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Prevalence and Population Attributable Risk for Early COPD in US Hispanics/Latinos

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Abstract

Background: In predominantly white populations, early COPD (i.e., COPD in people aged <50 years) has been linked to higher hospitalization rates and mortality; however, the prevalence, risk factors, and population attributable risk (PAR) of early COPD remain to be determined in non-white populations. We aimed to examine the prevalence, risk factors, and PARs of early COPD among Hispanics/Latinos, the largest US minority.

Methods: We used baseline data from the Hispanic Community Health Study/Study of Latinos, a population-based probability sample of 16,415 Hispanics/Latinos aged 18-74 years. Participants aged <50 years were included (N=7,323). Early COPD was defined as forced expiratory volume in one second to forced vital capacity ratio less than the lower limit of normal. We used survey logistic regression analysis to identify risk factors and estimate the prevalence of early COPD. PARs of the risk factors identified were estimated.

Results: 524 participants met the criteria for early COPD, yielding a sex- and age-adjusted prevalence of 7.6% [95% Confidence interval, 6.8 – 8.6]. Asthma (Odds Ratio (OR) 3.37 [2.57 – 4.41]), smoking status (ever vs. never, OR 1.65 [1.24 – 2.20]), and chronic sinusitis (OR 1.71 [1.09 – 2.66]) were associated with increased odds of early COPD. Immigrants vs. US born have lower odds of early COPD (age at immigration <15 years and living in the US <10 years, OR 0.94 [0.39 – 2.27]); age at immigration <15 years and living in the US ≥10 years, OR 0.55 [0.37 – 0.84]; age at immigration ≥15 years and living in the US <10 years, OR 0.86 [0.57 – 1.30]; and age at immigration ≧<1~~1~~5 years and living in the US ≥10 years, OR 0.63 [0.42 – 0.95]). Among smokers, pack-years was not associated with early COPD (5-9.9 vs <5 pack-years, OR 1.04 [0.59 – 1.82]; ≥10 vs. <5 pack-years, OR 1.20 [0.74 – 1.94]) The mean PAR for asthma, smoking status, and chronic sinusitis was 26.3% [22.1 – 30.3], 22.4% [17.4 – 27.1], and 6.9% [4.3 – 9.4] respectively.

Conclusion: Among US Hispanics/Latinos, asthma is one of the most important risk factors for early COPD, followed by smoking and chronic sinusitis. Immigrants appear to have a lower risk of early COPD than US-born Hispanics/Latinos.

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Introduction

Chronic obstructive pulmonary disease (COPD) affects over 29 million people and is the 4th leading cause of death in the United States (US).(1, 2) The disease develops slowly over many years and is typically diagnosed when patients are over 60 years old and have substantial airflow obstruction, making therapies less effective.(3, 4) Because of this, experts have proposed to shift the focus on younger individuals.(5-7) In a predominantly white population, early COPD (i.e., COPD in those under 50 years) has been linked to higher hospitalization rates and mortality.(8)

Identifying risk factors will inform preventive strategies and interventions targeted to treat early COPD and halt its progression. Several studies in predominantly white older populations have identified various risk factors for COPD, including smoking and asthma.(9, 10) However, early COPD studies focusing to other populations are lacking. Hispanics/Latinos are the largest and youngest minority in the US —in 2018, over 60 million or 18% of the population, median age 30 years, 48% 18-49 years.(11) Thus, identifying risk factors and estimating population attributable risk (PAR) of early COPD in this minority is of public health and clinical relevance.

Prior studies demonstrated that compared to non-US-born Hispanics/Latinos, US-born Hispanics/Latinos have higher risk of asthma and chronic bronchitis, suggesting that place of birth and immigration to a new country might be linked to disease risk.(12-14) Hispanic/Latino ethnicity encompasses several heritage backgrounds, including Mexicans, Cubans, Puerto Ricans.(15) The prevalence of known COPD risk factors, such as smoking and asthma, varies by heritages and sex. Smoking rates and pack-years are the highest among Cubans and Puerto Ricans and higher in men than women of any heritage.(16) The prevalence of asthma is the

highest in Puerto Ricans and is higher in Hispanic/Latino women than their men counterparts.(12) Additionally, a less known potential risk factor for COPD, chronic sinusitis, has not been examined in this population. Chronic sinusitis and COPD are considered chronic inflammatory processes, and paranasal sinus opacities were found to be associated with COPD,(17) suggesting a link between these two conditions. Therefore, we aimed to determine the prevalence, risk factors, and PARs for early COPD in US Hispanics/Latinos in this cross-sectional study.

Methods

We used the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), described elsewhere,(18, 19) to conduct this analysis. Details about this study are in the online supplement. Briefly, this is a population-based study in 4 US communities that enrolled self-identified Hispanic/Latino men and women aged 18-74 years from households selected in a random, multistage fashion. In this analysis, we included participants aged 18-49 years enrolled at baseline (between 2008 and 2011) who completed the respiratory questionnaire and performed valid spirometry (Figure 1).(12) Informed consent was obtained from all study participants and each site's IRB approved HCHS/SOL. The current study was approved by the Partners Human Research Committee (2017P001688/PHS).

Outcome

The outcome was early COPD, defined as age <50 years old, and prebronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio less than the lower limit of normal. Although the proposed definition of early COPD included 10 or more pack-years of cigarette smoked as criterium,(5) we included never-smoking participants because a prior study showed that they contributed 23.4% to the burden of airflow obstruction in the US population.(20)

Covariates

Standardized questionnaires were used to obtain information on age, sex, heritage background, country of birth, years living in the US, age at immigration, education level, health insurance, smoking history, maternal smoking, number of smokers at home, tuberculosis, chronic sinusitis,

childhood pneumonia, asthma, nasal/eye symptoms to allergen exposures, and occupational exposures (available at http://www.cscc.unc.edu/hchs). Details on those covariates are in the online supplement. Age was categorized into three groups (18-29, 30-39, 40-49). Country of birth, age at immigration, and the number of years living in the US were collapsed into a 5-category variable termed immigration history as follows: US-born (non-immigrant); age at immigration <15 years and living in the US <10 years; age at immigration <15 years and living in the US ≥10 years; age at immigration ≥15 years and living in the US <10 years; and age at immigration ≥15 years and living in the US ≥10 years. We used this approach based on prior studies(12, 13) and reflected the variation of Hispanics/Latinos immigration history. Heritage backgrounds included Mexican, Cuban, Republic Dominican, Puerto-Rican, Central American, South American, and Other/Mixed heritage. Education level was classified as high school or General Education Diploma (GED) and greater than high school or GED. Health insurance was dichotomized as yes/no.(12) Smoking status was categorized as never and ever. Never smoking was defined as smoking fewer than 100 cigarettes ever. Pack-years of smoking were categorized as <5, 5-9.9, and ≥10 pack-years.(16) Maternal smoking was considered present if the participant had a female caregiver who smokes in his/her home. The number of smokers at home was dichotomized as 0 vs. ≥1. A history of tuberculosis, chronic sinusitis, childhood pneumonia, asthma, and nasal/eye allergy was based on the respiratory questionnaire.(12) Occupational exposure to cleaning and disinfecting solutions and vapors, gas, dust, or fumes was extracted from the occupational questionnaire.(14) Tuberculosis, chronic sinusitis, childhood pneumonia,

asthma, nasal/eye allergy, and occupational exposures were treated as binary variables. The body mass index (BMI) was calculated using weight and height measurements performed in a standardized manner.

Spirometry

Spirometry was performed following the American Thoracic Society/European Respiratory Society guidelines using a dry rolling sealed spirometer with automated quality checks (Occupational Marketing, Houston, TX) with overreading by one investigator.(12, 21) All participants, except those with recent cardiovascular events or surgery, were asked to perform prebronchodilator spirometry. Prediction equations for the general US population were used to calculate predicted values.(22)

Statistical Analysis

To account for the sampling design, stratification, and clustering, means and prevalence rates were weighted.(18, 19) Models for early COPD were built using survey logistic regression analysis.(14) Modeling for early COPD was guided by the directed acyclical graph (DAG) approach (Figure 2).(23) First, we selected all the following 17 factors based on clinical knowledge and prior studies(9, 10, 13, 17, 19, 24): sex, age, immigration history (control, US-born), heritage background, education level, health insurance, smoking status (ever vs. never), pack-years smoked, maternal smoking, number of smokers at home, tuberculosis, chronic sinusitis, childhood pneumonia, asthma, nasal/eye allergy, occupational exposure to cleaning and disinfecting solutions and vapors, gas, dust or fume. We then considered the following variables as main exposures: smoking status, pack-years smoked (among smokers only), asthma, chronic

sinusitis, and immigration history. The rest of the variables above were considered confounders of the relationships between the main exposures and early COPD (Figure 2). We also conducted a smoking status-stratified analyses (ever- vs. never-smoking) to estimate the association between the pack-year categories and early COPD among ever-smoking participants.

The prevalence of early COPD was estimated using logistic-regression conditional marginal analysis. In this analysis, the estimated mean is the expected outcome for an individual conditional on belonging to a specific group (e.g., Hispanic background) and having covariate values equal to the weighted average covariates.(14) We report the prevalence of early COPD for all the main exposures used in the overall analysis and by sex, age categories, and heritage background. These estimates are of clinical and epidemiological interest. Finally, we calculated the population attributable risk, which is the excess prevalence of early COPD attributable to risk factors.(24) We estimated PARs using the following two equations: a) Population Attributable Fraction, PAF= Pe (RR-1)/RR, where Pe is the proportion of cases exposed to the risk factor, and RR is the relative risk; and b) PAR= PAF*Pd, where Pd is the prevalence of early COPD.(24) We report PAR estimates for the entire population and stratified by sex. A sex-stratified analysis was conducted because of sex differences in the prevalence of risk factors for COPD, such as smoking and asthma, in Hispanics/Latinos. PAR estimation was performed using the STDRATE procedure of SAS 9.4 (SAS Institute, Cary, NC). Analyses were performed by a statistician (W.W.).

