. Intense physical activity and greater FEV₁ % predicted were associated with a longer 6MWD [9, 33, 39]. Comorbidity was not associated with the test performance, which could be due to the fact that subjects with moderate/severe comorbidities who fulfilled the 6MWT exclusion criteria were not considered. In other words, only the association of mild residual comorbidity with the test performance could be investigated.

Limitations and Strengths

The major limitation of this study is that participants were not familiarized with the 6MWT. It is known that the test performance increases and usually reaches a plateau at the third walk [21]. A practice walk was not feasible because of time constraints. As a consequence, we cannot rule out that the differences observed among cases and controls may be at least in part due to a differential 'learning effect' across cases and controls. Other tests, like the Cooper's 12-minute running test, could have been more accurate to measure exercise capacity in a nearly normal population [8], but the 6MWT was chosen because it is easier to perform in a population-based epidemiological study. Finally, on the basis of our hierarchical case-control definition, subjects with asthma or CB could also have had rhinitis. Therefore, the coexistence of respiratory diseases could partly explain our findings. A strength of the multi-case control design is that it makes it possible to simultaneously compare cases of several diseases to controls. Unlike the common case-control design, our controls did not have any of the disease conditions under investigation.

Conclusions

Nonasthmatic CB and asthma, even at the level of severity usually found in the general population, could influence the 6MWD, an outcome that may reflect daily physical activities. To our knowledge, this is the first population-based study that compared the 6MWD of cases of asthma, CB and rhinitis with that of healthy subjects. We also observed that the negative association between ageing and the test performance was particularly strong for subjects with CB. Our report adds to the mounting evidence that CB is not a trivial condition, but it can po-

tentially affect everyday life by means of a reduction in functional exercise capacity, especially in the ageing adult population. Moreover, our findings support the importance of monitoring functional capacity and of physical reconditioning in mild asthma.

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ONLINE SUPPLEMENTARY MATERIAL

Marcon A, et al.

Mild asthma and chronic bronchitis seem to influence functional exercise capacity: a multi-case control study

Int Arch Allergy Immunol 2012, DOI: 10.1159/000345137

METHODS

Participation in GEIRD stage 1

In the Verona centre, the screening questionnaire was sent to 7,415 subjects, of whom 3,544 belonged to a new random sample from the general population (age 20-64 years at February 2007), 2,154 belonged to the Italian Study on Asthma in Young Adults (ISAYA) cohort (age 28-53) and 1,717 belonged to the Italian branch of the European Community Respiratory Health Survey (ECRHS) cohort (age 35-59). Overall, 5,203 (68%) subjects answered the questionnaire (Figure S1), and 5,014 of these subjects consented to participate in GEIRD stage 2. On the basis of their answers to the screening questionnaire, the subjects were hierarchically classified as follows (see Table S1 for a detailed classification):

1. subjects with symptoms suggestive of chronic bronchitis/COPD (n=310): subjects older than 35, who reported cough/phlegm for at least three months/year for ≥ 10 years or a diagnosis of obstructive lung disease or hospitalizations for respiratory diseases,
2. subjects with symptoms suggestive of asthma (n=682): lifetime asthma or recent symptoms/medicines for asthma,
3. subjects with symptoms suggestive of rhinitis (n=720): recent symptoms/medicines for rhinitis, without sinusitis or nasal polyps,

4. subjects without respiratory symptoms (n=2,049): no respiratory symptoms, diagnoses or hospitalizations.

Sampling for and participation in GEIRD stage 2

COPD, asthma and chronic bronchitis had top priority in the GEIRD study. Therefore, all the subjects with symptoms suggestive of chronic bronchitis/COPD and asthma were invited to the clinics. A 28% random sample of the subjects who reported symptoms of rhinitis, and a 40% random sample of the subjects without respiratory symptoms were selected for the clinical stage. The sampling fraction for the latter was chosen to balance asthma cases (which were the most numerous group of cases). The sampling fraction for the group of subjects with symptoms of rhinitis was the maximum possible sampling fraction after financial and logistical considerations (de Marco et al. 2010).

Skin prick tests

Positive histamine and negative diluent controls were used. A reaction of 3 mm greater than the negative control was regarded as positive. A subject was considered to be atopic if he/she was positive to at least one out of 14 allergens (*Alternaria tenuis*, *Ambrosia artemisiifolia*, *Artemisia vulgaris*, *Betula verrucosa*, *cat fur*, *Cladosporium herbarum*, *Corylus avellana*, *Cupressus arizonica*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *dog dandruff*, *Olea europea*, *Parietaria judaica*, and *Phleum pratense*) (ALK diagnostics, Denmark) (Mailing 1993).

