Original Research

Body Mass Index and Bronchodilator Responsiveness in Adults: Analysis of 2 Population-Based Studies in 4 South American Countries

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Abstract

Introduction: In South America, the rise in chronic respiratory diseases and weight-related issues due to the ongoing epidemiological transition has prompted research into their interrelationship.

Methods: We sought to assess the association between body mass index (BMI) and bronchodilator responsiveness (BDR) among adults in Peru, Chile, Uruguay, and Argentina, using population-based data from two cohort studies. We defined BDR as a ≥12% and ≥200 mL increase in either forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC) after administration of a short-acting bronchodilator. The analysis also distinguished between FEV_1- and FVC-specific BDR. We used logistic regression adjusted for confounders to evaluate associations with BMI.

Results: Among 7,160 participants (55.2% men, mean age 57.3 years), 23.7% had a BMI <25 kg/m² and 35.5% had a BMI ≥30 kg/m². Overall, 9.5% met the criteria for BDR; with 7.8% showing FEV_1-specific and 4.9% FVC-specific responses. Compared to a BMI of 20–24.9 kg/m², a BMI ≥30 kg/m² was associated with higher odds of FVC-specific BDR (adjusted OR = 1.47, 95% CI 1.08–2.03), whereas a BMI <20 kg/m² was associated with FEV_1-specific BDR among participants with asthma (6.34, 1.16–35.1) and chronic bronchitis (4.71, 1.28–15.9), and with higher odds of any BDR in those with chronic bronchitis (3.90, 1.19–11.93).

Conclusion: There was a differential relationship between BMI and types of BDR: higher BMI was associated with FVC-specific responsiveness, whereas lower BMI was linked to FEV_1-specific BDR in individuals with asthma and chronic bronchitis and to overall BDR in those with chronic bronchitis.

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INTRODUCTION

The prevalence of chronic respiratory diseases is increasing worldwide, and South America is no exception. A recent systematic review estimated that the incidence of chronic obstructive pulmonary disease (COPD) in South America was 3.4% over a nine-year follow-up period among individuals aged ≥ 35 years, while its prevalence was estimated at 8.9% (1). Uruguay (10.2%) and Argentina (11.7%) suffer the highest burden of COPD in the continent (1). High prevalence rates of asthma have also been reported. For example, in 2002, the overall prevalence of current wheezing was 15.9% in Latin America, higher than the global average of 14.1%. Lima, Peru, has one of the highest asthma prevalence rates in the world, with 19.6% for current wheezing and 33.1% for lifetime asthma (2). Chile (15.4%), Argentina (11.2%), and Uruguay (11.2%) also reported having a high prevalence of current wheezing when compared to other countries around the world (3).

Bronchodilator responsiveness (BDR) is commonly evaluated in individuals with chronic respiratory diseases (4). Indeed, BDR may help to identify patients who benefit from inhaler therapy (5), and it is widely used in both asthma and COPD research studies (6). The presence of BDR has been associated with more respiratory symptoms, frequent exacerbations, and lower quality of life among individuals with asthma and COPD (7). Additionally, its presence is linked to a higher likelihood of experiencing wheezing, shortness of breath, and fatigue, even in individuals without a history of respiratory disease (8). In earlier studies, BDR prevalence was found to be between 3.1% and 7.0% (7, 9, 10). Investigators of the PLATINO study, conducted in Brazil, Mexico, Uruguay, Chile, and Venezuela found a mean BDR prevalence of 7.0% in adults aged ≥ 40 years (10).

The epidemiology of BDR, however, is not well understood. Factors such as anthropometric characteristics may also influence its variability. Several mechanisms have been proposed to explain how obesity-related physiological changes could potentially affect BDR. Obesity-related hyperinsulinemia has been shown to aggravate airway bronchoconstriction through increased vagal stimulation. This effect is mediated by a reduction in the inhibitory function of presynaptic M2 muscarinic receptors, which leads to excessive acetylcholine release and enhanced cholinergic tone in the airways, even without altering smooth muscle contractility (11). Obesity reduces tidal volume and functional residual capacity, which limits the stretch of airway smooth muscle during breathing. This lack of mechanical strain favors a sustained contractile state known as the latch mechanism, in which muscle relaxation is delayed and tone remains elevated. This phenomenon contributes to impaired airway function, even in the absence of structural obstruction (12). Third, leptin, has been shown to induce a proinflammatory cascade in the airways due activates the spliced form of X-box binding protein 1, which triggers endoplasmic reticulum stress and promotes the production of Th2 cytokines such as IL-4, IL-5, and IL-13 (13). These cytokines are involved in eosinophilic airway inflammation and have been associated with increased bronchodilator responsiveness by clinical studies that have evidence that individuals with eosinophilic asthma tend to have poorer baseline lung function but exhibit a larger improvement in FEV_1 after salbutamol administration, reflecting highly reversible airflow obstruction (14).

Studies examining the relationship between BMI and BDR have reported inconsistent results. Some studies have found BMI to be a risk factor for BDR (7, 15, 16) , while others have not (8, 9, 17–19). One population-based study found that individuals with higher BMI had a greater bronchodilator-induced change in FEV_1, even after excluding those with obstructive disease (16). In contrast, other studies have not demonstrated an independent effect of BMI after adjusting for baseline lung function or respiratory comorbidities. For example, a multicenter study in adults aged ≥40 years found that a higher BMI was associated with having BDR in single variable analysis, but not in multivariable analysis (8). These findings suggest that while some evidence supports an association

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between adiposity and increased spirometric reversibility, it remains unclear whether BMI has a consistent and independent effect on BDR.

Understanding the association between BMI and BDR has become increasingly important, as excess weight has reached epidemic proportions in South America, where one in three adults is overweight or obese (20). Despite the high prevalence of obesity and the clinical importance of BDR, few studies have explored this relationship using standardized spirometry in large population-based samples across different settings. We aimed to assess the association between BMI and BDR using prospectively collected data in adults from four South American countries. We hypothesized that higher BMI would be associated with increased BDR, based on prior evidence and through its inflammatory effects on airway physiology. We also explored whether this association differed according to the presence or absence of chronic respiratory diseases.

METHODS

Study design

We analyzed cross-sectional data from two population cohort studies conducted in South America. The CRONICAS study (21) was conducted in four settings in Peru, while the PRISA study (22) was conducted in two cities in Argentina, one in Chile, and one in Uruguay. Both studies were designed as prospective observational studies to assess chronic conditions in the general population, with a minimum follow-up of four years. The CRONICAS study was approved by the ethics committees of Universidad Peruana Cayetano Heredia and the Bloomberg School of Public Health at Johns Hopkins University. The PRISA study was evaluated and approved by ethics committees in Argentina, Chile, Uruguay, and the United States. In both studies, all participants provided informed consent before data collection. This secondary analysis was reviewed and approved by the UPCH Ethics Committee before its implementation.

Study population

We summarized the study designs of the CRONICAS and PRISA cohorts in Table 1. Both studies included permanent residents who could provide informed consent and complete the data collection procedures. Participants were excluded if they intended to move within the next four years, were unable to respond to the questionnaire or provide informed consent, had active tuberculosis, were pregnant, or had contraindications for spirometry.