Results

Participants' characteristics

Out of 16,415 HCHS/SOL participants, 7,980 were aged 18-49 years, and 657 out of those 7,980 had missing data, leaving a final sample with complete data of 7,323 (Figure 1). A comparison between participants with and without valid spirometry was reported.(12) Briefly, compared to participants with valid spirometry, those without valid spirometry were older, females, and had lower education attained, higher health insurance rate, and higher pack-years. The characteristics of the participants by early COPD status are in Table 1. Compared to those without early COPD, participants with early COPD were more often males, US-born, and of Puerto Rican heritage, and had lower education level and health insurance rate. Early COPD participants were more often ever smokers and fell in the category of ≥10 pack-years than those without early COPD. These participants had a higher prevalence of maternal smoking exposure, ≥1 smoker at home, tuberculosis, chronic sinusitis, childhood pneumonia, asthma, and nasal/eye allergy. Early COPD participants also had a higher prevalence of respiratory symptoms, and a substantial lung function impairment with a lower mean FEV_1% predicted (82.7% vs. 95.9%) and a higher proportion of participants with <80% (42.6% vs. 8.7%).

Factors Associated with early COPD

Overall, in the adjusted multivariable model, asthma (Odds Ratio [OR] [95% Confidence Interval (CI)], 3.37 [2.57 – 4.41]), ever-smoking status (OR 1.65 [1.24 – 2.20]), and chronic sinusitis (OR 1.71 [1.09 – 2.66]) were significantly associated with increased odds of early COPD. Compared with US-born Latinos/Hispanics, the odds of early COPD were lower for all four immigration history groups, with the estimates being statistically significant ~~being precise~~

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(i.e., CIs do not cross 1) in two groups (Figure 3). The ORs for the four immigration groups vs. US-born were as follows: age at immigration <15 years and living in the US <10 years, OR 0.94 [0.39 – 2.27]; age at immigration <15 years and living in the US ≥10 years, OR 0.55 [0.37 – 0.84]); age at immigration ≥15 years and living in the US <10 years, OR 0.86 [0.57 – 1.30]; and age at immigration ≥<15 years and living in the US ≥10 years, OR 0.63 [0.42 – 0.95]. Full model results for the overall study participants are shown in Table E1 in the online supplement.

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The estimates of the association between main exposures and early COPD from the smoking status-stratified analysis are shown in Figure 3. Among never-smoking participants, asthma and immigration history but not chronic sinusitis were associated with early COPD. Among ever-smoking participants, asthma and chronic sinusitis were associated with early COPD, while pack-years smoked and immigration history were not. Additional results among participants without asthma are in Table E2.

Prevalence of early COPD

The overall age- and sex-adjusted prevalence of early COPD was 7.6% (95% Confidence interval [CI], 6.8 – 8.6). The prevalence of early COPD estimated from the final multivariable model above was significantly higher in ever-smoking participants, those with asthma, and those with chronic sinusitis than never-smoking participants, those without asthma and those without chronic sinusitis. Compared to US-born Hispanics/Latinos, the prevalence of early COPD was lower in all four immigration history groups, with a varied magnitude of the differences and precision of estimates (Figure 4). Table E3 shows the prevalence of early COPD by sex, age category, and heritage.

Population Attributable Risk

The estimates of early COPD risk attributable to three factors identified in this analysis are shown in Table 2. The most important risk factor for early COPD was asthma (PAR, 26.3 %) followed by smoking status (PAR 22.4%), and chronic sinusitis (PAR, 6.9%). The PARs differed by sex in that compared to men, women had higher PAR for asthma (35.6% vs. 19.4%) and lower for ever-smoking status (18.2% vs. 24.2%) and chronic sinusitis (5.2% vs. 8.4%).

Discussion

In this population-based study of over 7,500 US Hispanics/Latinos younger than 50 years, we found that the prevalence of early COPD was 7.6% and identified asthma, ever-smoking status, and chronic sinusitis as risk factors of early COPD. Hispanic/Latino immigrants appear to have a lower risk of early COPD. We also determined that the PAR of early COPD for asthma was the highest, followed by smoking and chronic sinusitis.

This study is one of the largest studies exploring risk factors of early COPD in Hispanics/Latinos, an understudied US population. We found that the prevalence of early COPD was 7.6%, which is lower than that of 15% reported in a recent European study,(8) a discrepancy that population differences might explain. The European study only included heavy smokers — 10 or more pack-years— and older participants (mean age, 45.9 years). However, our figure is similar to the prevalence of COPD of 8.2% in HCHS/SOL participants aged 45 years or older,(12) suggesting that younger Hispanics/Latinos seem to be similarly susceptible to the disease and supporting the notion of comprehensibly understand the disease in younger people.

We also found that asthma was the strongest risk factor associated with early COPD in this minority and that the association remained the strongest in both smoking and never-smoking participants, strengthening the relevance of this factor. This finding is in line with two recent studies in predominantly white populations showing that the prevalence of asthma was higher in early COPD defined with 10 or more pack-years of smoking.(8, 25) The relevance of asthma for early COPD in Hispanics/Latinos may be due to a couple of reasons. A decreasing trend in smoking rates from 42% to 16% in the US general population in the last five decades has been

noted, and that this ethnicity has a lower smoking rate than non-Hispanic whites.(26) The prevalence of asthma in HCHS/SOL was 15.3%,(12) almost two-fold higher than that of average 8.0 ~~7.7~~% among US adults in 2019~~8~~.(27)

Although this study cannot tease out the complex interplay between asthma and early COPD, it is known that poorly controlled asthma can lead to fixed airflow obstruction, and also asthma has been proposed as a risk factor for COPD. Explanations for the latter include the following: first, a prevalence of asthma up to 26% in mild-moderate smoking COPD;(28) second, longitudinal studies have demonstrated a rapid decline in lung function in adult smokers with asthma and asthma was associated with a greater risk for developing COPD;(9, 29) and third, in smokers with childhood-onset asthma, smaller airways are associated with lower lung function and a higher risk of COPD.(30) Collectively, our and prior findings support the notion that asthma might be a risk factor for early COPD, a finding that deserves further research.

In this study, chronic sinusitis was associated with early COPD, a factor that has not been widely explored in COPD. The association we observed is in line with prior studies showing that participants with chronic rhinosinusitis have higher rates of adult-onset asthma and that sinus opacities on MRI were associated with COPD.(17, 31) Note that the cross-sectional nature of this study does not allow to establish the directionality of the relationship between chronic sinusitis and early COPD nor claim causality. We believe that one reason to support the plausibility of the observed association is inflammatory changes in the upper and lower airways. Studies have demonstrated elevated nasal interleukin 8 in stable COPD and upper airway inflammation in

those with COPD exacerbations.(32) Thus, our finding warrants further investigation in other populations.

Our study also confirmed that ever-smoking ~~status~~ is a risk factor for early COPD in Hispanics/Latinos. Thise finding is in line ~~important because the smokers of this population only smoked, on average, 4.1 pack-years, which is much lower compared to a range from 16.5 to 31.6 pack years in recent~~ with other early smoking COPD studies conducted in predominantly white participants where the smoking intensity was higher (16.5-31.6 pack-years), compared to what was seen in our study, suggesting differential susceptibility to tobacco smoke.(8, 25) ~~This low smoking intensity observed might be due to a couple of reasons. It reflects a pattern characterized by intermittent (nondaily) and light (<6 cigarettes/day) smoking that is more prevalent in US Hispanics/Latinos than whites. Since most of the participants included in this analysis were younger than 40 years, young smokers accumulate low lifetime pack-years, shifting the pack years toward the lower values. That low smoking intensity in the Hispanic/Latino population may explain that pack-years were not significantly associated with early COPD. Also, note that among never-smoking participants the prevalence of early COPD was~~ Our finding that 5.35% of never-smokers (Figure 4) had early COPD supports the belief that future investigations of early COPD should include never-smokers and people with a range of smoking histories. ~~This latter finding supports a complete understanding of early phases of COPD that might be achieved by including never-smoking individuals, as has been proposed by some investigators.~~(33)

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We found that Hispanic/Latino immigrants had lower odds of early COPD, a finding replicated among never-smoking participants only (Figure 3). This finding aligns with prior studies demonstrating that US-born Hispanics/Latinos had a higher risk of asthma and chronic bronchitis than non-US-born counterparts.(13, 14) In contrast, a prior study did not find such differences in COPD risk among older US Hispanics/Latinos.(12) A reason for this discrepancy between the current and that prior study might rely on differences in disease susceptibility between younger and older immigrants. Explanations for the lower odds of early COPD in US-born Hispanics/Latinos, particularly among non-smokers, include differences in exposures to environmental respiratory hazards and health status. For instance, 80% of US Hispanics/Latinos reside in areas that do not meet one Environmental Protection Agency standard of clean air, and 28.3% reside near a major highway.(15, 34) It is conceivable that Hispanics/Latinos born in the US might have been exposed longer and during a more critical period of lung development than those coming from abroad. Additionally, immigrants tend to be healthier than the home-country population, likely decreasing their risk for chronic respiratory diseases.(15) Further investigation is warranted to study the interaction between immigration, environmental exposures, and lung disease risk.

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We have estimated PARs of early COPD in Hispanics/Latinos, which is a novel addition to understand the proportion of the disease in this minority exposed to identified risk factors. Thoseese PARs indicate ~~figures explain an understanding of~~ the burden of early COPD that would be eliminated if the exposures were eliminated. Smoking is a known modifiable cause of COPD, and eliminating tobacco exposure would benefit 2221.4% of the HCHS/SOL participants under 50 years of age. Our findings may inform public health policies toward smoking cessation

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programs in the Hispanic/Latino population. The Burden of Obstructive Lung Disease study, an international effort for studying COPD, also showed PARs for other factors, such as poor education, were more relevant than smoking in certain countries.(24) In this study, we found that asthma was the most important factor followed by smoking and chronic sinusitis. We also observed sex differences in PARs. Since the prevalence of early COPD did not differ significantly between sexes, some PARs differences might be due to sex disparities in the prevalence of the risk factors (for asthma, women 18.0% [16.3 – 19.7] vs. men 15.0% [13.4 – 16.7]; for ever-smoking status, women 26.4% [24.3 – 28.7] vs. men 44.5% [42.1 – 47.0]). We believe that assessing PARs across populations and countries may be an important tool to understand the public health impact of early COPD and inform policies to reduce its burden.