RESULTS

Among the asthma cases who did the methacholine challenge test, 20% satisfied the criterion of being both positive to the methacholine challenge test and having at least one among: 1) asthma-like symptoms (asthma attacks, wheeze, shortness of breath or chest tightness) in the last 12 months and/or 2) use of medicines for asthma in the last 12 months.

6-minute walk test: exclusion criteria

Out of the 985 cases and controls, 871 (88%) subjects completed the 6MWT; 110 were excluded because of the test exclusion criteria (disabled from walking but not for a lung/heart disease; symptomatic peripheral artery disease [*claudicatio intermittens*]; use of beta-blocker; use of medicine for heart disease; high blood pressure; high heart rate; recent heart attack; use of medicine for epilepsy; pregnancy; breastfeeding), 1 refused, and 3 did not complete the test (and were excluded from the analyses).

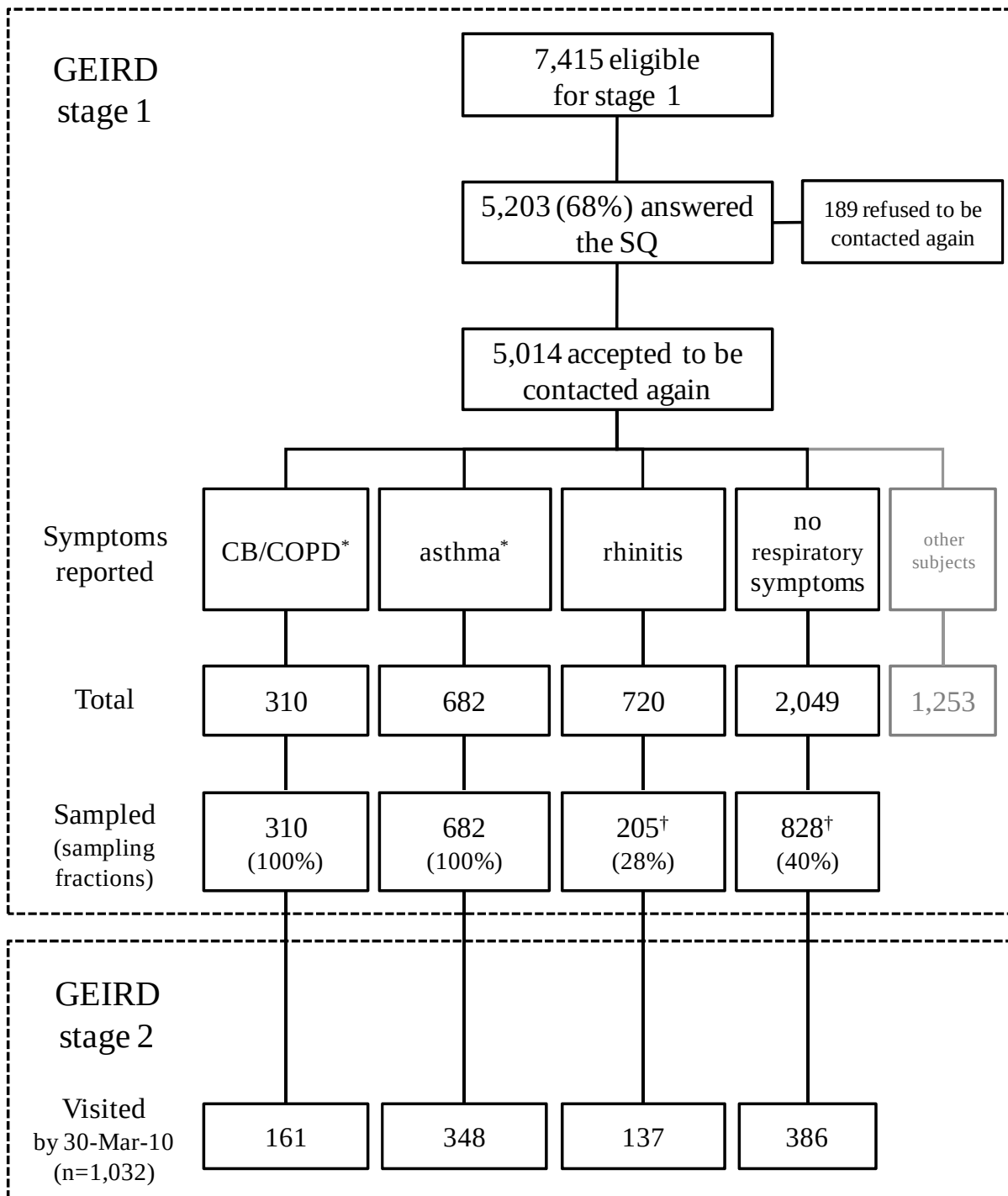
6-minute walk distance of asthma and rhinitis phenotypes