We used spirometry and anthropometry data collected during the enrollment visit of both studies. CRONICAS enrolled 1,000 participants each from Lima and Tumbes, both found at sea level, and 500 each from the urban and rural areas of Puno, at 3,825 meters above sea level. Participants were selected through stratified random sampling by sex and age. PRISA enrolled a total of 1,500 participants per city, using a three-stage stratified cluster sampling method. In the first stage, 60 clusters were randomly selected from the latest national census data, stratified by socioeconomic status. In the second stage, 40 households per cluster were selected using systematic sampling. In the third stage, one randomly selected household member was enrolled, ensuring an equal distribution of men and women.

Only one randomly selected participant per household was enrolled in both cohorts. After obtaining informed consent, field workers conducted face-to-face interviews using standardized questionnaires to collect sociodemographic information, clinical history, respiratory conditions, and smoking habits. They also performed clinical evaluations, including spirometry and anthropometric assessments.

Spirometry

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Data collection teams in both studies received spirometry training and were subsequently evaluated to ensure proficiency in the procedure and the performance of high-quality tests. In both studies, field staff visited the homes of participants selected through sampling as described above. Those who met the eligibility criteria were invited to participate in the study, and those who agreed provided informed consent. Spirometry was performed according to the 2005 ATS/ERS guidelines (23). These guidelines include ensuring that participants remain seated for at least 15 minutes before testing, educating them about the procedure, and conducting the test. FEV_1, FVC, and FEV_1/FVC were measured before and after administering 200 µg of inhaled salbutamol. This procedure was conducted using Easy-On-PC spirometers in the CRONICAS study and EasyOne spirometers in the PRISA study (ndd, Zurich, Switzerland). These spirometers are commonly used for lung function evaluation in research studies, and have shown to maintain accuracy over time (24). BDR was evaluated using $FEV_1$and FVC measurements. In this study, we defined BDR by ATS criteria as a post-bronchodilator increase of ≥12% and ≥200 mL in either FEV_1or FVC (25). We also evaluated FEV_1-specific BDR and FVC-specific BDR separately, using the same thresholds applied to each parameter independently.

Body mass index

In the CRONICAS study, height was measured with a stadiometer and weight with the TBF-300A (Tanita, Tokyo, Japan) body composition analyzer that includes a scale (26). In the PRISA study, weight was measured using a scale placed on a stable surface, and height was measured with a stadiometer. Both weight and height were measured twice to ensure accuracy. The main independent variable was body mass index (BMI), calculated as weight (kg) divided by height squared (m^2) (27). BMI was categorized into four groups: <20, 20-24.9, 25-29.9, and ≥30 kg/m^2. These categories were informed by the World Health Organization (WHO) classification, which defines 25–29.9 kg/m^2 as overweight and ≥30 kg/m^2 as obesity (28). Participants with BMI <18.5 kg/m^2 — classified by WHO as underweight — were included in the <20 kg/m^2 category. This decision was guided by the low number of individuals in the underweight range (n=46; 0.64%) and previous studies highlighting the relevance of a <20 kg/m^2 threshold when assessing BDR in respiratory disease populations (7).

Potential confounders

Potential confounders included sociodemographic characteristics and chronic respiratory diseases. Sociodemographic characteristics included place of origin, age, education, sex, tobacco smoking, and biomass smoke. Secondary school education or higher was defined according to each country's education law. Exposure to biomass fuel smoke was defined as the current use of biomass as the primary cooking fuel (29). Chronic respiratory diseases included COPD, asthma, previous tuberculosis, and chronic bronchitis. We defined COPD as a post-bronchodilator FEV_1/FVC Z-score ≤ -1.645 standard deviations of the 2012 Global Lung Function Initiative mixed population reference (30) and no history of asthma (7). Asthma, previous tuberculosis, and chronic bronchitis were self-reported, with asthma defined as a previous physician diagnosis, chronic bronchitis as the presence of cough with sputum production for at least three months per year over two consecutive years, and previous tuberculosis as self-reported by participants. Given that individuals with previous tuberculosis have higher rates of obstructive and restrictive lung disease compared to those without tuberculosis (31), it was considered a chronic respiratory disease.

Biostatistical methods

The primary aim of this analysis was to study the association between BMI and BDR. Since BDR is a dichotomous outcome, we used simple and multivariable logistic regression models to calculate crude and adjusted odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). We adjusted for sex, age group, daily smoking, secondary school or higher education, and city, that were identified through a causal diagram (eFigure 1). As a secondary analysis, we conducted a

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multivariable logistic regression model that included all available covariates as independent variables to assess their potential association with BDR above and beyond BMI. This model was not based on the causal diagram but aimed to explore a broader range of clinical and demographic predictors. We stratified our analyses by chronic respiratory disease status (asthma, COPD, chronic bronchitis, and previous tuberculosis). Collinearity in the adjusted models was assessed by calculating the variance inflation factor (32) with a value greater than 10 indicating collinearity. In all regression models, a BMI of 20–24.9 kg/m² was used as the reference category. We tabulated categorical variables into absolute and relative frequencies and summarized continuous variables with mean and standard deviation. We used chi-square tests to compare categorical variables and Wilcoxon rank-sum test compare continuous variables between groups. The associations between BMI and FEV_1 and FVC Z-scores and BDR were examined using exploratory data analyses. We calculated the difference in post- and pre-bronchodilator FEV_1 and FVC Z-scores by each exact value of BMI, and the percentage of BDR by deciles of BMI. We conducted statistical analysis in R version 4.03 (33).

RESULTS

Participant characteristics

The original studies enrolled 7,311 participants: 2,957 from the CRONICAS study and 4,354 from the PRISA study. One participant was excluded due to an implausible FEV_1 value, and 150 participants (2.0%) were excluded due to missing data (Figure 1). The final sample included 7,160 participants, representing 97.9% of the original cohort. The mean age was 57.3 ± 10.3 years, and 55.2% were men. A total of 23.7% had a BMI <25.0 kg/m², and 35.5% had a BMI ≥30 kg/m². In addition, 18.5% had a history of respiratory diseases.

Sociodemographic characteristics and BDR

The overall prevalence of BDR was 9.5%. FEV_1-specific BDR (7.8%) was more frequent than FVC-specific BDR (4.9%). Across study sites, the prevalence of BDR ranged from 5.0% to 17.0%, with the highest rate in Rural Puno and the lowest in Temuco, Chile. Regarding the individual components, Rural Puno had the highest prevalence of FEV_1-specific BDR (16.6%), while Bariloche had the highest rate of FVC-specific BDR (8.2%) (Table 2).

In all three outcomes, older participants and those with a history of asthma, COPD, or chronic bronchitis had higher odds of a positive BDR compared to younger individuals. In contrast, lower prevalence was observed among those with secondary or higher education. Participants exposed to biomass smoke showed higher frequencies of BDR by ATS criteria and FEV_1-specific BDR, but not FVC-specific BDR.

