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Original Research

ASTHMA

Increased Risk of Exacerbation and Hospitalization in Subjects With an Overlap Phenotype

COPD-Asthma

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Background: **Several COPD phenotypes have been described; the COPD-asthma overlap is one of the most recognized. The aim of this study was to evaluate the prevalence of three subgroups (asthma, COPD, and COPD-asthma overlap) in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study population, to describe their main characteristics, and to determine the association of the COPD-asthma overlap group with exacerbations, hospitalizations, limitations due to physical health, and perception of general health status (GHS).**

Methods: **The PLATINO study is a multicenter population-based survey carried out in five Latin American cities. Outcomes were self-reported exacerbations (defined by deterioration of breathing symptoms that affected usual daily activities or caused missed work), hospitalizations due to exacerbations, physical health limitations, and patients' perception of their GHS obtained by questionnaire. Subjects were classified in three specific groups: COPD—a postbronchodilator (post-BD) FEV_1/FVC ratio of < 0.70; asthma—presence of wheezing in the last year and a minimum post-BD increase in FEV_1 or FVC of 12% and 200 mL; and overlap COPD-asthma—the combination of the two.**

Results: **Out of 5,044 subjects, 767 were classified as having COPD (12%), asthma (1.7%), and COPD-asthma overlap (1.8%). Subjects with COPD-asthma overlap had more respiratory symptoms, had worse lung function, used more respiratory medication, had more hospitalization and exacerbations, and had worse GHS. After adjusting for confounders, the COPD-asthma overlap was associated with higher risks for exacerbations (prevalence ratio [PR], 2.11; 95% CI, 1.08-4.12), hospitalizations (PR, 4.11; 95% CI, 1.45-11.67), and worse GHS (PR, 1.47; 95% CI, 1.18-1.85) compared with those with COPD.**

Conclusions: **The coexisting COPD-asthma phenotype is possibly associated with increased disease severity.**

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Abbreviations: BD = bronchodilator; GHS = general health status; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal; PLATINO = Latin American Project for the Investigation of Obstructive Lung Disease; PR = prevalence ratio; SF-12 = Short Form 12 questionnaire

COPD and asthma are the most prevalent obstructive airway diseases worldwide. Several surveys have yielded varied global prevalence of COPD because of differences in diagnostic criteria and in study designs.[1-4] The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) found an overall prevalence of COPD of 14.3%, according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I to IV, among people > 40 years of age in five Latin American cities.[3]

Few data exist on asthma prevalence in adults. Based on the application of standardized methods, it appears that the global prevalence of asthma ranges from 1% to 18% in different countries.[5]

In the past years, there has been great interest in identifying subgroups of COPD, the so-called COPD

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phenotypes. Experts have proposed a definition for COPD phenotype as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)."[6] Several COPD phenotypes have been proposed; however, one of the most recognized is the overlap COPD-asthma.

Hardin et al[7] compared subjects with COPD and asthma to subjects with COPD alone in the COPDGene Study, and they found that 13% of subjects with COPD reported physician-diagnosed asthma. These subjects had worse health-related quality of life and experienced more frequent and severe respiratory exacerbations, despite younger age and reduced lifetime smoking history. In PLATINO, we found that 23% of the subjects with COPD have self-reported medically diagnosed asthma.[8] Marsh et al[9] estimated the prevalence of asthma in a COPD cohort to be 55.2% using a composite definition of asthma (post-bronchodilator [post-BD] increase in $FEV_1 > 15\%$, or peak flow variability > 20% during 1 week of testing, or physician diagnosis of asthma in conjunction with current symptoms). The comparison of different estimates is problematic because of different definitions of asthma.[9]

The aims of the present study are: (1) to evaluate the prevalence of three subgroups: asthma, COPD, and COPD-asthma overlap in the PLATINO population; (2) to explore the main characteristics among the three subgroups; and (3) to determine the association between COPD-asthma overlap with the outcomes: exacerbation, hospitalization, limitation due do physical health, and perception of general health status (GHS).

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*A complete list of PLATINO team participants is located in e-Appendix 1.