This study has several strengths and limitations. We analyzed a large, representative population-based cohort of Hispanics/Latinos, including several of its heritage backgrounds. HCHS/SOL used standardized procedures to collect data, including the respiratory questionnaire and spirometric testing. However, some limitations should be noted. First, we used participants that may not have reached their lung function peak (e.g., those aged 18-30 years) and those who did. However, we found that the prevalence of COPD did not differ by age categories. Second, we used pre-bronchodilator spirometric data. Compared with post-bronchodilator spirometric values, pre-bronchodilator values ~~which~~ may overestimate the prevalence of COPD, but it does not appear to~~not~~ be discrepancy in ~~its~~ diagnostic~~tic~~ discrimination~~accuracy~~ for COPD between them.(35) Further, two recent early COPD studies have used prebronchodilator data, which is an acceptable approach for epidemiological studies.(8, 36) Third, participants with restrictive lung physiology were not excluded, which may bias the odds ratio estimates toward the null. Fourth,

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although an array of risk factors was used in the models, they were collected by questionnaires, which have inherent biases, such as recall bias. Also, other factors, including air pollution and childhood crowding, were not available. Despite this limitation, we identified plausible risk factors, all of which have already been linked to COPD.(9, 10, 17) Fifth, the cross-sectional nature of this observational study does not allow to make inferences about causality. Sixth, we deliberately included never-smoking participants, a diversion of the proposed definition of early COPD.(5) By doing so, we could determine the prevalence of early COPD in never-smoking participants, supporting the arguments to include that population in the proposed definition.(33) Seven, we also caution that PARs estimates are based on the assumption of causality. While for smoking, an assumption of causality is supported,(10) for asthma and chronic sinusitis is an ongoing debate. Eighth, HCHS/SOL has no chest imaging data available, so we could not account for structural changes of the lung, which can occur even before the spirometric criterion for early COPD is met.

In summary, we have demonstrated that the prevalence of early COPD in Hispanics/Latinos is 7.6 % and is higher in ever-smoking participants and those with asthma and chronic sinusitis. The population risk attributable to asthma was the highest, followed by smoking and chronic sinusitis. Latino/Hispanic immigrants appear to have a lower risk of early COPD than their US-born counterparts.

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Figure legends

Figure 1 Flow chart of Hispanic Community Health Study/Study of Latinos (HCHS/SOL) participants' selection.

Figure 2 The directed acyclic graph (DAG) was the basis to inform the survey logistic regression models used in this cross-sectional study to assess relationships of main exposures (purple circles) and early COPD. Yellow circles represent ancestors of main exposures and the outcome (confounders). Blackue arrows and blueack arrows represent paths between confounders and main exposures and between confounders and Early COPD, respectively. Green arrows represent paths between main exposures and Early COPD. This DAG is intended to depict a simple framework for early COPD used in this analysis. It does not reflect the complex relationships that exist or potentially exist between all the variables shown. For visual clarity, blue arrows are shortened.
*Pack-years was used among ever-smoking participants only

Figure 3 Association between main exposures and early Chronic Obstructive Pulmonary Disease (COPD) in the overall Hispanic/Latino cohort and never-smoking and ever-smoking Hispanic/Latino participants. Odds Ratios (OR) and Confidence Intervals (95% CI) estimates are from a survey logistic regression multivariable model. Asthma and chronic sinusitis are binary (yes/no) variables. Referent for ever-smoking, pack-years smoked, and immigration history was never-smoking, <5 pack-years, and US-born (non-immigrant), respectively. The model was adjusted for heritage background, sex, age category, education level, maternal smoking, ≥1 smokers at home, nasal/eye allergy, health insurance, childhood pneumonia, tuberculosis, exposure to cleaning and disinfecting solutions, and exposure to vapors, gas, dust, or fume. The estimates are weighted to account for HCHS/SOL sampling design, stratification, and clustering.
Supplementary Table E1 shows estimates for all the variables.
*Smoking status was used in the overall participants' analysis only.
†Pack-years were used in the ever-smoking participants' analysis only.
‡OR for the group age at immigration <15 years and living in the US <10 years was not estimated in ever-smoking participants because there are no individuals in one of the outcome categories.

Figure 4 Prevalence of early Chronic Obstructive Pulmonary Disease (COPD) in US Hispanics/Latinos aged 18-49 years. The estimates (%) and confidence intervals for the prevalence of early COPD by smoking status (red, ever vs. never), asthma (peach), chronic sinusitis (purple), and immigration history (blue) are from a multivariable model described in the Statistical Analysis section.
For immigration history, P-values vs. US-born (non-immigrant) category.

Table 1 Characteristics of US Hispanic/Latino participants aged 18-49 years by early COPD status and overall

Variable	Non-COPD (n=6799)	Early COPD (n=524)	Overall (n=7323)
Age, years median [IQR]	32.7 [24.5 - 41.0]	31.9 [23.1- 41.6]	32.7 [24.4 - 41.0]
Age category, % (SE)			
18-29	38.3 (1.0)	40.6 (3.3)	38.4 (1.0)
30-39	30.3 (0.9)	25.7 (3.0)	29.9 (0.9)
40-49	31.5 (0.9)	33.7 (2.9)	31.6 (0.8)
Male Sex, % (SE)	49.4 (0.8)	55.6 (3.0)	49.9 (0.8)
BMI, median [IQR]	28.3 [24.8 - 32.6]	27.6 [24.6 - 32.7]	28.3 [24.8 - 32.6]
Heritage background, % (SE)			
Dominican	10.0 (0.9)	9.4 (1.9)	9.9 (0.8)
Central American	8.1 (0.7)	4.9 (1.0)	7.9 (0.7)
Cuban	18.2 (1.6)	17.9 (3.1)	18.2 (1.6)
Mexican	39.9 (1.7)	37.6 (3.4)	39.7 (1.7)
Puerto Rican	13.6 (0.8)	21.5 (2.9)	14.2 (0.8)
South American	4.9 (0.4)	3.9 (0.9)	4.9 (0.4)
Mixed/Other	5.3 (0.5)	4.7 (1.1)	5.2 (0.4)
Immigration history, % (SE)			
US born (no immigrant)	29.1 (1.1)	40.1 (3.5)	29.9 (1.1)
Age at immigration <15 years and living in the US <10 years	1.9 (0.2)	2.1 (0.8)	1.9 (0.2)
Age at immigration <15 years and living in the US ≥10 years	14.5 (0.6)	10.5 (1.7)	14.2 (0.6)
Age at immigration ≥15 years and living in the US <10 years	28.9 (1.1)	27.6 (3.0)	28.8 (1.1)
Age at immigration ≥15 years and living in the US ≥10 years	25.7 (0.7)	19.7 (2.3)	25.2 (0.7)
Education Level, % (SE)			
High school/GED or less	26.0 (0.9)	29.6 (2.8)	26.3 (0.9)
More than High school/GED	74.0 (0.9)	70.4 (2.8)	73.7 (0.9)
Health insurance, % (SE)	45.2 (1.1)	46.3 (3.1)	45.3 (1.1)
Smoking status, % (SE)			
Never	65.5 (0.9)	49.9 (3.2)	64.3 (0.8)
Ever	34.5 (0.9)	50.1 (3.2)	35.7 (0.8)
Pack-years smoked, median [IQR]	3.8 [1.2 - 10.1]	4.1 [1.9 - 13.0]	3.9 [1.3 - 10.4]
Pack-years smoked category*, % (SE)			
<5	58.2 (1.6)	51.9 (5.1)	57.5 (1.5)
5-9.9	15.5 (1.0)	16.8 (4.3)	15.6 (1.0)
≥10	26.3 (1.3)	31.3 (3.8)	26.9 (1.3)
Maternal smoking, % (SE)	23.2 (0.9)	30.6 (2.8)	23.8 (0.8)

≥1smokers at home, % (SE)	22.7 (0.9)	26.1 (2.5)	23.0 (0.8)
Tuberculosis, % (SE)	2.6 (0.3)	4.1 (1.2)	2.8 (0.3)
Chronic sinusitis, % (SE)	6.3 (0.4)	13.2 (2.5)	6.8 (0.4)
Childhood pneumonia, % (SE)	3.3 (0.3)	5.6 (2.0)	3.5 (0.3)
Asthma, % (SE)	14.7 (0.6)	38.5 (2.7)	16.5 (0.6)
Nasal/Eye allergy, % (SE)	38.3 (0.9)	47.0 (3.2)	38.9 (0.9)
Exposure to cleaning and disinfecting solutions, % (SE)	22.5 (0.8)	20.7 (2.3)	22.4 (0.8)
Exposure to vapors, gas, dust or fumes, % (SE)	25.2 (0.8)	25.3 (2.5)	25.2 (0.8)
Respiratory symptoms, % (SE)			
Cough	5.5 (0.4)	9.8 (2.1)	5.8 (0.4)
Phlegm	7.6 (0.5)	11.5 (2.1)	7.9 (0.5)
Shortness of breath	25.0 (0.8)	36.2 (2.9)	25.8 (0.8)
FEV_1 % predicted, median [IQR]	95.9 [88.0 - 103.6]	82.7 [73.1 - 90.5]	95.1 [86.9 - 102.9]
FEV_1 % predicted <80, % (SE)	8.7 (0.5)	42.6 (3.1)	11.3 (0.5)
FVC % predicted, median [IQR]	95.9 [87.6 - 103.4]	98.4 [87.2 - 107.5]	96.0 [87.6 - 103.8]
FEV1/FVC ratio, median [IQR]	83.6 [80.5 - 87.0]	70.4 [67.1 - 73.3]	83.1 [79.5 - 86.6]

Data are presented as median [Interquartile range, IQR] for continuous variables and percentage (standard error, SE) for categorical variables.

Estimates are weighted to account for the HCHS/SOL design, stratification, and clustering.

*Computed only among ever-smoking participants.