We present the results of single variable regression analysis in eTables 1 and 2. In multivariable regression models, participants aged ≥60 years had higher odds of BDR (OR=1.43, 95% CI 1.20–1.69), FEV_1-specific BDR (1.29, 1.07–1.55), and FVC-specific BDR (OR=1.55; 95% CI, 1.23–1.95). Secondary school or higher education was associated with lower odds of BDR (OR=0.81; 95% CI, 0.68–0.96) and FVC-specific BDR (0.73, 95% CI 0.57–0.93). Asthma and COPD were strongly associated with all three outcomes. Chronic bronchitis was associated with BDR (1.39, 95% CI, 1.06–1.79) and FVC-specific BDR (1.57, 1.12–2.16), but not with FEV_1-specific BDR. BMI ≥30 kg/m² showed a significant association with FVC-specific BDR (1.55, 1.13–2.16), when compared to the reference category (20–24.9 kg/m²) (Table 3).

Association between BMI and BDR

We plotted the difference between post-bronchodilator and pre-bronchodilator Z-scores by BMI values (Figure 2). Overall, both mean post-bronchodilator FEV_1 and FVC Z-scores were higher than pre-bronchodilator values across the full BMI range. A negative trend in the mean difference

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between post- and pre-bronchodilator FEV_1 Z-scores was observed between 20 and 45 kg/m². For BMI values ≥45 kg/m², the data were too sparse and variable to establish a clear pattern. In contrast, there was no consistent trend in the mean difference for FVC Z-scores across BMI values.

We also plotted the prevalence of BDR by BMI deciles (Figure 3). The prevalence, which averaged 9.5%, dropped to about 4% between 24 and 28 kg/m². A similar decline was observed in FEV_1-specific BDR within the same BMI range. In contrast, FVC-specific BDR showed a progressive increase starting at approximately 25.2 kg/m².

After adjusting for potential confounders, participants with a BMI ≥30 kg/m² had higher odds of FVC-specific BDR (1.47, 95% CI 1.08–2.03), compared to those with BMI 20–24.9 kg/m². In stratified analyses, participants with a BMI <20 kg/m² and asthma (6.34, 1.16–35.1) or chronic bronchitis (4.71, 1.28–15.9) had a higher odds of FEV_1-specific BDR. Participants with a BMI <20 kg/m² and chronic bronchitis also had a higher odds of BDR (3.90, 1.19–11.93) (Table 4).

DISCUSSION

In this cross-sectional analysis of population-based data from four Latin American countries, we explored the association between BMI and BDR. We found that a BMI ≥30 kg/m² was associated with higher odds of FVC-specific BDR. In stratified analyses, a BMI <20 kg/m² was associated with higher odds of FEV_1-specific BDR in participants with asthma or chronic bronchitis, and with higher odds of any BDR in those with chronic bronchitis. Older adults and individuals with obstructive respiratory diseases had higher odds of BDR. We also observed substantial variation in BDR prevalence across study sites.

Higher BMI was associated with overall and FVC-specific BDR in the total population, while low BMI was associated with FEV_1-specific BDR among participants with asthma and chronic bronchitis. Previous studies have found a positive association between higher BMI and BDR. Janson and colleagues observed that, after adjusting for confounding variables, a BMI below 20 kg/m² was associated with lower odds (OR, 0.53; 95% CI, 0.32–0.90) of exhibiting a post-bronchodilator increase in FEV_1 ≥12% and ≥200 mL, compared to a BMI ≥ 20 kg/m² in participants with asthma and COPD (7). In our study, we did not find an association between BMI and FEV_1-specific BDR when using all the data; however, in stratified analyses we found that BMI <20 kg/m² was associated with higher odds of FEV_1-specific BDR among participants with asthma and chronic bronchitis. Lehmann et al. conducted another cross-sectional analysis using population-based data from Norway and found that BMI was positively associated with the percent increase in FEV_1 after administration of salbutamol (16). Yoo and colleagues reported that the bronchodilator response measured as the percent increase in FEV_1 after administration of 200 µg of salbutamol was greater in overweight or obese men compared to those with normal BMI. They also reported a weak positive correlation between serum leptin levels and the percent increase in FEV_1 among men (15).

The fact that we found differences in BDR when using FVC but not FEV_1 supports the hypothesis that different spirometric criteria used to define BDR may capture distinct physiological changes. FEV_1-specific BDR is more sensitive to changes in airflow limitation and bronchial caliber, which are typically seen in obstructive airway diseases such as asthma or COPD. In contrast, FVC-specific BDR may reflect changes related to dynamic lung volumes and hyperinflation. In individuals with obesity, reduced baseline lung volumes, early airway closure, and limited chest wall compliance may lead to incomplete exhalation during spirometry. After bronchodilator use, the reopening of previously collapsed airways and reduced air trapping can result in a greater increase in FVC, even in the absence of airflow obstruction (11). However, previous studies (7, 15, 16) have also reported associations between BMI and FEV_1-specific BDR. Our stratified results suggest that such

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associations may become evident only in subgroups with obstructive conditions, highlighting the importance of effect modification. This discrepancy suggests that the relationship may vary across populations or study designs, highlighting the need for further research.

The prevalence of BDR was higher among participants with asthma and COPD, with both conditions showing similar prevalences of BDR, and was also higher among those with chronic bronchitis compared to individuals without these conditions. This aligns with findings from previous studies. For example, in the PLATINO study, participants with COPD had a BDR prevalence of 28%, compared to 7% in healthy individuals (10). In the BOLD study, BDR was 1.5 to 2 times more frequent in individuals with asthma or COPD (34). These findings suggest that the prevalence of BDR in the general population ranges between 5% and 10%, while BDR is two to three times higher in individuals with chronic respiratory diseases such as asthma and COPD. More importantly, they indicate that BDR may not be a reliable parameter to distinguish between COPD and asthma, as it occurs with similar frequency in both conditions and is not exclusive to asthma, as previously thought. Participants aged ≥60 years had approximately 43% higher odds of BDR compared to younger individuals. This is consistent with studies evaluating the association with age in different populations, including individuals with previously normal spirometry (8, 9), and those with asthma or COPD (7, 15). Since lung function declines with age (35) and BDR has been associated with worsening respiratory symptoms (7, 8), these observations suggest that BDR could be a marker of both aging and chronic lung disease in the general population. Future studies could explore whether BDR is also associated with cardiovascular risk or with the likelihood of severe exacerbations in individuals with asthma, COPD, or other chronic lung diseases (36).

BDR varied substantially across study sites. Most locations had a prevalence between 8% and 12%, but two sites, Temuco in Chile with 5% and Marcos Paz in Argentina with 7%, had lower-than-expected prevalence. In contrast, Rural Puno in Peru showed a notably higher prevalence of 17 percent. Even within Puno, we observed a difference between rural areas with 17% and urban areas with 12%. These findings suggest that the factors influencing BDR vary considerably not only between countries but also within them. Environmental and geographic factors may partly explain this variation. However, previous studies have rarely considered this type of variability. Although we adjusted for study site to capture environmental differences, residual confounding from unmeasured exposures such as air pollution may have influenced the observed associations. These results point to the need for more precise and detailed measurements of environmental exposures to better understand their role in BDR and its relationship with BMI.