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Materials and Methods

The PLATINO study was a population-based survey carried out in Latin America; subjects performed spirometry with a portable spirometer (EasyOne spirometer; ndd Medical Technologies, Inc) at baseline and 15 min after the administration of 200 μg of salbutamol, according to the American Thoracic Society criteria of acceptability and reproducibility.[10] Complete details of the methodology have been published elsewhere.[11]

The outcomes of this paper were self-reported exacerbations in the last year defined as deterioration of breathing symptoms that affected usual daily activities or caused missed work (yes/no), number of self-reported exacerbations in the last year, hospitalizations in the last year due to the exacerbations (yes/no), number of hospitalizations in the last year, limitations due to physical health, and patients' perception of their GHS (in general you would say that your health is excellent, very good, good, fair, or poor, assessed by the Short Form-12 questionnaire (SF-12) Quality of Life Questionnaire; the last two options were joined for the multivariate analysis).

The independent variables were the three phenotypes: (1) COPD—based on the ratio of the post-BD $FEV_1/FVC < 0.70$[12]; (2) asthma—those who had answered positively for the question of wheezing in the last 12 months plus post-BD increase in FEV_1 or FVC of 200 mL and 12%; (3) overlap—the combination of the two previous diseases. "Medical diagnosis of asthma" (a self-reported prior diagnosis of asthma) was also applied as another definition for asthma, and the lower limit of normal (LLN) (defined as the lower fifth percentile for predicted post-BD FEV_1/FEV_6 and FEV_1/FVC using equations derived from our own population)[13] as another criterion for COPD (e-Appendix 2). Other variables were included as potential confounders (e-Appendix 2). The ethical committee of each site approved the study protocol, and the participants gave signed informed consent (listed in e-Appendix 2).

Statistical Analysis

Descriptive analysis was performed to obtain mean and SD for numerical variables and absolute and relative frequencies for categorical variables. Pearson χ^2 test was used for categorical variables and *t* test and analysis of variance for numerical ones. Poisson regression models were fit to assess the association of the outcomes and the exposures including estimates of the prevalence ratios (PRs) for dichotomous variables and the relative risk for count variables with 95% CI. In the multivariate analyses, the COPD group, as the largest group, was considered as the reference category.

Results

Out of the population of 5,044 subjects, 767 were classified as having one phenotype; 594 (11.7%) belonged to the COPD group, 84 (1.7%) to the asthmatic group, and 89 (1.8%) to the overlap group (Fig 1). The prevalence of these phenotypes using "medical diagnosis of asthma" is shown as e-Figure 1. e-Figure 2 shows the prevalence of these phenotypes calculated with a denominator of 767 (only those affected with asthma and COPD) rather than 5,044, as shown in Figure 1. The prevalence for overlap among only the affected population was 11.6% (95% CI, 9.2-14.0). Table 1 describes the characteristics of the groups; the asthmatic group showed younger age, fewer men, highest

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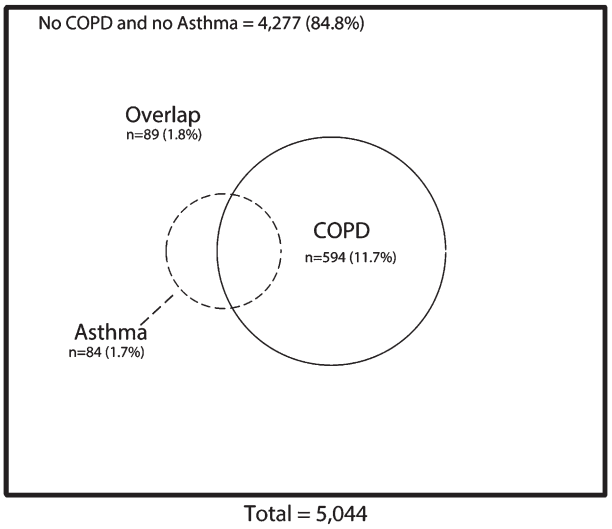

FIGURE 1. A proportional Venn diagram presenting the three phenotypes (asthma, COPD, and overlap COPD-asthma) in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) Study. Asthma is defined as the presence of wheezing in the last year and a minimum postbronchodilator increase in FEV_1 or FVC of 12% and 200 mL. Overlap COPD-asthma is defined as the combination of COPD and asthma.