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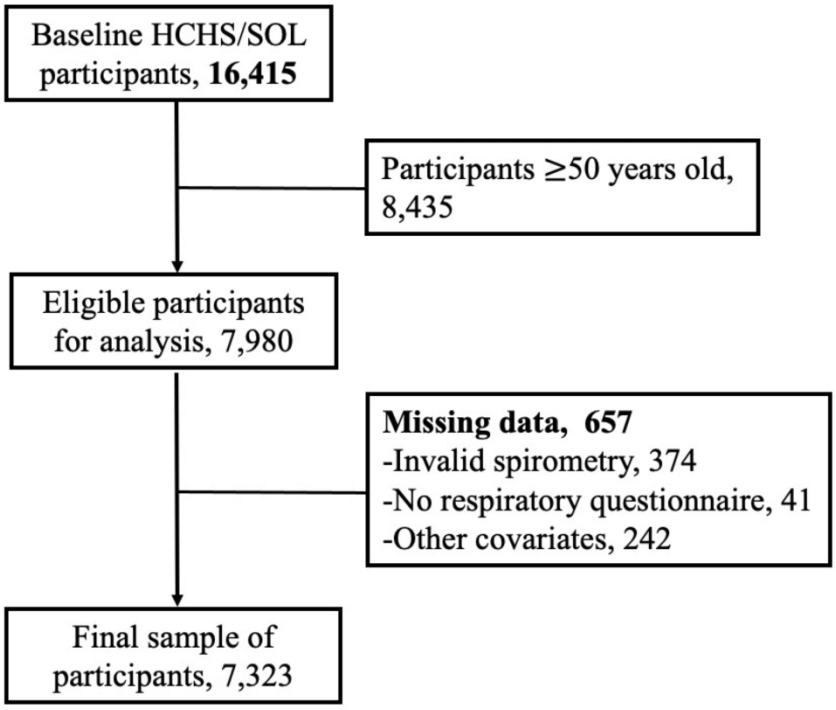
Table 2 Population attributable risk (PAR*) for early COPD by risk factor and sex among US Hispanics/Latinos aged 18-49 years

	Overall	Women	Men
Risk Factor	PAR (%) [95% Confidence Interval]	PAR (%) [95% Confidence Interval]	PAR (%) [95% Confidence Interval]
Asthma	26.3 [22.1 – 30.3]	35.6 [29.0 – 41.7]	19.4 [14.1 – 24.4]
Smoking Status (ever vs. never)	22.4 [17.4 – 27.1]	18.2 [11.3 – 24.6]	24.2 [16.9 – 30.9]
Chronic Sinusitis	6.9 [4.32 – 9.4]	5.2 [1.3 – 8.9]	8.4 [4.8 – 11.8]

*PAR is the percentage of the population aged <50 years with early COPD attributable to the identified risk factor. For details about PAR estimation, see the Statistical Analysis section. The estimates are weighted to account for HCHS/SOL sampling design, stratification, and clustering.



Flow chart of Hispanic Community Health Study/Study of Latinos (HCHS/SOL) participants' selection.

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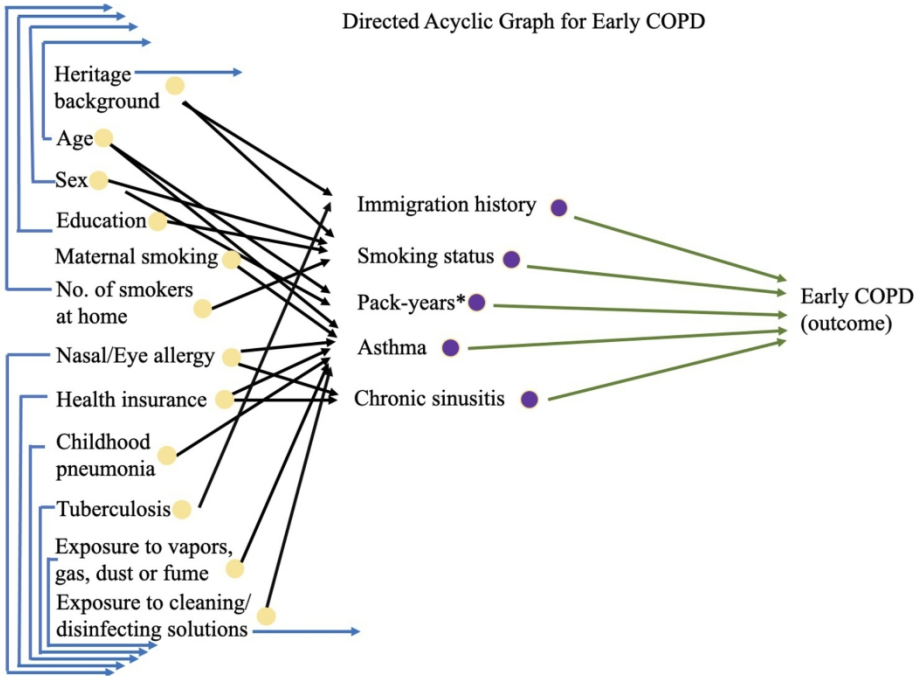

The directed acyclic graph (DAG) was the basis to inform the survey logistic regression models used in this cross-sectional study to assess relationships of main exposures (purple circles) and early COPD. Yellow circles represent ancestors of main exposures and the outcome (confounders). Black arrows and blue arrows represent paths between confounders and main exposures and between confounders and Early COPD, respectively. Green arrows represent paths between main exposures and Early COPD. This DAG is intended to depict a simple framework for early COPD used in this analysis. It does not reflect the complex relationships that exist or potentially exist between all the variables shown. For visual clarity, blue arrows are shortened.
*Pack-years was used among ever-smoking participants only

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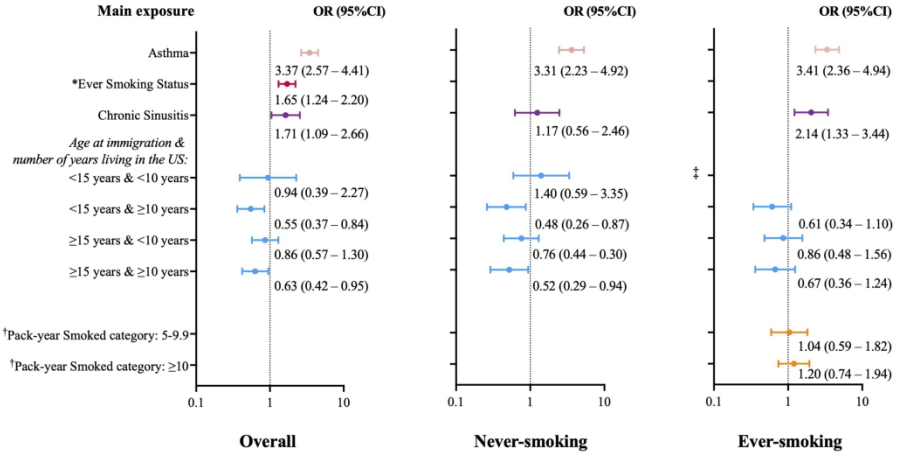

Association between main exposures and early Chronic Obstructive Pulmonary Disease (COPD) in the overall Hispanic/Latino cohort and never-smoking and ever-smoking participants. Odds Ratios (OR) and Confidence Intervals (95% CI) estimates are from a survey logistic regression multivariable model. Asthma and chronic sinusitis are binary (yes/no) variables. Referent for ever-smoking, pack-years smoked, and immigration history was never-smoking, <5 pack-years, and US-born (non-immigrant), respectively. The model was adjusted for heritage background, sex, age category, education level, maternal smoking, ≥1 smokers at home, nasal/eye allergy, health insurance, childhood pneumonia, tuberculosis, exposure to cleaning and disinfecting solutions, and exposure to vapors, gas, dust, or fume.
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‡OR for the group age at immigration <15 years and living in the US <10 years was not estimated in ever-smoking participants because there are no individuals in one of the outcome categories.

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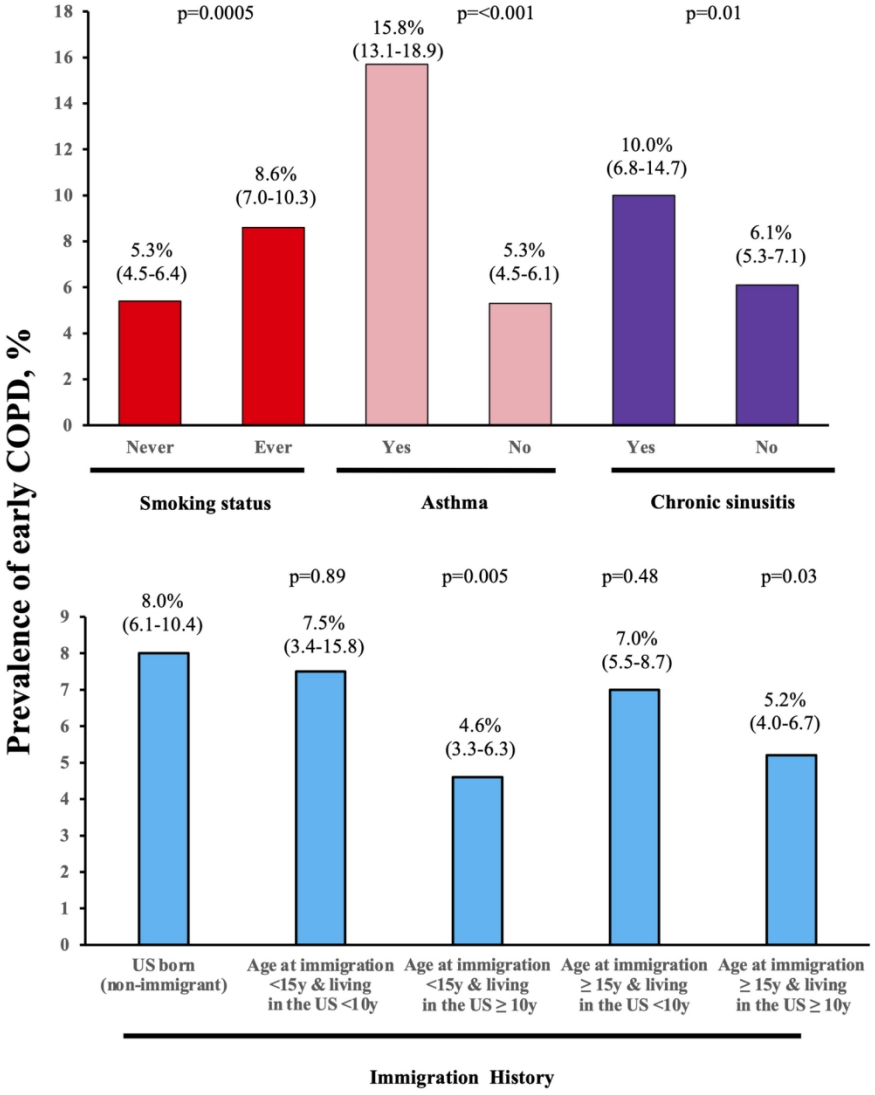

Prevalence of early Chronic Obstructive Pulmonary Disease (COPD) in US Hispanics/Latinos aged 18-49 years. The estimates (%) and confidence intervals for the prevalence of early COPD by smoking status (red, ever vs. never), asthma (peach), chronic sinusitis (purple), and immigration history (blue) are from a multivariable model described in the Statistical Analysis section.
For immigration history, P-values vs. US-born (non-immigrant) category.