Our study also has some important strengths. We analyzed data from representative samples of multiple cities in four South American countries, considering diverse contexts of urbanization and altitude above sea level. Unlike previous research, our study addressed this association through a stratified approach that included both individuals with chronic respiratory disease and those without. To our knowledge, this is the first study to provide evidence of a possible association between body mass index and BDR in a population without a prior diagnosis of chronic respiratory disease.

Our analysis also has some limitations. First, the analyzed study samples are not representative of the entire countries, as only ten localities were included. Moreover, the CRONICAS study included participants aged 35 years and older, whereas the PRISA study included participants aged 45 to 75 years. Second, although we adjusted for study site, grouping data from different countries may introduce heterogeneity. These populations may differ in key environmental and social factors. Unmeasured differences, such as exposure to air pollutants and allergens, may have influenced our results (37–39). Although evidence on the relationship between BMI and environmental pollutants is still limited, it suggests potential effects on fat metabolism (40, 41). Measuring environmental

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exposures remains complex and costly, but future studies should consider incorporating these variables to improve our understanding of the relationship between nutritional status and lung function. Third, the cross-sectional design limits our ability to assess temporality between exposures and outcomes. On one hand, it is difficult to determine when BDR developed. On the other hand, we could not account for how long participants had maintained the BMI levels observed at the time of evaluation. Although it is likely that obese individuals sustain high BMI over time (42), BMI also changes with age, usually increasing until around age 50–60 years and decreasing thereafter (43). Longitudinal studies with repeated assessments of both BMI and BDR could help clarify this association. Fourth, while BMI is a simple and widely used tool, it is not a perfect marker of obesity. It does not account for body fat distribution, muscle mass, or metabolic health. Although BMI has a moderate correlation with adipose tissue volume (44), especially in Hispanic populations, this correlation may decrease with age, particularly in men (45). Other obesity indicators may produce different results. For example, COPD has been associated with lower BMI (46), but higher waist circumference (47, 48), and studies evaluating serum leptin levels have found a positive association with BDR (15, 49). Although BMI remains a practical indicator, future studies may benefit from incorporating additional anthropometric and biochemical markers. Finally, asthma was based on self-report, and COPD was defined using spirometric criteria only.

In conclusion, we found evidence that higher BMI was associated with FVC-specific BDR, while low BMI was linked to FEV_1-specific BDR in individuals with asthma and chronic bronchitis, and to overall BDR in those with chronic bronchitis. Additionally, age and a history of asthma, COPD, or chronic bronchitis were independently associated with higher odds of BDR. These findings highlight the importance of BMI and respiratory comorbidities when interpreting bronchodilator response in population-based settings.

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Competing interests
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Table 1. Characteristics Between the CRONICAS and PRISA cohorts

Characteristic	CRONICAS	PRISA
Design	Prospective cohort	Prospective cohort
Countries where the study was conducted	Peru	Argentina, Chile, and Uruguay
Type of zones evaluated	Urban and rural	Urban
Average altitude of evaluated localities	3 m to 3827 m	26 m to 893 m
Inclusion criteria	Age ≥35 years Permanent residents Able to perform procedures and provide informed consent	Age 45-75 years Permanent residents Able to perform procedures and provide informed consent
Exclusion criteria	Pregnant women Cognitive or physical limitations Active tuberculosis Intention to move within the next 4 years Contraindications for spirometry	Pregnant women Cognitive or physical limitations Active tuberculosis Intention to move within the next 4 years Contraindications for spirometry
Target number of participants	3000	6000
Sampling method	Age-and sex-stratified random sample	Multi-stage clustering sampling
Spirometer model used	Easy-On-PC (ndd, Zürich, Switzerland)	EasyOne (ndd, Zürich, Switzerland)
Body mass index measurement	Weight was assessed using a TBF-300A body composition analyzer, and height with a stadiometer	Weight was assessed using a calibrated scale and height with a stadiometer
Protocol for spirometry used to assess BDR	American Thoracic Society/European Respiratory Society 2005 (5)	American Thoracic Society/European Respiratory Society 2005 (5)

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Table 2. Characteristics associated with bronchodilator responsiveness (BDR) in 7,160 participants. We compared categorical variables using chi-square tests and continuous variables using Wilcoxon rank-sum tests.

Characteristics	BDR	p-value	FEV_1-specific BDR	p-value	FVC-specific BDR	p-value
Sample size, n (%)	681 (9.5%)		561 (7.8%)		349 (4.9%)	
City						
Temuco, Chile	52 (5.0%)		41 (4.0%)		29 (2.8%)	
Marcos Paz, Argentina	82 (6.6%)		51 (4.1%)		60 (4.9%)	
Tumbes, Peru	78 (8.3%)		70 (7.4%)		44 (4.7%)	
Canelones, Uruguay	81 (9.6%)	<0.001	64 (7.5%)	<0.001	47 (5.5%)	<0.001
Lima, Peru	109 (10.9%)		94 (9.4%)		46 (4.6%)	
Urban Puno, Peru	60 (11.9%)		59 (11.7%)		11 (2.2%)	
Bariloche, Argentina	134 (12.2%)		99 (9.0%)		90 (8.2%)	
Rural Puno, Peru	85 (17.0%)		83 (16.6%)		22 (4.4%)	
Sex						
Male	365 (9.2%)	0.39	291 (7.4%)	0.10	194 (4.9%)	0.87
Female	316 (9.8%)		270 (8.4%)		155 (4.8%)	
Age in years, mean (SD)	59.4 (11.3)	<0.001	58.6 (11.3)	0.005	61.4 (10.8)	<0.001
Adult aged ≥ 60 years, n (%)						
No	357 (8.3%)	<0.001	308 (7.1%)	0.006	170 (3.9%)	<0.001
Yes	324 (11.4%)		253 (8.9%)		179 (6.3%)	
Secondary school of higher, n (%)						
No	411 (11.0%)	<0.001	332 (8.9%)	<0.001	225 (6.0%)	<0.001
Yes	270 (7.9%)		229 (6.7%)		124 (3.6%)	
Daily smoking, n (%)						
No	589 (9.5%)	0.90	497 (8.0%)	0.10	292 (4.7%)	0.14
Yes	92 (9.4%)		64 (6.5%)		57 (5.8%)	
Biomass smoke, n (%)						
No	532 (8.9%)	<0.001	429 (7.2%)	<0.001	282 (4.7%)	0.225
Yes	149 (12.4%)		132 (11.0%)		67 (5.6%)	
Any respiratory disease, n (%)						
No	233 (17.6%)	<0.001	172 (13.0%)	<0.001	152 (11.5%)	<0.001
Yes	448 (7.7%)		389 (6.7%)		197 (3.4%)	
Asthma, n (%)						
No	593 (8.7%)	<0.001	495 (7.3%)	<0.001	285 (4.2%)	<0.001
Yes	88 (23.9%)		66 (17.9%)		64 (17.4%)	
COPD, n (%)						
No	581 (8.6%)	<0.001	493 (7.3%)	<0.001	285 (4.2%)	<0.001
Yes	100 (23.9%)		68 (16.3%)		64 (15.3%)	
Chronic bronchitis, n (%)						
No	592 (9.0%)	<0.001	494 (7.5%)	0.003	293 (4.5%)	<0.001
Yes	89 (14.5%)		67 (10.9%)		56 (9.1%)	
Previous tuberculosis, n (%)						
No	663 (9.5%)	0.37	546 (7.8%)	0.39	339 (4.8%)	0.36
Yes	18 (11.6%)		15 (9.7%)		10 (6.5%)	
BMI in kg/m^2, mean (SD)	28.7 (5.5)	0.71	28.5 (5.4)	0.15	29.6 (5.5)	0.001
Categories of BMI in kg/m^2, n (%)						
<20	22 (14.3%)		19 (12.3%)		7 (4.5%)	
<20-24.9	158 (10.3%)	0.083	135 (8.8%)	0.062	64 (4.2%)	0.05
25–29.9	258 (8.8%)		216 (7.4%)		130 (4.4%)	
≥30	243 (9.6%)		191 (7.5%)		148 (5.8%)	