The 6MWD was 596 (SD, 72) m for cases of past asthma; 592 (SD, 70) m and 589 (SD, 65) m for cases of current asthma without and with fixed airflow obstruction, respectively (p-value for trend=0.58).

The 6MWD was 602 (SD, 56) m for cases of asthma who were hyperresponsive to methacholine and 609 (SD, 60) m for cases of asthma who were not hyperresponsive to methacholine (p-value =0.57).

Subjects with allergic and non-allergic rhinitis walked on average 601 (SD, 69) and 591 (SD, 68) m, respectively (p=0.37). See the definition of asthma/rhinitis phenotypes and the number of the subjects with these conditions in Table S3.

Figure S1: Number of the subjects who were eligible and who took part in the GEIRD study.*



* As a consequence of the hierarchical classification, subjects in the group of chronic bronchitis (CB)/COPD could also have reported symptoms of rhinitis (n=74, 26%), and subjects in the group of asthma could also have reported symptoms of rhinitis (n=262, 38%) or CB/COPD (n=149, 22%).

† 27 subjects with symptoms of rhinitis and 256 subjects without respiratory symptoms could not be contacted and were replaced.

Table S1: items of the postal screening questionnaire administered during the GEIRD stage 1 that were used to classify the responders into groups with/without specific respiratory symptoms.

Symptoms reported	Definition
asthma	<i>AT LEAST ONE AMONG:</i> Asthma attacks in the last 12 months Current use of asthma medicine Lifetime asthma
chronic bronchitis /COPD	≥35 years-old <i>PLUS AT LEAST ONE AMONG:</i> Chronic cough and phlegm (at least three months each year, for ≥10 years) Diagnosis of COPD, emphysema, chronic bronchitis Hospital admission for respiratory disease in the last 10 years Daily wheezing
rhinitis	<i>AT LEAST ONE AMONG:</i> Lifetime nasal allergies, including “hay fever” for ≥2 years Lifetime problem with sneezing, or a runny or a blocked nose (without cold/flu) for ≥2 years <i>PLUS AT LEAST ONE AMONG:</i> Current reporting of the above symptoms Rhinitis medicine in the last 12 months <i>PLUS ALL OF THE FOLLOWING:</i> No nasal polyps No sinusitis
no respiratory symptoms	<i>NONE OF THE FOLLOWING:</i> Wheezing, chest tightness, shortness of breath, asthma attacks in the last 12 months Dyspnea Current use of asthma medicine Lifetime asthma Nasal allergies, including “hay fever” Problem with sneezing, or a runny or a blocked nose (without cold/flu) Chronic cough and phlegm for ≥2 years Diagnosis of COPD, emphysema, chronic bronchitis Hospital admission for respiratory disease in the last 10 years

Table S2: comparison of the subjects who did and did not participate in the GEIRD stage 2 in the centre of Verona (ongoing by March 2010).

	<i>Participation in stage 2</i>	female (%)	age (year)*	smoking habits (%)†		
Symptoms reported				<i>non- smoker</i>	<i>past smoker</i>	<i>current smoker</i>
rhinitis	<i>yes (n=137)</i>	52	41 (11)	51	31	18
	<i>no (n=95)</i>	56	38 (10)	56	23	21
<i>p-value</i>		<i>0.55</i>	<i>0.04</i>		<i>0.38</i>	
CB/COPD	<i>yes (n=161)</i>	53	46 (9)	40	24	36
	<i>no (n=149)</i>	56	47 (8)	42	25	34
<i>p-value</i>		<i>0.61</i>	<i>0.19</i>		<i>0.90</i>	
asthma	<i>yes (n=348)</i>	52	41 (9)	48	27	25
	<i>no (n=334)</i>	52	42 (10)	52	27	21
<i>p-value</i>		<i>0.95</i>	<i>0.06</i>		<i>0.44</i>	
no symptoms	<i>yes (n=386)</i>	52	43 (9)	53	30	18
	<i>no (n=698)</i>	58	42 (10)	55	24	21
<i>p-value</i>		<i>0.09</i>	<i>0.23</i>		<i>0.15</i>	

* Means (SD) reported.