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Prevalence and Population Attributable Risk for Early COPD in US Hispanics/Latinos

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Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Drs. Khalid and Diaz.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Dr. Wang.

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Supervision: Dr. Diaz

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Abstract

Background: In predominantly white populations, early COPD (i.e., COPD in people aged <50 years) has been linked to higher hospitalization rates and mortality; however, the prevalence, risk factors, and population attributable risk (PAR) of early COPD remain to be determined in non-white populations. We aimed to examine the prevalence, risk factors, and PARs of early COPD among Hispanics/Latinos, the largest US minority.

Methods: We used baseline data from the Hispanic Community Health Study/Study of Latinos, a population-based probability sample of 16,415 Hispanics/Latinos aged 18-74 years. Participants aged <50 years were included (N=7,323). Early COPD was defined as forced expiratory volume in one second to forced vital capacity ratio less than the lower limit of normal. We used survey logistic regression analysis to identify risk factors and estimate the prevalence of early COPD. PARs of the risk factors identified were estimated.

Results: 524 participants met the criteria for early COPD, yielding a sex- and age-adjusted prevalence of 7.6% [95% Confidence interval, 6.8 – 8.6]. Asthma (Odds Ratio (OR) 3.37 [2.57 – 4.41]), smoking status (ever vs. never, OR 1.65 [1.24 – 2.20]), and chronic sinusitis (OR 1.71 [1.09 – 2.66]) were associated with increased odds of early COPD. Immigrants vs. US born have lower odds of early COPD (age at immigration <15 years and living in the US <10 years, OR 0.94 [0.39 – 2.27]); age at immigration <15 years and living in the US ≥10 years, OR 0.55 [0.37 – 0.84]; age at immigration ≥15 years and living in the US <10 years, OR 0.86 [0.57 – 1.30]; and age at immigration ≥15 years and living in the US ≥10 years, OR 0.63 [0.42 – 0.95]). Among smokers, pack-years was not associated with early COPD (5-9.9 vs <5 pack-years, OR 1.04 [0.59 – 1.82]; ≥10 vs. <5 pack-years, OR 1.20 [0.74 – 1.94]) The mean PAR for asthma, smoking status, and chronic sinusitis was 26.3% [22.1 – 30.3], 22.4% [17.4 – 27.1], and 6.9% [4.3 – 9.4] respectively.

Conclusion: Among US Hispanics/Latinos, asthma is one of the most important risk factors for early COPD, followed by smoking and chronic sinusitis. Immigrants appear to have a lower risk of early COPD than US-born Hispanics/Latinos.

Introduction

Chronic obstructive pulmonary disease (COPD) affects over 29 million people and is the 4th leading cause of death in the United States (US).(1, 2) The disease develops slowly over many years and is typically diagnosed when patients are over 60 years old and have substantial airflow obstruction, making therapies less effective.(3, 4) Because of this, experts have proposed to shift the focus on younger individuals.(5-7) In a predominantly white population, early COPD (i.e., COPD in those under 50 years) has been linked to higher hospitalization rates and mortality.(8)

Identifying risk factors will inform preventive strategies and interventions targeted to treat early COPD and halt its progression. Several studies in predominantly white older populations have identified various risk factors for COPD, including smoking and asthma.(9, 10) However, early COPD studies focusing to other populations are lacking. Hispanics/Latinos are the largest and youngest minority in the US —in 2018, over 60 million or 18% of the population, median age 30 years, 48% 18-49 years.(11) Thus, identifying risk factors and estimating population attributable risk (PAR) of early COPD in this minority is of public health and clinical relevance.

Prior studies demonstrated that compared to non-US-born Hispanics/Latinos, US-born Hispanics/Latinos have higher risk of asthma and chronic bronchitis, suggesting that place of birth and immigration to a new country might be linked to disease risk.(12-14) Hispanic/Latino ethnicity encompasses several heritage backgrounds, including Mexicans, Cubans, Puerto Ricans.(15) The prevalence of known COPD risk factors, such as smoking and asthma, varies by heritages and sex. Smoking rates and pack-years are the highest among Cubans and Puerto Ricans and higher in men than women of any heritage.(16) The prevalence of asthma is the

highest in Puerto Ricans and is higher in Hispanic/Latino women than their men counterparts.(12) Additionally, a less known potential risk factor for COPD, chronic sinusitis, has not been examined in this population. Chronic sinusitis and COPD are considered chronic inflammatory processes, and paranasal sinus opacities were found to be associated with COPD,(17) suggesting a link between these two conditions. Therefore, we aimed to determine the prevalence, risk factors, and PARs for early COPD in US Hispanics/Latinos in this cross-sectional study.

Methods

We used the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), described elsewhere,(18, 19) to conduct this analysis. Details about this study are in the online supplement. Briefly, this is a population-based study in 4 US communities that enrolled self-identified Hispanic/Latino men and women aged 18-74 years from households selected in a random, multistage fashion. In this analysis, we included participants aged 18-49 years enrolled at baseline (between 2008 and 2011) who completed the respiratory questionnaire and performed valid spirometry (Figure 1).(12) Informed consent was obtained from all study participants and each site's IRB approved HCHS/SOL. The current study was approved by the Partners Human Research Committee (2017P001688/PHS).

Outcome

The outcome was early COPD, defined as age <50 years old, and prebronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio less than the lower limit of normal. Although the proposed definition of early COPD included 10 or more pack-years of cigarette smoked as criterium,(5) we included never-smoking participants because a prior study showed that they contributed 23.4% to the burden of airflow obstruction in the US population.(20)

Covariates

Standardized questionnaires were used to obtain information on age, sex, heritage background, country of birth, years living in the US, age at immigration, education level, health insurance, smoking history, maternal smoking, number of smokers at home, tuberculosis, chronic sinusitis,

childhood pneumonia, asthma, nasal/eye symptoms to allergen exposures, and occupational exposures (available at http://www.cscc.unc.edu/hchs). Details on those covariates are in the online supplement. Age was categorized into three groups (18-29, 30-39, 40-49). Country of birth, age at immigration, and the number of years living in the US were collapsed into a 5-category variable termed immigration history as follows: US-born (non-immigrant); age at immigration <15 years and living in the US <10 years; age at immigration <15 years and living in the US ≥10 years; age at immigration ≥15 years and living in the US <10 years; and age at immigration ≥15 years and living in the US ≥10 years. We used this approach based on prior studies(12, 13) and reflected the variation of Hispanics/Latinos immigration history. Heritage backgrounds included Mexican, Cuban, Republic Dominican, Puerto-Rican, Central American, South American, and Other/Mixed heritage. Education level was classified as high school or General Education Diploma (GED) and greater than high school or GED. Health insurance was dichotomized as yes/no.(12) Smoking status was categorized as never and ever. Never smoking was defined as smoking fewer than 100 cigarettes ever. Pack-years of smoking were categorized as <5, 5-9.9, and ≥10 pack-years.(16) Maternal smoking was considered present if the participant had a female caregiver who smokes in his/her home. The number of smokers at home was dichotomized as 0 vs. ≥1. A history of tuberculosis, chronic sinusitis, childhood pneumonia, asthma, and nasal/eye allergy was based on the respiratory questionnaire.(12) Occupational exposure to cleaning and disinfecting solutions and vapors, gas, dust, or fumes was extracted from the occupational questionnaire.(14) Tuberculosis, chronic sinusitis, childhood pneumonia,

asthma, nasal/eye allergy, and occupational exposures were treated as binary variables. The body mass index (BMI) was calculated using weight and height measurements performed in a standardized manner.

Spirometry

Spirometry was performed following the American Thoracic Society/European Respiratory Society guidelines using a dry rolling sealed spirometer with automated quality checks (Occupational Marketing, Houston, TX) with overreading by one investigator.(12, 21) All participants, except those with recent cardiovascular events or surgery, were asked to perform prebronchodilator spirometry. Prediction equations for the general US population were used to calculate predicted values.(22)

Statistical Analysis

To account for the sampling design, stratification, and clustering, means and prevalence rates were weighted.(18, 19) Models for early COPD were built using survey logistic regression analysis.(14) Modeling for early COPD was guided by the directed acyclical graph (DAG) approach (Figure 2).(23) First, we selected all the following 17 factors based on clinical knowledge and prior studies(9, 10, 13, 17, 19, 24): sex, age, immigration history (control, US-born), heritage background, education level, health insurance, smoking status (ever vs. never), pack-years smoked, maternal smoking, number of smokers at home, tuberculosis, chronic sinusitis, childhood pneumonia, asthma, nasal/eye allergy, occupational exposure to cleaning and disinfecting solutions and vapors, gas, dust or fume. We then considered the following variables as main exposures: smoking status, pack-years smoked (among smokers only), asthma, chronic

sinusitis, and immigration history. The rest of the variables above were considered confounders of the relationships between the main exposures and early COPD (Figure 2). We also conducted a smoking status-stratified analyses (ever- vs. never-smoking) to estimate the association between the pack-year categories and early COPD among ever-smoking participants.

The prevalence of early COPD was estimated using logistic-regression conditional marginal analysis. In this analysis, the estimated mean is the expected outcome for an individual conditional on belonging to a specific group (e.g., Hispanic background) and having covariate values equal to the weighted average covariates.(14) We report the prevalence of early COPD for all the main exposures used in the overall analysis and by sex, age categories, and heritage background. These estimates are of clinical and epidemiological interest. Finally, we calculated the population attributable risk, which is the excess prevalence of early COPD attributable to risk factors.(24) We estimated PARs using the following two equations: a) Population Attributable Fraction, PAF= Pe (RR-1)/RR, where Pe is the proportion of cases exposed to the risk factor, and RR is the relative risk; and b) PAR= PAF*Pd, where Pd is the prevalence of early COPD.(24) We report PAR estimates for the entire population and stratified by sex. A sex-stratified analysis was conducted because of sex differences in the prevalence of risk factors for COPD, such as smoking and asthma, in Hispanics/Latinos. PAR estimation was performed using the STDRATE procedure of SAS 9.4 (SAS Institute, Cary, NC). Analyses were performed by a statistician (W.W.).