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* Categorical variables were compared using chi-square tests, and continuous variables using the Wilcoxon rank-sum test

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Table 3. Exploratory multivariable logistic regression analysis of bronchodilator responsiveness (BDR) including all demographic and clinical covariates as independent variables in 7,160 participants.

Characteristics	BDR			FEV_1-specific BDR			FVC-specific BDR		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
City									
Temuco, Chile	1.00			1.00			1.00		
Marcos Paz, Argentina	1.09	0.75 – 1.60	0.66	0.89	0.58 – 1.39	0.62	1.41	0.87 – 2.31	0.17
Tumbes, Peru	2.06	1.42 – 3.03	<0.001	2.22	1.48 – 3.38	<0.001	2.30	1.40 – 3.84	0.001
Canelones, Uruguay	1.69	1.17 – 2.47	0.006	1.74	1.15 – 2.65	0.009	1.68	1.03 – 2.78	0.039
Lima, Peru	2.36	1.65 – 3.41	<0.001	2.47	1.68 – 3.71	<0.001	1.71	1.04 – 2.86	0.036
Urban Puno, Peru	3.01	2.01 – 4.52	<0.001	3.60	2.35 – 5.55	<0.001	0.99	0.46 – 1.98	0.97
Bariloche, Argentina	2.70	1.93 – 3.83	<0.001	2.45	1.68 – 3.63	<0.001	3.25	2.11 – 5.16	<0.001
Rural Puno, Peru	4.44	2.88 – 6.90	<0.001	5.30	3.34 – 8.54	<0.001	1.82	0.95 – 3.46	0.07
Sex									
Male	1.00			1.00			1.00		
Female	1.03	0.87 – 1.22	0.72	1.09	0.91 – 1.30	0.347	0.99	0.79 – 1.24	0.945
Age ≥ 60 years									
No	1.00			1.00			1.00		
Yes	1.43	1.20 – 1.69	<0.001	1.29	1.07 – 1.55	0.007	1.55	1.23 – 1.95	<0.001
Secondary school or higher									
No	1.00				1.00		1.00		
Yes	0.81	0.68 – 0.96	0.017	0.84	0.69 – 1.01	0.07	0.73	0.57 – 0.93	0.01
Daily smoking									
No	1.00				1.00		1.00		
Yes	1.13	0.87 – 1.46	0.36	1.02	0.75 – 1.37	0.89	1.15	0.82 – 1.59	0.42
Biomass smoke									

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	No	1.00				1.00		1.00		
	Yes	0.96	0.72 – 1.27	0.78	0.95	0.70 – 1.29	0.76	1.11	0.78 – 1.57	0.55
Asthma										
	No	1.00				1.00		1.00		
	Yes	4.01	3.04 – 5.24	<0.001	3.39	2.50 – 4.56	<0.001	5.65	4.07 – 7.75	<0.001
COPD										
	No	1.00				1.00		1.00		
	Yes	3.76	2.89 – 4.86	<0.001	2.79	2.06 – 3.74	<0.001	5.05	3.64 – 6.94	<0.001
Chronic bronchitis										
	No	1.00				1.00		1.00		
	Yes	1.39	1.06 – 1.79	0.014	1.31	0.98 – 1.74	0.066	1.57	1.12 – 2.16	0.007
Previous tuberculosis										
	No	1.00				1.00		1.00		
	Yes	0.88	0.51 – 1.46	0.648	0.94	0.52 – 1.61	0.84	0.98	0.47 – 1.86	0.96
Body mass index (kg/m^2)										
	<20	0.99	0.58 – 1.62	0.97	1.09	0.62 – 1.83	0.741	0.62	0.25 – 1.33	0.25
	20-24.9	1.00			1.00			1.00		
	25-29.9	1.00	0.81 – 1.25	0.99	0.98	0.78 – 1.24	0.86	1.23	0.90 – 1.70	0.20
	≥ 30	1.16	0.93 – 1.46	0.19	1.10	0.86 – 1.41	0.47	1.55	1.13 – 2.16	0.007

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Table 4. Multivariable logistic regressions of the association between body mass index and bronchodilator responsiveness (BDR) overall and by condition (asthma, COPD, chronic bronchitis, previous tuberculosis, or without chronic respiratory disease). Multivariable models were adjusted for sex, age ≥ 60 years, daily smoking, secondary school or higher education, and city (except for the model of asthma and previous tuberculosis, which was adjusted for country instead of city due to the few cases observed).

Categories of body mass index (kg/m²)	BDR			FEV_1-specific BDR			FVC-specific BDR		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Overall sample (n=7,160)									
<20	1.33	0.80 – 2.13	0.25	1.37	0.79 – 2.25	0.24	0.99	0.40 – 2.06	0.97
20-24.9	1.00			1.00			1.00		
25-29.9	0.98	0.79 – 1.21	0.84	0.96	0.76 – 1.22	0.75	1.18	0.87 – 1.62	0.30
≥ 30	1.13	0.90 – 1.41	0.29	1.08	0.85 – 1.38	0.53	1.47	1.08 – 2.03	0.015
Asthma (n=368)									
<20	4.35	0.89 – 20.8	0.06	6.61	1.23 – 35.6	0.03	3.55	0.43 – 20.9	0.18
20-24.9	1.00			1.00			1.00		
25-29.9	1.50	0.70 – 3.37	0.31	1.42	0.62 – 3.45	0.42	1.74	0.70 – 4.79	0.25
≥ 30	1.22	0.58 – 2.76	0.61	0.94	0.41 – 2.32	0.89	1.76	0.73 – 4.81	0.23
COPD (n=418)									
<20	0.73	0.26 – 1.86	0.53	0.98	0.29 – 2.82	0.97	0.57	0.15 – 1.76	0.36
20-24.9	1.00			1.00			1.00		
25-29.9	1.18	0.66 – 2.16	0.58	1.24	0.63 – 2.50	0.54	0.95	0.45 – 2.01	0.89
≥ 30	1.43	0.74 – 2.80	0.29	1.57	0.72 – 3.44	0.26	1.62	0.76 – 3.54	0.22
Chronic bronchitis (n=613)									
<20	3.90	1.19 – 11.9	0.019	4.71	1.28 – 15.9	0.014	2.42	0.48 – 9.58	0.23
20-24.9	1.00			1.00			1.00		
25-29.9	1.13	0.58 – 2.25	0.72	1.38	0.66 – 3.01	0.40	1.02	0.44 – 2.52	0.96
≥ 30	1.95	1.00 – 3.93	0.06	1.73	0.81 – 3.92	0.17	2.09	0.94 – 5.07	0.08
Previous tuberculosis (n=155)*									
<20	2.59	0.11 – 29.5	0.47	3.41	0.14 – 41.8	0.36		-	
20-24.9	1.00			1.00				-	
25-29.9	0.89	0.24 – 3.53	0.87	0.89	0.24 – 3.50	0.87		-	
≥ 30	1.62	0.41 – 6.65	0.49	0.70	0.13 – 3.28	0.65		-	
Without respiratory disease (n=5,835)									
<20	1.10	0.53 – 2.06	0.78	1.12	0.53 – 2.16	0.75	0.28	0.02 – 1.30	0.21
20-24.9	1.00			1.00			1.00		
25-29.9	0.94	0.73 – 1.23	0.67	0.93	0.70 – 1.22	0.59	1.26	0.84 – 1.90	0.27
≥ 30	1.12	0.85 – 1.47	0.43	1.11	0.83 – 1.48	0.50	1.49	0.99 – 2.28	0.06

