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Lack of association between chronic exposure to biomass fuel smoke and markers of right ventricular pressure overload at high altitude

Maria A. Caravedo, MD¹, Matthew S. Painschab, MD¹, Victor G. Davila-Roman, MD², Aldo De Ferrari, MD¹, Robert H. Gilman, MD, DTMH³, Angel D. Vasquez-Villar, MD⁴, Suzanne L. Pollard, MSPH¹, J. Jaime Miranda, MD, PhD^{5,6}, and William Checkley, MD, PhD^{1,3,5}

CRONICAS Cohort Study Group

¹Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MD, USA

²Cardiovascular Imaging and Clinical Research Core Laboratory, Cardiovascular Division, Washington University School of Medicine, St. Louis, MO, USA

³Program in Global Disease Epidemiology and Control, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

⁴Hospital Nacional Guillermo Almenara Irigoyen, EsSalud, Lima, Peru

⁵CRONICAS Center of Excellence for Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru

⁶Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

Abstract

Background—Chronic exposure to biomass fuel smoke has been implicated in the development of pulmonary hypertension and right ventricular pressure/volume overload through activation of inflammation, increase in vascular resistance and endothelial dysfunction. We sought to compare N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and echocardiography-derived pulmonary artery systolic pressure (PASP) levels in a high-altitude population-based study in Peru with and without chronic exposure to biomass fuel smoke.

Methods—NT-pro-BNP levels were measured in 519 adults (275 with and 244 without chronic exposure to biomass fuel smoke). Participants answered sociodemographics and clinical history

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Correspondence: William Checkley, MD, PhD; Division of Pulmonary and Critical Care; School of Medicine; Johns Hopkins University; 1800 Orleans St, Suite 9121; Baltimore, MD 21205; Telephone: 443-287-8741; wcheckl1@jhmi.edu.

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questionnaires, underwent a clinical examination and blood testing for cardiopulmonary biomarkers. PASP was measured in a subgroup of 153 (31%) subjects.

Results—The study group consisted of 280 men (54%) and 239 women (46%). Average age was 56 years and average body mass index was 27 kg/m². In multivariable analysis, there was no association between chronic exposure to biomass fuel smoke and NT-pro-BNP ($p=0.31$) or PASP ($p=0.31$). In the subgroup in which both NT-pro-BNP levels and PASP were measured, there was strong evidence of an association between these two variables ($\rho=0.24$, 95% CI 0.09-0.39; $p=0.003$). We found that age, high sensitivity C-reactive protein, being male and systolic blood pressure were positively associated with NT-pro-BNP levels whereas body mass index, LDL/HDL ratio and HOMA-IR were negatively associated (all $p<0.01$).

Conclusions—In this population-based study in a high-altitude setting, neither NT-pro-BNP levels nor echocardiography-derived PASP were associated with chronic exposure to biomass fuel smoke.

Keywords

biomass fuels; pro-BNP; pulmonary pressures

Chronic exposure to biomass fuel smoke is a major public health problem in low- and middle-income countries (LMIC). It is estimated that 3 billion people worldwide depend on biomass fuels as a source of energy, placing them at risk for chronic obstructive pulmonary disease, chronic bronchitis, interstitial lung disease, lung cancer, acute respiratory tract infections and tuberculosis [1-4]. Although ambient air pollution and second hand smoke have been associated with cardiovascular disease (CVD), the long-term effects of chronic exposure to biomass fuel smoke on CVD has not been well characterized [5].

The adverse effects of ambient air pollution on CVD are thought to be mediated via the inhalation of fine and ultra-fine particulate matter [6-8]. High concentrations of particulate matter are found in households burning biomass fuels, and recent observational studies have linked these to worse CVD outcomes, including myocardial ischemia, heart failure, arrhythmias, stroke and atherosclerosis [5, 9-10]. The proposed mechanisms by which chronic exposure to biomass fuel smoke increase CVD risk includes lung-mediated and systemic inflammation via oxidative stress, endothelial damage, pro-coagulation and autonomic stimulation [5]. Baumgartner *et al.* found a positive relation between fine particulate matter and blood pressure among rural Chinese women aged >50 years [11]. A recent large-scale cross-sectional study in 14,000 Chinese adults found a significant association between in-home use of solid biomass fuels and increased odds of hypertension, stroke and diabetes [12]. Another cross-sectional study showed that Indian women who cooked with biomass fuels had a higher prevalence of hypertension, platelet hyperactivity and elevated levels of oxidized low-density lipoprotein compared with women who cooked with clean fuels [13]. A recent randomized field trial of improved cookstoves in Guatemala demonstrated that a reduction of particulate matter exposure was associated with a significant decrease in blood pressures in those who received improved cookstoves compared to those who did not [14].

N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) and echocardiography-derived measurements of pulmonary artery systolic pressure (PASP) are two well-accepted biomarkers: NT-pro-BNP is a pro-hormone produced by both left and right ventricular myocytes in response to stretch (i.e., pressure/volume overload), whereas PASP is used to non-invasively estimate prevalence and severity of pulmonary hypertension. Left ventricular systolic and diastolic dysfunction, chronic lung disease, pulmonary hypertension and the resultant right ventricular pressure/volume overload have been associated with increased levels of NT-pro-BNP [15-19]. A recent small study of 70 subjects showed an association between BNP levels and echocardiographically-determined right ventricular dysfunction in 39 women with long-term exposure to biomass fuel smoke [20]. We sought to investigate whether chronic biomass exposure is associated with right ventricular pressure/volume overload and pulmonary hypertension in a population-based cohort in Peru. We hypothesized that chronic exposure to biomass fuel smoke is associated with increased NT-pro-BNP and a higher PASP.