† Percentages may not sum up to 100% because of rounding.

Table S3: number and definition of cases and controls identified in GEIRD stage 2 (Verona centre only, April 2008-March 2010). For each group, the number (%) of subjects with coexistent rhinitis and the number (%) of subjects with a measured 6-minute walk distance (6MWD) are reported. The source of each questionnaire item is indicated as *SQ*, screening questionnaire or *I*, clinical interview.

case/control status (clinical definition)	definition	coexistence with rhinitis* n (%)	n (%) with measured 6MWD
cases of asthma ** (N=360)	<i>AT LEAST ONE AMONG:</i> He/she reported symptoms of asthma at the SQ[†] Ever asthma (I) <i>OR</i> <i>AT LEAST ONE AMONG:</i> Asthma-like symptoms (asthma attacks, wheeze, shortness of breath or chest tightness) in the last 12 months (I) Use of medicines for asthma in the last 12 months (I) <i>PLUS AT LEAST ONE AMONG:</i> Positive methacholine challenge test with PD₂₀ < 1 mg Pre-bdl^{††} FEV₁/FVC < LLN[‡] or <70% and positive reversibility test Pre-bdl^{††} FEV₁/FVC < LLN[‡] or <70%, and a post-bronchodilator FEV₁/FVC > LLN[‡] and >70%, and a post-bdl^{††} FEV₁ >80% predicted (Quanjer et al. 1993)	rhinitis +, 289 (80) rhinitis –, 71 (20)	320 (89)
cases of COPD *** (N=8)	He/she is not a case of asthma Post-bdl^{††} FEV₁/FVC < LLN[‡] or <70%	rhinitis +, 4 (50) rhinitis –, 4 (50)	4 (50)
cases of chronic bronchitis (N=120)	He/she is neither a case of asthma nor COPD He/she reports symptoms of chronic bronchitis (cough and/or phlegm for >3 months/year for ≥2 years) (I, SQ)	rhinitis +, 89 (74) rhinitis –, 31 (26)	102 (85)

(continues on the next page)

cases of rhinitis ^{†††} (N=203)	He/she is neither a case of asthma nor COPD nor chronic bronchitis <i>PLUS AT LEAST ONE AMONG:</i> He/she reported symptoms of rhinitis at the SQ [†] Nasal allergies, including “hay fever” (I) Problem with sneezing, or a runny or a blocked nose (without cold/flu) (I) Sneezing, or a runny or a blocked nose, itchy or watery eyes in the presence of plants or pollens, animals, pillows or duvets or in a dusty part of the house (I)	–	172 (85)
controls (N=302)	<i>ALL OF THE FOLLOWING:</i> He/she reported no respiratory symptoms at the SQ [†] He/she is neither a case of asthma nor COPD nor chronic bronchitis nor rhinitis Pre-bdl ^{††} FEV ₁ /FVC >LLN [‡] and >70% FEV ₁ >70% predicted (Quanjer et al. 1993)	–	277 (92)
<i>unclassified</i> (N=39)	–	<i>none</i>	27 (69)

* coexistence with rhinitis was possible because of the hierarchical definition of cases. Percentages do not sum up to 100% because of rounding

** which included 125 (35%) subjects with *past asthma* (self-reported asthma but no current signs or symptoms); 214 (59%) subjects with *current asthma* (a combination of self-reported asthma with current symptoms/medicines and/or “positive” clinical tests) *without fixed airflow obstruction* (post-bronchodilator FEV₁/FVC < 70% or <LLN); and 21 (6%) subjects with *current asthma with fixed airflow obstruction*

*** COPD was not considered in the analyses because there were so few cases

[†] see Table S1

^{††} bdl, bronchodilator

^{†††} which included 114 (57%) subjects with *allergic rhinitis* (at least one positive skin prick test), 74 (36%) subjects with *non-allergic rhinitis*, and 15 (7%) subjects who did not undergo the skin prick tests

[‡] LLN, lower limit of normal according to the reference equations by Quanjer et al. (1993)

^{||} increase in FEV₁ >12% and >200 mL with respect to pre-bronchodilator FEV₁ after 400 µg of salbutamol

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