* Too few datapoints to estimate ORs for FVC-specific BDR across the 4 categories.

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Figure 1. Participant flowchart. The percentages of missing data for each variable do not sum to the total percentage excluded, as there were participants who had more than one missing variable.

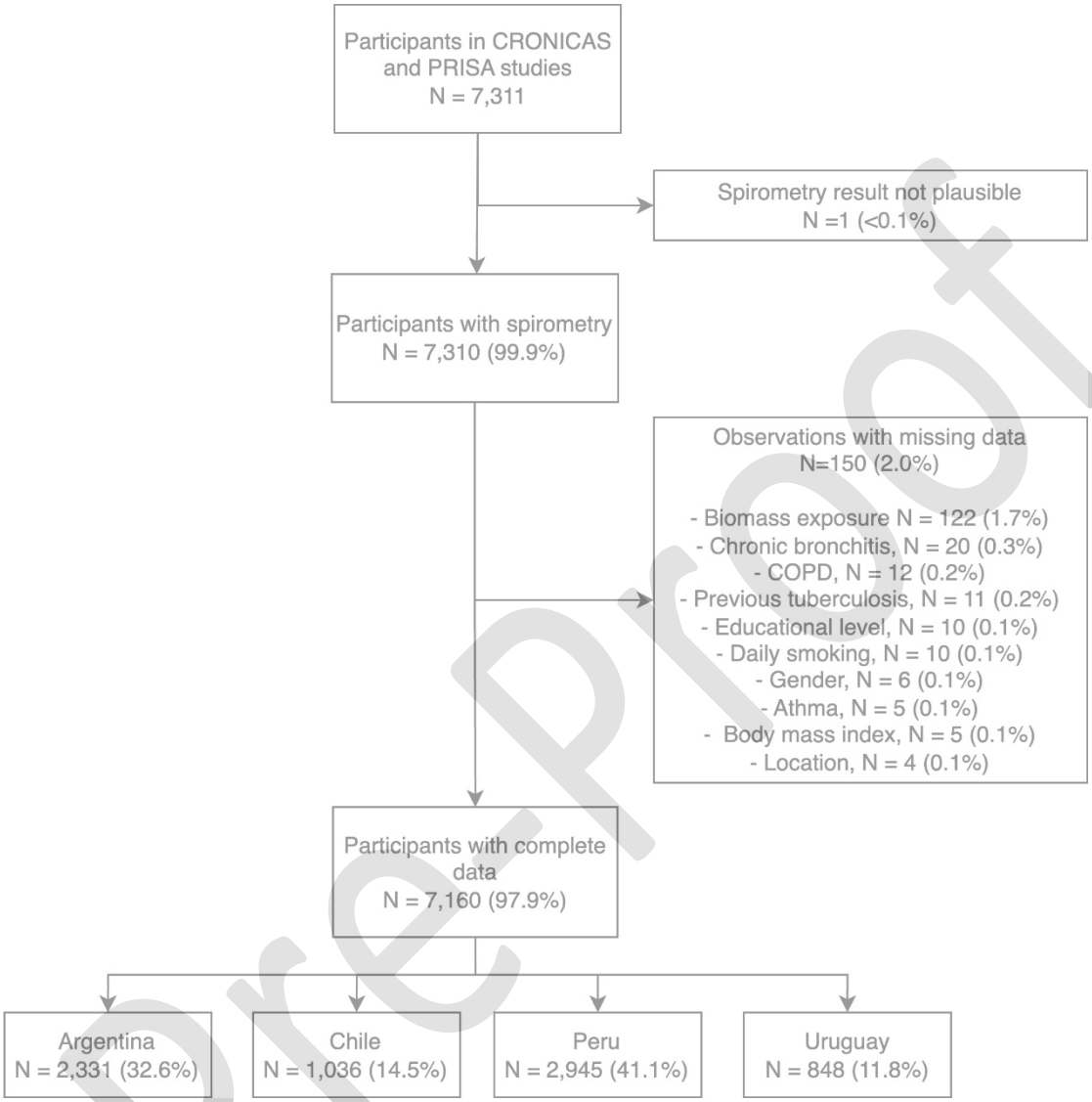

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Figure 2. Differences in mean post- and prebronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) Z-scores by exact values of body mass index (BMI). We plotted the mean difference (Δ) between post- and prebronchodilator FEV_1 (panel A) and FVC Z-scores (panel B) at each exact value of BMI (in kg/m^2), represented as blue circles. The size of the blue circles is proportional to sample size. We also fitted smoothing splines and corresponding 95% confidence bands weighted by sample size, represented by a blue line and a light grey shadow, respectively. We plotted a rug plot of body mass index values along the x-axis.