Results

Participants' characteristics

Out of 16,415 HCHS/SOL participants, 7,980 were aged 18-49 years, and 657 out of those 7,980 had missing data, leaving a final sample with complete data of 7,323 (Figure 1). A comparison between participants with and without valid spirometry was reported.(12) Briefly, compared to participants with valid spirometry, those without valid spirometry were older, females, and had lower education attained, higher health insurance rate, and higher pack-years. The characteristics of the participants by early COPD status are in Table 1. Compared to those without early COPD, participants with early COPD were more often males, US-born, and of Puerto Rican heritage, and had lower education level and health insurance rate. Early COPD participants were more often ever smokers and fell in the category of ≥10 pack-years than those without early COPD. These participants had a higher prevalence of maternal smoking exposure, ≥1 smoker at home, tuberculosis, chronic sinusitis, childhood pneumonia, asthma, and nasal/eye allergy. Early COPD participants also had a higher prevalence of respiratory symptoms, and a substantial lung function impairment with a lower mean FEV_1% predicted (82.7% vs. 95.9%) and a higher proportion of participants with <80% (42.6% vs. 8.7%).

Factors Associated with early COPD

Overall, in the adjusted multivariable model, asthma (Odds Ratio [OR] [95% Confidence Interval (CI)], 3.37 [2.57 – 4.41]), ever-smoking status (OR 1.65 [1.24 – 2.20]), and chronic sinusitis (OR 1.71 [1.09 – 2.66]) were significantly associated with increased odds of early COPD. Compared with US-born Latinos/Hispanics, the odds of early COPD were lower for all four immigration history groups, with the estimates being statistically significant (i.e., CIs do not

cross 1) in two groups (Figure 3). The ORs for the four immigration groups vs. US-born were as follows: age at immigration <15 years and living in the US <10 years, OR 0.94 [0.39 – 2.27]; age at immigration <15 years and living in the US ≥10 years, OR 0.55 [0.37 – 0.84]); age at immigration ≥15 years and living in the US <10 years, OR 0.86 [0.57 – 1.30]; and age at immigration ≥15 years and living in the US ≥10 years, OR 0.63 [0.42 – 0.95]. Full model results for the overall study participants are shown in Table E1 in the online supplement.

The estimates of the association between main exposures and early COPD from the smoking status-stratified analysis are shown in Figure 3. Among never-smoking participants, asthma and immigration history but not chronic sinusitis were associated with early COPD. Among ever-smoking participants, asthma and chronic sinusitis were associated with early COPD, while pack-years smoked and immigration history were not. Additional results among participants without asthma are in Table E2.

Prevalence of early COPD

The overall age- and sex-adjusted prevalence of early COPD was 7.6% (95% Confidence interval [CI], 6.8 – 8.6). The prevalence of early COPD estimated from the final multivariable model above was significantly higher in ever-smoking participants, those with asthma, and those with chronic sinusitis than never-smoking participants, those without asthma and those without chronic sinusitis. Compared to US-born Hispanics/Latinos, the prevalence of early COPD was lower in all four immigration history groups, with a varied magnitude of the differences and precision of estimates (Figure 4). Table E3 shows the prevalence of early COPD by sex, age category, and heritage.

Population Attributable Risk

The estimates of early COPD risk attributable to three factors identified in this analysis are shown in Table 2. The most important risk factor for early COPD was asthma (PAR, 26.3 %) followed by smoking status (PAR 22.4%), and chronic sinusitis (PAR, 6.9%). The PARs differed by sex in that compared to men, women had higher PAR for asthma (35.6% vs. 19.4%) and lower for ever-smoking status (18.2% vs. 24.2%) and chronic sinusitis (5.2% vs. 8.4%).

Discussion

In this population-based study of over 7,500 US Hispanics/Latinos younger than 50 years, we found that the prevalence of early COPD was 7.6% and identified asthma, ever-smoking status, and chronic sinusitis as risk factors of early COPD. Hispanic/Latino immigrants appear to have a lower risk of early COPD. We also determined that the PAR of early COPD for asthma was the highest, followed by smoking and chronic sinusitis.

This study is one of the largest studies exploring risk factors of early COPD in Hispanics/Latinos, an understudied US population. We found that the prevalence of early COPD was 7.6%, which is lower than that of 15% reported in a recent European study,(8) a discrepancy that population differences might explain. The European study only included heavy smokers — 10 or more pack-years— and older participants (mean age, 45.9 years). However, our figure is similar to the prevalence of COPD of 8.2% in HCHS/SOL participants aged 45 years or older,(12) suggesting that younger Hispanics/Latinos seem to be similarly susceptible to the disease and supporting the notion of comprehensibly understand the disease in younger people.

We also found that asthma was the strongest risk factor associated with early COPD in this minority and that the association remained the strongest in both smoking and never-smoking participants, strengthening the relevance of this factor. This finding is in line with two recent studies in predominantly white populations showing that the prevalence of asthma was higher in early COPD defined with 10 or more pack-years of smoking.(8, 25) The relevance of asthma for early COPD in Hispanics/Latinos may be due to a couple of reasons. A decreasing trend in smoking rates from 42% to 16% in the US general population in the last five decades has been

noted, and that this ethnicity has a lower smoking rate than non-Hispanic whites.(26) The prevalence of asthma in HCHS/SOL was 15.3%,(12) almost two-fold higher than that of average 8.0 % among US adults in 2019.(27)

Although this study cannot tease out the complex interplay between asthma and early COPD, it is known that poorly controlled asthma can lead to fixed airflow obstruction, and also asthma has been proposed as a risk factor for COPD. Explanations for the latter include the following: first, a prevalence of asthma up to 26% in mild-moderate smoking COPD;(28) second, longitudinal studies have demonstrated a rapid decline in lung function in adult smokers with asthma and asthma was associated with a greater risk for developing COPD;(9, 29) and third, in smokers with childhood-onset asthma, smaller airways are associated with lower lung function and a higher risk of COPD.(30) Collectively, our and prior findings support the notion that asthma might be a risk factor for early COPD, a finding that deserves further research.

In this study, chronic sinusitis was associated with early COPD, a factor that has not been widely explored in COPD. The association we observed is in line with prior studies showing that participants with chronic rhinosinusitis have higher rates of adult-onset asthma and that sinus opacities on MRI were associated with COPD.(17, 31) Note that the cross-sectional nature of this study does not allow to establish the directionality of the relationship between chronic sinusitis and early COPD nor claim causality. We believe that one reason to support the plausibility of the observed association is inflammatory changes in the upper and lower airways. Studies have demonstrated elevated nasal interleukin 8 in stable COPD and upper airway inflammation in

those with COPD exacerbations.(32) Thus, our finding warrants further investigation in other populations.

Our study also confirmed that ever-smoking is a risk factor for early COPD in Hispanics/Latinos. This finding is in line with other early smoking COPD studies conducted in predominantly white participants where the smoking intensity was higher (16.5-31.6 pack-years), compared to what was seen in our study, suggesting differential susceptibility to tobacco smoke.(8, 25). Our finding that 5.3% of never-smokers (Figure 4) had early COPD supports the belief that future investigations of early COPD should include never-smokers and people with a range of smoking histories.(33)

We found that Hispanic/Latino immigrants had lower odds of early COPD, a finding replicated among never-smoking participants only (Figure 3). This finding aligns with prior studies demonstrating that US-born Hispanics/Latinos had a higher risk of asthma and chronic bronchitis than non-US-born counterparts.(13, 14) In contrast, a prior study did not find such differences in COPD risk among older US Hispanics/Latinos.(12) A reason for this discrepancy between the current and that prior study might rely on differences in disease susceptibility between younger and older immigrants. Explanations for the lower odds of early COPD in US-born Hispanics/Latinos, particularly among non-smokers, include differences in exposures to environmental respiratory hazards and health status. For instance, 80% of US Hispanics/Latinos reside in areas that do not meet one Environmental Protection Agency standard of clean air, and 28.3% reside near a major highway.(15, 34) It is conceivable that Hispanics/Latinos born in the US might have been exposed longer and during a more critical period of lung development than

those coming from abroad. Additionally, immigrants tend to be healthier than the home-country population, likely decreasing their risk for chronic respiratory diseases.(15) Further investigation is warranted to study the interaction between immigration, environmental exposures, and lung disease risk.

We have estimated PARs of early COPD in Hispanics/Latinos, which is a novel addition to understand the proportion of the disease in this minority exposed to identified risk factors. Those PARs indicate the burden of early COPD that would be eliminated if the exposures were eliminated. Smoking is a known modifiable cause of COPD, and eliminating tobacco exposure would benefit 22.4% of the HCHS/SOL participants under 50 years of age. Our findings may inform public health policies toward smoking cessation programs in the Hispanic/Latino population. The Burden of Obstructive Lung Disease study, an international effort for studying COPD, also showed PARs for other factors, such as poor education, were more relevant than smoking in certain countries.(24) In this study, we found that asthma was the most important factor followed by smoking and chronic sinusitis. We also observed sex differences in PARs. Since the prevalence of early COPD did not differ significantly between sexes, some PARs differences might be due to sex disparities in the prevalence of the risk factors (for asthma, women 18.0% [16.3 – 19.7] vs. men 15.0% [13.4 – 16.7]; for ever-smoking status, women 26.4% [24.3 – 28.7] vs. men 44.5% [42.1 – 47.0]). We believe that assessing PARs across populations and countries may be an important tool to understand the public health impact of early COPD and inform policies to reduce its burden.