mean BMI, and more dyspnea. Among subjects in the COPD group, the opposite was observed; they presented with the highest mean age and largest proportion of men and the smallest mean BMI. They also reported fewer symptoms and less use of respiratory medication and reported less previous spirometry. Those in the overlap group had the highest percentage of symptoms (cough and phlegm), use of any respiratory medication, prior spirometry, and self-reported medically diagnosed asthma (Table 1) and the lowest values for several lung function parameters (Table 2), with the exception of the changes in FEV_1 and FVC (absolute and relative), FVC before and after BD (absolute and % predicted), and FEV_1/FVC change.

The highest percentage reporting exacerbations in the last year, the highest number of exacerbations, the highest number of hospitalizations, and the worse GHS were noted in the overlap group (Table 3), whereas there were similar percentages of subjects with exacerbation requiring a visit to the doctor in the asthma group and in the overlap group. The lowest mental SF-12 score was seen in the subjects with asthma. Subjects with COPD reported the lowest percentage of exacerbation in the last year and the highest mean of the mental SF-12 score (Table 3). In the multivariate analysis (Table 4), the risks for exacerbations in the asthmatic group and in the overlap group were 2.54 and 3.01, respectively; in the adjusted analysis, these risks were reduced, although the risk for exacerbations in the overlap group was 2.11 times more than in the COPD group. We recorded no hospitalization for exacerbation in the subjects with asthma; however, the risk was around four times higher in the overlap group compared with the reference group, even after adjustment for confounders. Number of exacerbations and number of hospitalizations showed an adjusted relative risk of 4.20 (95% CI, 1.05-16.62) and 5.24 (95% CI, 1.49-8.38) in the overlap group. Limitations due to physical health were not statistically different in any of the phenotypes. Overlap subjects compared with subjects with COPD had a higher risk (64%) to categorize their GHS as regular or bad; this risk was reduced to 47% in the adjusted analysis. Applying "medical diagnosis of asthma" as definition for asthma, there was also a higher risk in the adjusted analysis for exacerbations, limitations due to physical health, and a self-perceived health as regular or bad in the overlap compared with the COPD group (e-Tables 1, 2).

The distribution of the exposure variables according to the phenotypes was very similar using the LLN (e-Table 3). Subjects in the COPD-asthma overlap group (COPD according to LLN) showed a higher risk for exacerbations (PR = 2.55; 95% CI, 1.31-4.98) and for hospitalizations (PR = 4.83; 95% CI, 1.69-13.74) in the adjusted analysis compared with the reference group (e-Table 4).

Discussion

The principal findings of this study were as follows. First, using the GOLD criteria to define COPD, the presence of both wheezing and acute BD responsiveness to define asthma, and the combination of the two previous criteria for classifying the overlap COPD-asthma, we found that 1.7% of the PLATINO population belonged to the asthmatic group, around 12% to the COPD group, and 1.8% were classified in the overlap group. Second, subjects with COPD-asthma overlap had more respiratory symptoms; worse lung function; and more use of lung medication, hospitalization, and exacerbations as worse GHS. Third, after adjusting for confounders, the COPD-asthma overlap was associated with worse GHS and higher risks for exacerbations and hospitalizations compared with those with COPD.

Reported prevalence rates of asthma vary within and among countries worldwide. Like for COPD, the comparison between studies is complicated by the use of different definitions of asthma. The European Community Respiratory Health Survey assessed the geographical variation in adult asthma[14] (approximately 140,000 individuals); it was shown that there are large geographical differences in the prevalence of asthma based on reported symptoms as well as differences in atopy and bronchial responsiveness, with high prevalence rates in English-speaking countries and low prevalence rates in the Mediterranean and

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Table 1—*Description of Subjects in Three Defined Phenotypes: Asthma, COPD, and COPD-Asthma Overlap: the PLATINO Study*