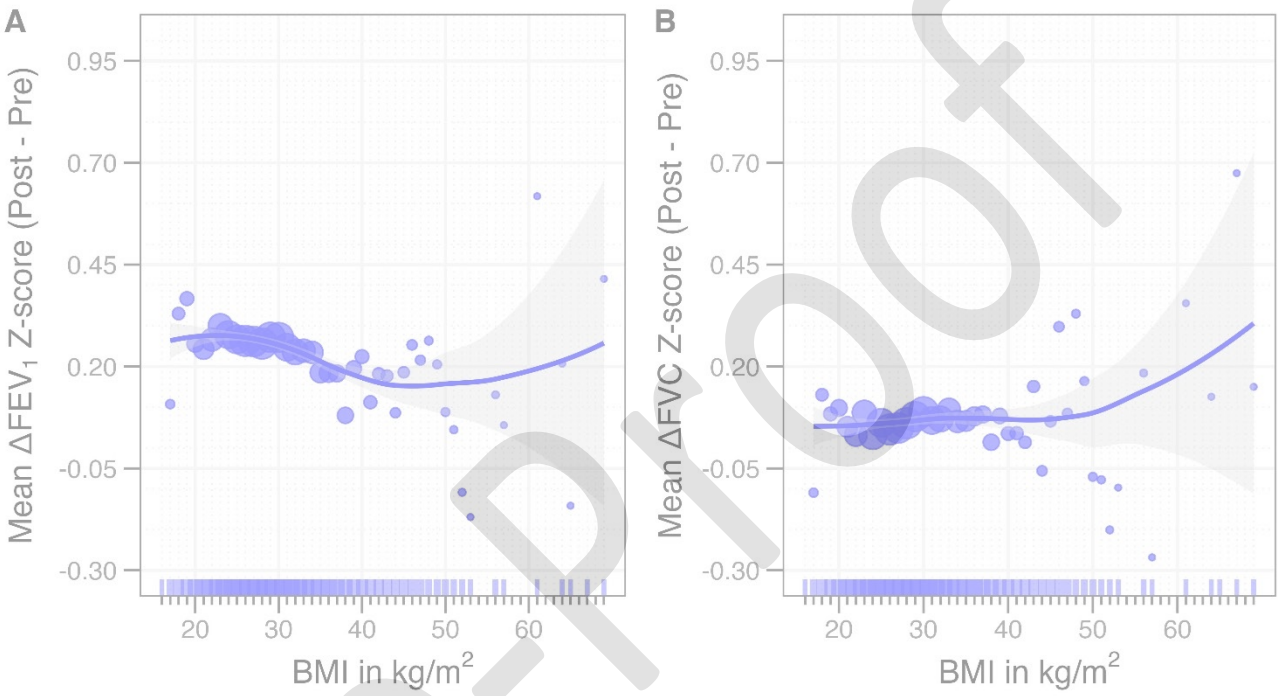

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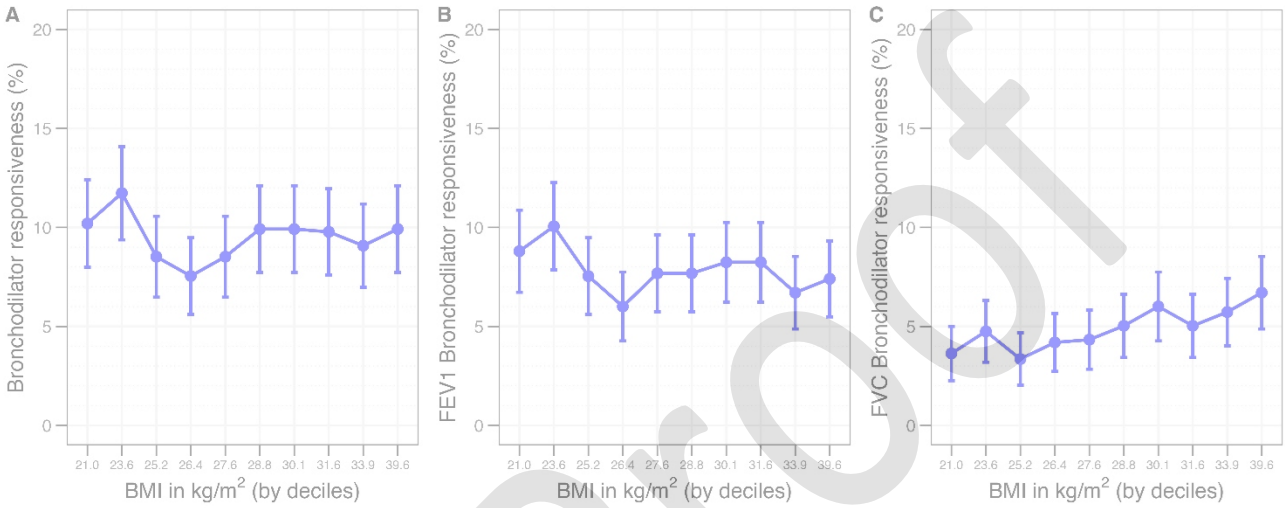
Figure 3. Prevalence of overall, forced expiratory volume in 1 second (FEV_1-) and forced vital capacity (FVC)-specific bronchodilator responsiveness (BDR) by deciles of body mass index (BMI). We plotted the prevalence of overall BDR in panel A, and FEV_1-specific and FVC-specific BDR in panels B and C, respectively. We categorized BMI into deciles and labeled the x-axis using the mean for each decile. Pointwise prevalences of BDR by deciles of BMI are represented with circles and corresponding 95% confidence intervals are represented with vertical lines.



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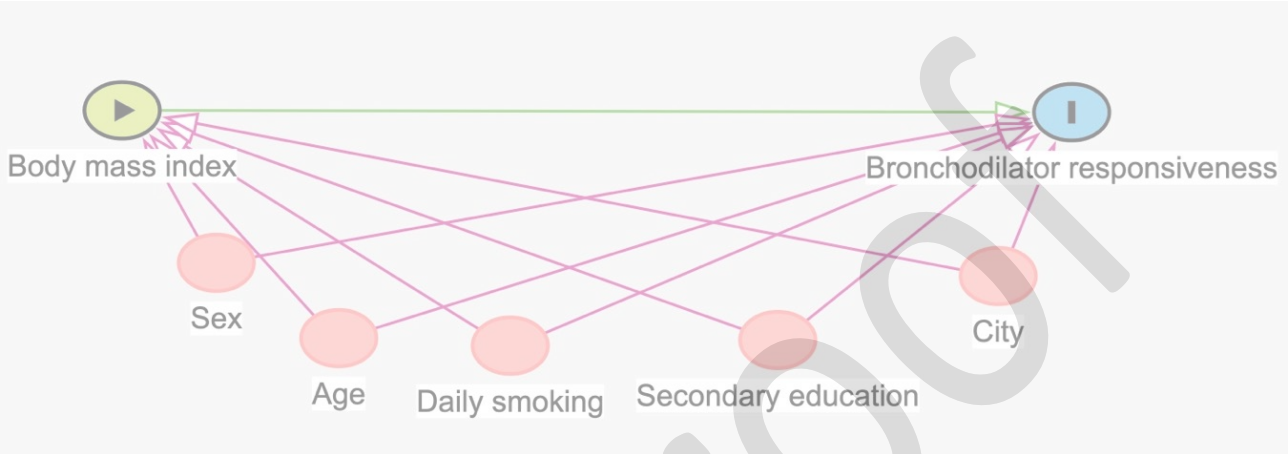
Online Supplement

Supplement to: Soriano-Moreno AN, et al. Body mass index and bronchodilator responsiveness in adults: analysis of two population-based studies in four South American countries

eFigure 1. Directed Acyclic Graph of the association between body mass index and bronchodilator responsiveness



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eTable 1. Single variable logistic regression analysis of positive bronchodilator responsiveness (BDR) according to individual characteristics in 7,160 participants, including city, sex, age ≥ 60 years, secondary school education, smoking, biomass exposure, respiratory diseases, and body mass index categories.