This study has several strengths and limitations. We analyzed a large, representative population-based cohort of Hispanics/Latinos, including several of its heritage backgrounds. HCHS/SOL used standardized procedures to collect data, including the respiratory questionnaire and spirometric testing. However, some limitations should be noted. First, we used participants that may not have reached their lung function peak (e.g., those aged 18-30 years) and those who did. However, we found that the prevalence of COPD did not differ by age categories. Second, we used pre-bronchodilator spirometric data. Compared with post-bronchodilator spirometric values, pre-bronchodilator values may overestimate the prevalence of COPD, but it does not appear to be discrepancy in diagnostic discrimination for COPD between them.(35) Further, two recent early COPD studies have used prebronchodilator data, which is an acceptable approach for epidemiological studies.(8, 36) Third, participants with restrictive lung physiology were not excluded, which may bias the odds ratio estimates toward the null. Fourth, although an array of risk factors was used in the models, they were collected by questionnaires, which have inherent biases, such as recall bias. Also, other factors, including air pollution and childhood crowding, were not available. Despite this limitation, we identified plausible risk factors, all of which have already been linked to COPD.(9, 10, 17) Fifth, the cross-sectional nature of this observational study does not allow to make inferences about causality. Sixth, we deliberately included never-smoking participants, a diversion of the proposed definition of early COPD.(5) By doing so, we could determine the prevalence of early COPD in never-smoking participants, supporting the arguments to include that population in the proposed definition.(33) Seven, we also caution that PARs estimates are based on the assumption of causality. While for smoking, an assumption of causality is supported,(10) for asthma and chronic sinusitis is an ongoing debate. Eighth,

HCHS/SOL has no chest imaging data available, so we could not account for structural changes of the lung, which can occur even before the spirometric criterion for early COPD is met.

In summary, we have demonstrated that the prevalence of early COPD in Hispanics/Latinos is 7.6 % and is higher in ever-smoking participants and those with asthma and chronic sinusitis. The population risk attributable to asthma was the highest, followed by smoking and chronic sinusitis. Latino/Hispanic immigrants appear to have a lower risk of early COPD than their US-born counterparts.

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Figure legends

Figure 1 Flow chart of Hispanic Community Health Study/Study of Latinos (HCHS/SOL) participants' selection.

Figure 2 The directed acyclic graph (DAG) was the basis to inform the survey logistic regression models used in this cross-sectional study to assess relationships of main exposures (purple circles) and early COPD. Yellow circles represent ancestors of main exposures and the outcome (confounders). Black arrows and blue arrows represent paths between confounders and main exposures and between confounders and Early COPD, respectively. Green arrows represent paths between main exposures and Early COPD. This DAG is intended to depict a simple framework for early COPD used in this analysis. It does not reflect the complex relationships that exist or potentially exist between all the variables shown. For visual clarity, blue arrows are shortened.
*Pack-years was used among ever-smoking participants only

Figure 3 Association between main exposures and early Chronic Obstructive Pulmonary Disease (COPD) in the overall Hispanic/Latino cohort and never-smoking and ever-smoking participants. Odds Ratios (OR) and Confidence Intervals (95% CI) estimates are from a survey logistic regression multivariable model. Asthma and chronic sinusitis are binary (yes/no) variables. Referent for ever-smoking, pack-years smoked, and immigration history was never-smoking, <5 pack-years, and US-born (non-immigrant), respectively. The model was adjusted for heritage background, sex, age category, education level, maternal smoking, ≥1 smokers at home, nasal/eye allergy, health insurance, childhood pneumonia, tuberculosis, exposure to cleaning and disinfecting solutions, and exposure to vapors, gas, dust, or fume.
The estimates are weighted to account for HCHS/SOL sampling design, stratification, and clustering.
Supplementary Table E1 shows estimates for all the variables.
*Smoking status was used in the overall participants' analysis only.
†Pack-years were used in the ever-smoking participants' analysis only.
‡OR for the group age at immigration <15 years and living in the US <10 years was not estimated in ever-smoking participants because there are no individuals in one of the outcome categories.

Figure 4 Prevalence of early Chronic Obstructive Pulmonary Disease (COPD) in US Hispanics/Latinos aged 18-49 years. The estimates (%) and confidence intervals for the prevalence of early COPD by smoking status (red, ever vs. never), asthma (peach), chronic sinusitis (purple), and immigration history (blue) are from a multivariable model described in the Statistical Analysis section.
For immigration history, P-values vs. US-born (non-immigrant) category.

Table 1 Characteristics of US Hispanic/Latino participants aged 18-49 years by early COPD status and overall

Variable	Non-COPD (n=6799)	Early COPD (n=524)	Overall (n=7323)
Age, years median [IQR]	32.7 [24.5 - 41.0]	31.9 [23.1- 41.6]	32.7 [24.4 - 41.0]
Age category, % (SE)			
18-29	38.3 (1.0)	40.6 (3.3)	38.4 (1.0)
30-39	30.3 (0.9)	25.7 (3.0)	29.9 (0.9)
40-49	31.5 (0.9)	33.7 (2.9)	31.6 (0.8)
Male Sex, % (SE)	49.4 (0.8)	55.6 (3.0)	49.9 (0.8)
BMI, median [IQR]	28.3 [24.8 - 32.6]	27.6 [24.6 - 32.7]	28.3 [24.8 - 32.6]
Heritage background, % (SE)			
Dominican	10.0 (0.9)	9.4 (1.9)	9.9 (0.8)
Central American	8.1 (0.7)	4.9 (1.0)	7.9 (0.7)
Cuban	18.2 (1.6)	17.9 (3.1)	18.2 (1.6)
Mexican	39.9 (1.7)	37.6 (3.4)	39.7 (1.7)
Puerto Rican	13.6 (0.8)	21.5 (2.9)	14.2 (0.8)
South American	4.9 (0.4)	3.9 (0.9)	4.9 (0.4)
Mixed/Other	5.3 (0.5)	4.7 (1.1)	5.2 (0.4)
Immigration history, % (SE)			
US born (no immigrant)	29.1 (1.1)	40.1 (3.5)	29.9 (1.1)
Age at immigration <15 years and living in the US <10 years	1.9 (0.2)	2.1 (0.8)	1.9 (0.2)
Age at immigration <15 years and living in the US ≥10 years	14.5 (0.6)	10.5 (1.7)	14.2 (0.6)
Age at immigration ≥15 years and living in the US <10 years	28.9 (1.1)	27.6 (3.0)	28.8 (1.1)
Age at immigration ≥15 years and living in the US ≥10 years	25.7 (0.7)	19.7 (2.3)	25.2 (0.7)
Education Level, % (SE)			
High school/GED or less	26.0 (0.9)	29.6 (2.8)	26.3 (0.9)
More than High school/GED	74.0 (0.9)	70.4 (2.8)	73.7 (0.9)
Health insurance, % (SE)	45.2 (1.1)	46.3 (3.1)	45.3 (1.1)
Smoking status, % (SE)			
Never	65.5 (0.9)	49.9 (3.2)	64.3 (0.8)
Ever	34.5 (0.9)	50.1 (3.2)	35.7 (0.8)
Pack-years smoked, median [IQR]	3.8 [1.2 - 10.1]	4.1 [1.9 - 13.0]	3.9 [1.3 - 10.4]
Pack-years smoked category*, % (SE)			
<5	58.2 (1.6)	51.9 (5.1)	57.5 (1.5)
5-9.9	15.5 (1.0)	16.8 (4.3)	15.6 (1.0)
≥10	26.3 (1.3)	31.3 (3.8)	26.9 (1.3)
Maternal smoking, % (SE)	23.2 (0.9)	30.6 (2.8)	23.8 (0.8)

≥1smokers at home, % (SE)	22.7 (0.9)	26.1 (2.5)	23.0 (0.8)
Tuberculosis, % (SE)	2.6 (0.3)	4.1 (1.2)	2.8 (0.3)
Chronic sinusitis, % (SE)	6.3 (0.4)	13.2 (2.5)	6.8 (0.4)
Childhood pneumonia, % (SE)	3.3 (0.3)	5.6 (2.0)	3.5 (0.3)
Asthma, % (SE)	14.7 (0.6)	38.5 (2.7)	16.5 (0.6)
Nasal/Eye allergy, % (SE)	38.3 (0.9)	47.0 (3.2)	38.9 (0.9)
Exposure to cleaning and disinfecting solutions, % (SE)	22.5 (0.8)	20.7 (2.3)	22.4 (0.8)
Exposure to vapors, gas, dust or fumes, % (SE)	25.2 (0.8)	25.3 (2.5)	25.2 (0.8)
Respiratory symptoms, % (SE)			
Cough	5.5 (0.4)	9.8 (2.1)	5.8 (0.4)
Phlegm	7.6 (0.5)	11.5 (2.1)	7.9 (0.5)
Shortness of breath	25.0 (0.8)	36.2 (2.9)	25.8 (0.8)
FEV_1 % predicted, median [IQR]	95.9 [88.0 - 103.6]	82.7 [73.1 - 90.5]	95.1 [86.9 - 102.9]
FEV_1 % predicted <80, % (SE)	8.7 (0.5)	42.6 (3.1)	11.3 (0.5)
FVC % predicted, median [IQR]	95.9 [87.6 - 103.4]	98.4 [87.2 - 107.5]	96.0 [87.6 - 103.8]
FEV1/FVC ratio, median [IQR]	83.6 [80.5 - 87.0]	70.4 [67.1 - 73.3]	83.1 [79.5 - 86.6]

Data are presented as median [Interquartile range, IQR] for continuous variables and percentage (standard error, SE) for categorical variables.

Estimates are weighted to account for the HCHS/SOL design, stratification, and clustering.

*Computed only among ever-smoking participants.

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Table 2 Population attributable risk (PAR*) for early COPD by risk factor and sex among US Hispanics/Latinos aged 18-49 years

	Overall	Women	Men
Risk Factor	PAR (%) [95% Confidence Interval]	PAR (%) [95% Confidence Interval]	PAR (%) [95% Confidence Interval]
Asthma	26.3 [22.1 – 30.3]	35.6 [29.0 – 41.7]	19.4 [14.1 – 24.4]
Smoking Status (ever vs. never)	22.4 [17.4 – 27.1]	18.2 [11.3 – 24.6]	24.2 [16.9 – 30.9]
Chronic Sinusitis	6.9 [4.3 – 9.4]	5.2 [1.3 – 8.9]	8.4 [4.8 – 11.8]

*PAR is the percentage of the population aged <50 years with early COPD attributable to the identified risk factor. For details about PAR estimation, see the Statistical Analysis section. The estimates are weighted to account for HCHS/SOL sampling design, stratification, and clustering.