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Age, y	54.9 ± 10.9	64.3 ± 12.1	60.4 ± 11.3	< .001
Sex, male	21 (25.0)	282 (47.5)	41 (46.1)	< .001
BMI, kg/m^2	29.1 ± 6.2	26.8 ± 5.1	27.5 ± 5.3	.001
Ethnicity, white	52 (61.9)	387 (65.2)	59 (66.3)	.908
Education, y	7.2 ± 4.9	6.8 ± 4.5	7.0 ± 5.1	.758
Employment, yes	44 (52.4)	242 (40.7)	43 (48.3)	.071
Smoking, pack-y	15.6 ± 25.4	20.0 ± 28.4	19.3 ± 25.6	.406
Smoking status				.403
Never	34 (40.4)	183 (30.8)	31 (34.8)	
Former	25 (29.8)	188 (31.7)	29 (32.6)	
Current	25 (29.8)	223 (37.5)	29 (32.6)	
Domestic exposure to coal or biomass, yes	16 (19.1)	149 (25.1)	19 (21.4)	.395
Childhood pulmonary hospitalization, yes	5 (6.0)	13 (2.2)	3 (3.4)	.130
Respiratory symptoms, yes				
Cough	35 (41.7)	163 (27.4)	45 (50.6)	< .001
Phlegm	33 (39.3)	151 (25.4)	38 (42.7)	< .001
Wheezing	84 (100.0)	174 (29.3)	89 (100.0)	< .001
Dyspnea	58 (69.1)	278 (47.4)	58 (65.2)	< .001
Any respiratory medication, yes	32 (38.1)	118 (19.9)	44 (49.4)	< .001
Any bronchodilator, yes[a]	18 (58.1)	65 (56.0)	22 (52.4)	.878
Any corticosteroid, yes[a]	6 (19.4)	65 (56.0)	10 (23.8)	.793
Prior spirometry, ever, yes	17 (20.2)	99 (16.7)	31 (34.8)	< .001
Self-reported diagnosis: COPD, yes	2 (2.4)	10 (1.7)	5 (5.6)	.063
Self-reported diagnosis: asthma, yes	31 (36.9)	102 (17.2)	45 (50.6)	< .001
Comorbidity score	1.2 ± 1.1	0.9 ± 0.9	0.9 ± 1.0	.079

Data are given as No. (%) or mean ± SD. Comorbity score is the sum of all chronic conditions investigated (heart disease, hypertension, stroke, lung cancer, ulcer, diabetes, and TB). PLATINO = Latin American Project for the Investigation of Obstructive Lung Disease.
[a]Including only those who reported use of medication for pulmonary diseases in the past year.

Eastern Europe.[14-16] Using the same sampling strategy and standardized questionnaire of the European Community Respiratory Health Survey, Manfreda et al[17] found that the prevalence rates of most asthma symptoms varied significantly among six Canadian sites. Using data from adults aged ≥ 20 years (National Health and Nutrition Examination Survey III project), Arif et al[18] reported a prevalence of self-reported current asthma as 4.5% and of wheezing in the previous 12 months as 16.4%.

Regarding Latin America, the prevalence of asthma is as high as observed in high prevalence "English-speaking

Table 2—*Lung Function Parameters of Subjects in Three Defined Phenotypes: Asthma, COPD, and COPD-Asthma Overlap: the PLATINO Study*