Characteristics	BDR			FEV_1-specific BDR			FVC-specific BDR		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
City									
Temuco, Chile	1.00			1.00			1.00		
Marcos Paz, Argentina	1.34	0.94 – 1.93	0.11	1.04	0.69 – 1.60	0.84	1.77	1.14 – 2.82	0.013
Tumbes, Peru	1.70	1.19 – 2.46	0.004	1.94	1.31 – 2.91	0.001	1.70	1.06 – 2.76	0.030
Canelones, Uruguay	2.00	1.40 – 2.88	<0.001	1.98	1.33 – 2.98	0.001	2.04	1.28 – 3.30	0.003
Lima, Peru	2.32	1.66 – 3.29	<0.001	2.53	1.74 – 3.72	<0.001	1.68	1.05 – 2.72	0.032
Urban Puno, Peru	2.56	1.74 – 3.79	<0.001	3.22	2.14 – 4.91	<0.001	0.78	0.37 – 1.52	0.48
Bariloche, Argentina	2.64	1.90 – 3.71	<0.001	2.41	1.67 – 3.54	<0.001	3.11	2.05 – 4.85	<0.001
Rural Puno, Peru	3.88	2.70 – 5.60	<0.001	4.83	3.29 – 7.20	<0.001	1.60	0.90 – 2.80	0.10
Sex									
Male	1.00			1.00			1.00		
Female	1.07	0.91 – 1.26	0.39	1.15	0.97 – 1.37	0.10	0.98	0.79 – 1.22	0.87
Age ≥ 60 years									
No	1.00			1.00			1.00		
Yes	1.43	1.22 – 1.67	<0.001	1.27	1.07 – 1.51	0.006	1.64	1.32 – 2.04	<0.001
Secondary school or higher									
No	1.00			1.00			1.00		
Yes	0.70	0.59 – 0.82	<0.001	0.74	0.62 – 0.88	0.001	0.59	0.47 – 0.74	<0.001
Daily smoking									
No	1.00			1.00			1.00		
Yes	0.98	0.78 – 1.23	0.90	0.80	0.61 – 1.04	0.10	1.25	0.92 – 1.66	0.14
Biomass smoke									
No	1.00			1.00			1.00		
Yes	1.44	1.18 – 1.74	<0.001	1.58	1.29 – 1.94	<0.001	1.18	0.89 – 1.55	0.23
Asthma									
No	1.00			1.00			1.00		
Yes	3.29	2.54 – 4.22	<0.001	2.78	2.08 – 3.66	<0.001	4.81	3.56 – 6.42	<0.001
COPD									
No	1.00			1.00			1.00		

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	Yes	3.33	2.61 – 4.23	<0.001	2.46	1.86 – 3.22	<0.001	4.10	3.04 – 5.45	<0.001
Chronic bronchitis										
	No	1.00			1.00			1.00		
	Yes	1.71	1.34 – 2.16	<0.001	1.50	1.14 – 1.96	0.003	2.15	1.58 – 2.87	<0.001
Previous tuberculosis										
	No	1.00			1.00			1.00		
	Yes	1.26	0.74 – 2.01	0.37	1.27	0.71 – 2.10	0.39	1.36	0.66 – 2.47	0.36
Body mass index (kg/m^2)										
	<20	1.46	0.88 – 2.31	0.124	1.46	0.85 – 2.39	0.144	1.10	0.45 – 2.28	0.818
	20-24.9	1.00			1.00			1.00		
	25-29.9	0.85	0.69 – 1.04	0.118	0.83	0.66 – 1.04	0.105	1.07	0.79 – 1.47	0.650
	≥ 30	0.92	0.75 – 1.14	0.464	0.85	0.67 – 1.07	0.152	1.43	1.06 – 1.94	**0.021**

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eTable 2. Single variable logistic regression models assessing the association between body mass index categories and bronchodilator responsiveness (BDR), in the overall sample and stratified by respiratory condition (asthma, COPD, chronic bronchitis, previous tuberculosis, or absence of respiratory disease).

Categories of body mass index in kg/m²	BDR			FEV_1-specific BDR			FVC-specific BDR		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Overall sample (n=7,160)									
<20	1.46	0.88 – 2.31	0.12	1.46	0.85 – 2.39	0.14	1.10	0.45 – 2.28	0.82
20-24.9	1.00			1.00			1.00		
25-29.9	0.85	0.69 – 1.04	0.12	0.83	0.66 – 1.04	0.11	1.07	0.79 – 1.47	0.65
≥ 30	0.92	0.75 – 1.14	0.46	0.85	0.67 – 1.07	0.15	1.43	1.06 – 1.94	**0.02**
Asthma (n=368)									
<20	3.07	0.67 – 13.42	0.13	3.84	0.83 – 17.21	0.08	2.08	0.27 – 10.94	0.41
20-24.9	1.00			1.00			1.00		
25-29.9	1.35	0.65 – 2.93	0.44	1.24	0.57 – 2.88	0.61	1.61	0.68 – 4.28	0.30
≥ 30	1.11	0.55 – 2.37	0.78	0.84	0.39 – 1.95	0.68	1.64	0.72 – 4.26	0.27
COPD (n=418)									
<20	0.83	0.31 – 2.02	0.70	0.91	0.28 – 2.51	0.87	0.81	0.22 – 2.41	0.73
20-24.9	1.00			1.00			1.00		
25-29.9	1.04	0.60 – 1.83	0.89	1.09	0.57 – 2.10	0.81	0.98	0.49 – 1.98	0.95
≥ 30	1.39	0.75 – 2.59	0.30	1.34	0.65 – 2.76	0.42	1.99	0.98 – 4.10	0.06
Chronic bronchitis (n=613)									
<20	2.79	0.90 – 7.93	0.06	3.01	0.87 – 9.28	0.06	2.21	0.46 – 8.20	0.26
20-24.9	1.00			1.00			1.00		
25-29.9	1.07	0.57 – 2.09	0.83	1.26	0.62 – 2.67	0.53	1.08	0.48 – 2.59	0.86
≥ 30	1.52	0.82 – 2.92	0.19	1.27	0.62 – 2.71	0.52	1.98	0.93 – 4.59	0.09
Previous tuberculosis (n=155)									
<20	2.10	0.10 – 18.30	0.54	2.10	0.10 – 18.30	0.54			
20-24.9	1.00			1.00				-	
25-29.9	0.97	0.27 – 3.57	0.96	0.97	0.27 – 3.57	0.96			
≥ 30	1.29	0.36 – 4.81	0.69	0.60	0.12 – 2.60	0.50			
Without respiratory disease (n=5,835)									
<20	1.23	0.60 – 2.26	0.54	1.25	0.60 – 2.37	0.52	0.31	0.02 – 1.44	0.25
20-24.9	1.00			1.00			1.00		
25-29.9	0.79	0.62 – 1.02	0.07	0.78	0.60 – 1.02	0.06	1.06	0.72 – 1.58	0.78
≥ 30	0.84	0.65 – 1.09	0.19	0.80	0.61 – 1.05	0.11	1.26	0.86 – 1.88	0.25

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