Supplement to

Prevalence and Population Attributable Risk for Early COPD in US Hispanics/Latinos

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Methods

Population

We used the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), described elsewhere,[1,2] to conduct this analysis. Briefly, this is a population-based study in 4 United States (US) communities (Bronx, NY; San Diego, CA; Miami, FL; and Chicago, IL). The goal of this study was to determine protective and risk factors associated with major diseases. Self-identified Hispanic/Latino men and women aged 18-74 years were recruited from households selected in a random, multistage fashion. In this analysis, we included participants 18-49 years enrolled at baseline (between 2008 and 2011) who completed the respiratory questionnaire and performed a valid spirometry. The participation rate for the respiratory questionnaire and pulmonary function testing was 98.2 and 95%, respectively.[3] The HCHS/SOL questionnaires were in English and Spanish, and participants chose which language to use.

Covariates

Standardized questionnaires were used to obtain information on age, sex, heritage background, country of birth, years living in the US, age at immigration, education level, health insurance, smoking history, maternal smoking, number of smokers at home, tuberculosis, chronic sinusitis, childhood pneumonia, asthma, nasal/eye symptoms to allergen exposures, and occupational exposures (available at http://www.cscc.unc.edu/hchs).

Age was categorized in three groups (18-29, 30-39, 40-49). The country of birth was coded as mainland US-born and non-mainland US-born. The age at immigration into the mainland US was defined as current age minus the number of years living in the US. We collapsed the variables

country of birth, age at immigration, and the number of years living in the US into a 5-category variable termed immigration history as follows: US-born (non-immigrant); age at immigration <15 years and living in the US <10 years; age at immigration <15 years and living in the US ≥10 years; age at immigration ≥15 years and living in the US <10 years; and age at immigration ≥15 years and living in the US ≥10 years. We used this approach based on prior studies[3,4] and reflected Hispanics/Latinos immigration history. Heritage was asked with the following question: "Which best describes your Hispanic/Latino heritage?" The responses were then coded in seven groups: Mexican, Cuban, Republic Dominican, Puerto-Rican, Central American, South American, and Other/Mixed heritage. Education level was classified as high school or General Education Diploma (GED) and greater than high school or GED. We identified health insurance status using the following questions: What type of health insurance coverage do you currently have? Do you have health insurance or other health care coverage? The variable was dichotomized as yes/no.[3] Never-smoking status was defined as smoking fewer than 100 cigarettes ever. If participants did not smoke a cigarette in the previous 30 days, they were considered former smokers. If participants self-reported smoking of a cigarette in the last 30 days, they were deemed current smokers. In this analysis, smoking status was categorized as never-smoking and ever-smoking (i.e., former smokers + current smokers). Pack-years of smoking were calculated as the number of exposure years multiplied by the average number of cigarettes smoked per day divided by 20. This variable was categorized as <5, 5-9.9, and ≥10 pack-years. Reproducibility of smoking variables was validated through repeated study visits, with a kappa value of 0.93 for smoking status and an intra-class correlation coefficient of 0.83 for lifetime average cigarettes per day.[5] Maternal smoking was

considered present if the participant answered yes to "Did your mother (or the primary female caregiver who lived in your home) smoke in your home?" The number of smokers at home was determined using the following: "Not counting yourself, how many people currently living in your household smoke regularly in the home?" The answers were dichotomized as 0 vs. ≥1. We counted a history of tuberculosis if the participant answered yes to the following two questions: "Were you ever told that you had active tuberculosis or TB?" and "Were you ever prescribed any medicine to treat active tuberculosis or TB?" Chronic sinusitis was considered present if the participant responded yes to "Do you have chronic sinusitis?" We counted a history of pneumonia if the participant responded yes to "Has a doctor ever told you that you had pneumonia or bronchopneumonia?" We deemed childhood pneumonia if the age of first pneumonia or bronchopneumonia was at <18 years. Asthma was present if the participants reported that they ever had asthma that was diagnosed by a doctor or health provider.[3] Nasal/eye allergy was considered present if the participant responded yes to least one of the following symptoms brought on by house dust, animals, or pollen in the past 12 months: stuffy, itchy or runny nose; and watery or itchy eyes. We counted occupational exposure to cleaning and disinfecting solutions if the participant answered yes to the option "cleaning or disinfecting solutions". That option was for "In your current job(s) are you exposed to any of the following?"[6] The exposure to vapors, gas, dust or fumes was present if the participant responded yes to "In your current job(s) are you exposed to

vapors, gas, dust or fume at work? Tuberculosis, chronic sinusitis, childhood pneumonia, asthma, nasal/eye allergy, maternal smoking, and occupational exposures were treated as binary variables. The body mass index (BMI) was calculated using weight and height measurements performed in standardized manner.

Results

Table E1 Full survey logistic model for early COPD in US Hispanics/Latinos aged 18-49 years

Factor	OR (95% Confidence Interval)	P value
Age category, years		
18-29	0.92 (0.65 - 1.31)	0.64
30-39	0.82 (0.57 - 1.16)	0.26
40-49	Ref	
Male sex	1.29 (0.99 - 1.69)	0.06
Heritage background		
Mexican	Ref	
Dominican	0.95 (0.59 - 1.53)	0.84
Central American	0.63 (0.40 - 0.98)	0.04
Cuban	0.75 (0.49 - 1.16)	0.20
Puerto Rican	0.88 (0.57 - 1.36)	0.57
South American	0.85 (0.53 - 1.38)	0.52
Mixed/Other	0.64 (0.35 - 1.14)	0.13
Immigration history		
US born (non-immigrant)	Ref	
Age at immigration <15 years and living in the US <10 years	0.94 (0.39 - 2.27)	0.89
Age at immigration <15 years and living in the US ≥10 years	0.55 (0.37 - 0.84)	0.005
Age at immigration ≥15 years and living in the US <10 years	0.86 (0.57 - 1.30)	0.48
Age at immigration ≥15 years and living in the US ≥10 years	0.63 (0.42 - 0.95)	0.03
Education Level		
High school/GED or less	Ref	
More than High school/GED	0.82 (0.63 - 1.07)	0.15
Health insurance	1.10 (0.82 - 1.49)	0.50
Smoking status		
Never	Ref	
Ever	1.65 (1.24 - 2.20)	0.0005
Maternal smoking	1.17 (0.87 - 1.56)	0.30
≥1 Smokers at home	0.99 (0.73 - 1.33)	0.94
Tuberculosis	1.72 (0.88 - 3.40)	0.11
Chronic Sinusitis	1.70 (1.09 - 2.66)	0.01
Childhood pneumonia	1.15 (0.60 - 2.21)	0.68
Asthma	3.37 (2.57 - 4.41)	<.0001
Nasal/eye allergy	1.00 (0.76 - 1.32)	0.99
Exposure to cleaning and disinfecting solutions	1.09 (0.80 - 1.49)	0.54
Exposure to vapors, gas, dust or fumes	0.91 (0.67 - 1.23)	0.58

Models for early COPD were performed using survey logistic regression analysis. Estimates are weighted to account for the HCHS/SOL design, stratification, and clustering.

GED, General education Diploma; COPD, Chronic Obstructive Pulmonary Disease

Table E2 Full survey logistic model for early COPD in US Hispanics/Latinos aged 18-49 years without asthma

Factor	OR (95% Confidence Interval)	P value
Age category		
18-29	1.10 (0.72 - 1.68)	0.66
30-39	0.90 (0.57 - 1.41)	0.63
40-49	Ref	
Male sex	1.44 (1.00 - 2.07)	0.05
Heritage background		
Mexican	Ref	
Dominican	0.97 (0.54 - 1.71)	0.90
Central American	0.69 (0.40 - 1.14)	0.15
Cuban	0.69 (0.39 - 1.22)	0.21
Puerto Rican	0.95 (0.53 - 1.67)	0.85
South American	0.77 (0.44 - 1.35)	0.36
Mixed/Other	0.59 (0.29 - 1.23)	0.16
Immigration history		
US-born (non-immigrant)	Ref	
Age at immigration <15 years and living in the US <10 years	0.58 (0.17 - 2.01)	0.39
Age at immigration <15 years and living in the US ≥ 10 years	0.44 (0.25 - 0.75)	0.003
Age at immigration ≥15 years and living in the US <10 years	0.79 (0.48 - 1.30)	0.36
Age at immigration ≥15 years and living in the US ≥10 years	0.72 (0.43 - 1.22)	0.22
Education Level		
High school/GED or less	Ref	
More than High school/GED	0.82 (0.59 - 1.13)	0.22
Health insurance	1.03 (0.71 - 1.52)	0.86
Smoking status		
Never	Ref	
Ever	1.62 (1.10 - 2.37)	0.01
Maternal smoking	0.94 (0.59 - 1.49)	0.78
≥1 Smokers at home	1.08 (0.74 - 1.59)	0.68
Tuberculosis	1.60 (0.75 - 3.41)	0.23
Chronic Sinusitis	1.91 (1.10 - 3.32)	0.02
Childhood pneumonia	0.59 (0.12 - 2.77)	0.50
Nasal/eye allergy	0.87 (0.60 - 1.26)	0.47
Exposure to cleaning and disinfecting solutions	0.90 (0.62 -1.29)	0.56
Exposure to vapors, gas, dust or fumes	1.04 (0.73 - 1.49)	0.83

Models for early COPD were performed using survey logistic regression analysis. Estimates are weighted to account for the HCHS/SOL design, stratification, and clustering.
GED, General education Diploma; COPD, Chronic Obstructive Pulmonary Disease

Table E3 Prevalence of early Chronic Obstructive Pulmonary Disease (COPD) in US Hispanics/Latinos aged 18-49 years by age category, sex, and heritage background.

Factor	Prevalence of early COPD %	95% Confidence Interval
Age category		
Age: <30	6.4	5.1- 8.0
Age: 30-39	5.7	4.3 -7.6
Age: 40-49	6.9	5.6 - 8.5
Sex		
Female	5.7	4.7 - 6.8
Male	7.2	6.0 - 8.6
Heritage background		
Dominican	6.9	4.6 -10.2
Central American	4.7	3.2 - 6.8
Cuban	5.6	3.9 - 7.9
Mexican	7.3	5.9 - 8.9
Puerto Rican	6.5	4.7 - 8.9
South American	6.3	4.2 - 9.3
Mixed/Other	4.8	2.9 - 7 .8

The prevalence was estimated from models for early COPD, using survey logistic regression analysis. Estimates are weighted to account for the HCHS/SOL design, stratification, and clustering. See details in the Statistical Analysis section of the main text.

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