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Prebronchodilator FEV_1, L	2.0 ± 0.6	2.1 ± 0.8	1.7 ± 0.6	< .001
Prebronchodilator FEV_1, % predicted	79.9 ± 17.2	81.4 ± 20.0	63.5 ± 18.9	< .001
Postbronchodilator FEV_1, L	2.5 ± 0.8	2.2 ± 0.8	2.0 ± 0.7	< .001
Postbronchodilator FEV_1, % predicted	94.0 ± 17.8	82.0 ± 19.2	72.1 ± 18.9	< .001
FEV_1 change, absolute, mL	448.5 ± 395.3	83.3 ± 185.5	295.7 ± 157.1	< .001
FEV_1 change, relative, %	24.1 ± 29.9	5.4 ± 12.7	19.2 ± 12.1	< .001
FEV_1 change, % predicted, %	20.5 ± 29.1	1.8 ± 12.3	15.4 ± 11.8	< .001
Prebronchodilator FVC, L	2.7 ± 0.9	3.3 ± 1.1	3.0 ± 0.9	< .001
Prebronchodilator FVC, % predicted	85.3 ± 18.4	98.0 ± 18.8	83.5 ± 17.8	< .001
Postbronchodilator FVC, L	3.2 ± 1.0	3.4 ± 1.1	3.4 ± 1.1	.099
Postbronchodilator FVC, % predicted	96.3 ± 17.5	100.6 ± 18.7	96.6 ± 21.3	.042
FVC change, absolute, mL	397.4 ± 489.9	103.5 ± 344.0	463.6 ± 348.9	< .001
FVC change, relative, %	16.1 ± 22.7	4.5 ± 13.2	17.0 ± 12.0	< .001
FVC change, % predicted, %	15.3 ± 23.0	3.5 ± 12.9	16.5 ± 11.8	< .001
Prebronchodilator FEV_1/FVC	73.7 ± 7.9	62.3 ± 9.6	57.7 ± 11.1	< .001
Postbronchodilator FEV_1/FVC	78.2 ± 4.7	62.7 ± 8.0	58.5 ± 9.5	< .001
FEV_1/FVC change	7.1 ± 11.6	1.4 ± 9.8	2.7 ± 12.4	< .001

Data are presented as mean ± SD. See Table 1 legend for expansion of abbreviation.

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Table 3—*Subjects' History of Exacerbations, Quality of Life, Physical Activity Limitation, and Self-Perceived Health in Three Defined Phenotypes: Asthma, COPD, and COPD-Asthma Overlap: the PLATINO Study*

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Any exacerbation within the past year, yes,	11 (13.1)	31 (5.2)	14 (15.7)	< .001
Exacerbation requiring doctor visit in the past year, yes	10 (11.9)	24 (4.0)	10 (11.2)	.001
No. of exacerbations in the past year	0.3 ± 0.9	0.3 ± 2.2	1.5 ± 6.4	.002
Hospitalization due to exacerbations in the past year, yes	0.0 (0.0)	7 (1.2)	5 (5.6)	.003
Number of hospitalizations	0.0 ± 0.0	0.0 ± 0.1	0.1 ± 2.2	.003
SF-12 physical score	47.8 ± 10.6	49.5 ± 9.0	47.5 ± 8.8	.058
SF-12 mental score	47.8 ± 12.4	51.4 ± 10.2	49.2 ± 12.2	.005
Limitation due to physical health, yes	26 (31.0)	127 (21.4)	26 (29.6)	.053
General health status, yes				.005
Excellent	6 (7.1)	44 (7.4)	7 (7.9)	
Very good	7 (8.3)	66 (11.1)	3 (3.4)	
Good	31 (36.9)	188 (48.5)	31 (34.8)	
Fair	36 (42.9)	180 (30.3)	43 (48.3)	
Poor	4 (4.8)	16 (2.7)	5 (5.6)	

Data are given as No. (%) or mean ± SD. SF-12 = Short Form 12 questionnaire. See Table 1 legend for expansion of other abbreviation.

countries." Brazil, for instance, had the highest prevalence of wheezing (24.3%) and the sixth-highest medical diagnosis of asthma (12%) among 70 countries in the World Health Survey.[19]

The differences in the prevalence of asthma reported in the literature could be partially related to different risk factors among countries. It is important, however, to highlight that the lack of consensus on a disease definition complicates the reliability of comparisons between different populations worldwide.

Asthma and COPD are considered different diseases, but many patients share characteristics from both entities. These cases can have different clinical presentation, evolution, and response to treatment. As has been widely commented, the existence of this mixed phenotype poses several unknowns that need to be evaluated scientifically. There is a need to identify these patients and evaluate their long-term condition to confirm that they really behave as a specific clinical phenotype with differential clinical events. It is clear that the coexistence of asthma-COPD has been recognized but not clearly defined. Few studies have investigated the prevalence and clinical characteristics of the overlap phenotype.[7,20,21] We have reported in the PLATINO population that 23% of the subjects with COPD report prior medically diagnosed asthma,[8] and the prevalence of overlap using this definition for asthma is 3% (e-Fig 1). A publication of

Table 4—*Crude and Adjusted Analysis in Three Defined Phenotypes With Exacerbations, Hospitalization, Limitations Due to Physical Health, and Self-Perceived Health: the PLATINO Study*

Variables	Asthma (n = 84)	COPD (n = 594)	COPD-Asthma Overlap (n = 89)	*P* Value
Exacerbations past year				
Unadjusted, PR (95% CI)	2.54 (1.42-4.52)	1.00 (Ref)	3.01 (1.74-5.21)	< .001
Adjusted,[a] PR (95% CI)	1.65 (0.93-2.92)	1.00 (Ref)	2.11 (1.08-4.12)	.056
Number of exacerbations past year				
Unadjusted, RR (95% CI)	1.04 (0.40-2.69)	1.00 (Ref)	5.48 (1.74-17.22)	.010
Adjusted,[a] RR (95% CI)	0.98 (0.32-3.02)	1.00 (Ref)	4.20 (1.05-16.62)	.069
Hospitalizations past year				
Unadjusted, PR (95% CI)	[b]	1.00 (Ref)	4.76 (1.70-13.31)	< .001
Adjusted,[a] PR (95% CI)	[b]	1.00 (Ref)	4.11 (1.45-11.67)	< .001
Number of hospitalizations past year				
Unadjusted, RR (95% CI)	[b]	1.00 (Ref)	5.90 (1.74-20.01)	< .001
Adjusted,[a] RR (95% CI)	[b]	1.00 (Ref)	5.24 (1.49-18.38)	< .001
Limitations due to physical health				
Unadjusted, PR (95% CI)	1.46 (1.00-2.13)	1.00 (Ref)	1.38 (0.95-1.99)	.074
Adjusted,[a] PR (95% CI)	1.18 (0.83-1.68)	1.00 (Ref)	1.27 (0.86-1.88)	.400
Self-perceived health (fair or poor)				
Unadjusted, PR (95% CI)	1.47 (1.16-1.86)	1.00 (Ref)	1.64 (1.33-2.02)	< .001
Adjusted,[a] PR (95% CI)	1.11 (0.86-1.42)	1.00 (Ref)	1.47 (1.18-1.85)	.004

PR = prevalence ratio; Ref = reference; RR = relative risk. See Table 1 legend for expansion of other abbreviation.

[a]Adjusted for age, sex, skin color, BMI, schooling, comorbidity score, pack-years, and any treatment (bronchodilator or corticosteroid).

[b]No hospitalizations in the past year.

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the COPDGene study indicates that 13% of subjects with COPD reported a history of physician-diagnosed asthma.[7] In the PLATINO study, we also found a high overall prevalence of wheezing (23.5%) and of self-report medical diagnosis of asthma (11.8%).

In the present study, we found a prevalence of overlap of 1.8%. This difference may be explained by differences in the samples, the definitions used for overlap, and the different denominators used for calculating the prevalence of overlap.

PLATINO included all subjects with COPD identified from a survey of urban populations (mainly mild COPD), and for this study we used the presence of both wheezing and BD response in subjects with a post-BD $FEV_1/FVC < 0.70$ to define overlap, whereas the COPDGene study included only patients with more severe COPD (GOLD stages II-IV) and defined the overlap as subjects with spirometric diagnosis of COPD with self-report of physician-diagnosed asthma. In our study, if we had defined asthma using the criterion of "medical diagnosis of asthma," we would have reported an overlap prevalence of 3% and a higher risk for all the outcomes in this phenotype compared with the COPD group.

The total sample size of 5,044 subjects was used for the calculation of the prevalence of the three phenotypes. Using a denominator of only subjects with asthma and COPD (N = 767), the prevalence of overlap would be 11.6% (95% CI, 9.2-1.0), which is similar to rates reported in papers found in the literature.[7,22,23] However, the authors of the present study believe that the prevalence of the phenotypes should be based on the total sample size in population-based studies, such as the PLATINO study, and not only on subjects with the disease. Using this approach to calculate the prevalence of overlap (total sample size as the denominator) in the Gene Environment Interactions in Respiratory Diseases study, de Marco et al[24] found a prevalence ranging from 1.6% (95% CI, 1.3%-2.0%) in the 20- to 44-year-old age group to 4.5% (95% CI, 3.2%-5.9%) in the 60- to 84-year-old age group. As the authors cited did not perform spirometry, the medical diagnosis of each disease was used for the definition of asthma and COPD.

Some authors have found that patients with overlap syndrome have worse lung function and more respiratory symptoms than either disease alone.[25] In contrast, the results of the COPDGene study did not show difference in lung function between COPD and overlap subjects. Our findings are consistent with the first study and confirm the presence of worse pulmonary function and more respiratory symptoms in the overlap group.

In the COPDGene cohorts, patients with overlap had worse disease-related quality of life, were more likely to have a severe COPD exacerbation, and experience frequent exacerbations,[7] as also described by Kauppi et al.[26] Our results show that overlap phenotype is associated with worse GHS and more hospitalization and exacerbations compared with the reference COPD group. The higher risk for all the outcomes in the overlap COPD-asthma phenotype was also observed using other definitions (medically diagnosed asthma and a post-BD $FEV_1/FVC < 0.70$). The mechanisms by which the overlap COPD-asthma may adversely affect health status and generate more exacerbations are difficult to explain with the present study data, but overlap identifies a group of individuals with more impaired pulmonary function, more respiratory symptoms, and more frequent exacerbations and hospitalization. The lack of similar information from other population-based studies similar to PLATINO makes difficult the comparisons with our results. Exacerbations and hospitalizations have an important implication in terms of public health because of high cost, particularly those exacerbations requiring hospitalization.[27-30]

Some limitations should be highlighted in our study; definition of asthma in an epidemiologic study differs considerably from the official definition from the GINA (Global Initiative for Asthma) committee. Wheezing in the last year is used commonly as a proxy of asthma, more sensitive and less specific than physician-diagnosed asthma. Adding BD response may increase specificity. Our findings were confirmed considering the definition of "medical diagnosis" of asthma.

COPD defined by the fixed criterion is known to overdiagnose disease in older individuals. However, we carried out the same analysis using the LLN, and we found a higher and significant risk for exacerbations and hospitalizations among the overlap group compared with the reference group. The overlap phenotype, even with some limitations pointed out here, identifies a group of individuals at an increased risk of exacerbation and hospitalization. Our definition of exacerbation was based on subjects' retrospective report of breathing symptoms, which is potentially subject to recall bias. Because the present is a cross-sectional study looking at a population at a given point in time, it only provides the frequency and characteristics of the disease in this population when the study was conducted. Thus, our results may tend to underestimate the true rate of COPD exacerbations.

In summary, our study helps to better understand the prevalence of adult asthma as well as the overlap COPD-asthma phenotype and suggests that coexisting COPD-asthma is possibly associated with increased disease severity and worse health status. However, it remains unclear which are the pathogenic characteristics of this group, the stability of the phenotype over time, the best treatment, and the long-term prognosis of these individuals.

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Dr Menezes: contributed by coordinating the PLATINO study, designed the analysis, wrote the manuscript, and revised and approved the article.
Dr Montes de Oca: contributed as the principal investigator in Caracas, designed the analysis, wrote the manuscript, and revised and approved the article.
Dr Pérez-Padilla: contributed as the principal investigator in Mexico City; was responsible for spirometry quality control; and contributed to designing the analysis, writing the manuscript, and revising and approving the article.
Mr Nadeau: contributed to designing the analysis, writing the manuscript, and revising and approving the article.
Dr Wehrmeister: contributed to conducting the statistical analysis and revising and approving the article.
Dr Lopez-Varela: contributed as the principal investigator in Montevideo and revised and approved the article.
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Dr Jardim: contributed as the principal investigator in São Paulo and revised and approved the article.
Dr Valdivia: contributed as the principal investigator in Santiago and revised and approved the article.
Dr Tálamo: contributed as the principal investigator in Caracas and revised and approved the article
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Additional information: The e-Appendixes, e-Figures, and e-Tables can be found in the "Supplemental Materials" area of the online article.

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