Methods

Study setting

The study population was comprised of adults (aged ≥ 35 years) living in Puno, Peru (population ~150,000) and surrounding rural communities at 3,825m above sea level. City-dwellers work chiefly in commerce and education and cook predominantly with clean fuels including liquid-propane gas, kerosene and electricity. Rural-dwellers live as subsistence farmers and cook indoors almost exclusively with traditional, open-fire stoves and use combinations of wood, animal dung and crop residue as fuel. All participants provided verbal informed consent after our research team read the entire informed consent document to them and any questions were answered. Informed consents were verbal because of high illiteracy rates. The study protocol was approved by the Johns Hopkins University in Baltimore, USA, and A.B. PRISMA and Universidad Peruana Cayetano Heredia in Lima, Peru. This work was supported by the Center for Global Health of Johns Hopkins University and by the National Heart, Lung, and Blood Institute, United States National Institutes of Health. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study design

In preparation for study activities for the CRONICAS cohort study [21], we conducted a door-to-door household census of 18,500 people in the study area from which a large, age-, sex- and site-stratified population-based cohort of 1066 participants with blood samples was derived. We then selected a random subset of 519 participants from the larger CRONICAS study for inclusion into this ancillary study in which we measured serum NT-pro-BNP (Figure 1). Trained field workers conducted a standardized questionnaire to assess cooking patterns, traditional cardiovascular risk factors, socioeconomic status, education, past medical history, and tobacco use, followed by a clinical assessment, including blood pressure, as described previously [21]. Certified phlebotomists collected blood for processing in a centralized testing facility for serum lipids, fasting glucose, fasting insulin, hemoglobin A1c and high sensitivity C-reactive protein (hs-CRP) and NT-pro-BNP. Plasma

NT-pro-BNP was quantified with an electrochemiluminescence immunoassay using the Elecsys pro-BNP II system (Roche, Basel, Switzerland).

We measured indoor particulate matter 2.5 μm in size ($\text{PM}_{2.5}$) and carbon monoxide (CO) concentrations in a subset of 86 households between February 2011 and December 2011. Indoor $\text{PM}_{2.5}$ concentrations (using the pDR-1000, Thermo Fisher Scientific, Waltham, MA) were recorded in intervals of 1 minute over a 24-hour period in each home. We also recorded relative humidity utilizing the HOBO U10 data-logger (Onset Corporation, Bourne, MA), and adjusted nephelometric $\text{PM}_{2.5}$ for relative humidity as previously described [22]. We also obtained a subsample of gravimetric measurements of $\text{PM}_{2.5}$ concentrations concurrently using the DataRAM pDR-1000 fitted with the PCXR4 universal sampling pump (SKC Inc., Eighty Four, PA) set to a flow rate of 4 L/min. We then applied a locally-derived correction factor to relative-humidity adjusted PM to calculate $\text{PM}_{2.5}$ -equivalent concentrations [23]. Indoor CO was measured using the EasyLog USB CO Monitor (Lascar Electronics, Erie, PA) over a 24-hour period. We also measured outdoor $\text{PM}_{2.5}$ concentrations between March 2011 and November 2011 as previously explained [23].

Echocardiography

We measured PASP in a subset of 159 participants who also had NT-pro-BNP levels measured. Two trained echocardiographers (MP and AV) performed all echocardiograms in a standardized manner. We performed a limited echocardiogram with a portable ultrasound (MicroMaxx, Sonosite, Bothell, WA). Right atrial pressure (RAP) was estimated based on imaging of the IVC as follows: if the IVC was normal in size (i.e., diameter $\leq 2.1\text{cm}$ and $>50\%$ respiratory collapse) or not visualized the RAP was assigned a value of 3mmHg; if the IVC was dilated ($>2.1\text{cm}$) and had $<50\%$ respiratory collapse, the RAP was assigned a value of 15mmHg; if the IVC met one normal criteria but not the other, the RAP was assigned a value of 8mmHg. We estimated PASP using the simplified Bernoulli equation as follows: $\text{PASP} = 4v^2 + \text{RAP}$, where v is the highest peak tricuspid regurgitation jet velocity (m/sec) from among the four standard echocardiographic views [24-27]. For participants without a visible tricuspid regurgitation jet and NT-pro-BNP $<125\text{ pg/mL}$, a normal transvalvular gradient of 16 mmHg was assigned, otherwise if pro-BNP $\geq 125\text{ pg/mL}$ these values were excluded from analysis ($n=6$). A total of 153 echocardiograms met criteria for estimation of PASP. All echocardiograms were reviewed by one investigator (MP). All studies with PASP $>35\text{ mmHg}$ were reviewed by a second experienced echocardiographer (VDR), with final PASP measurements made by consensus. For those with PASP $\leq 35\text{ mmHg}$, a 10% sample was reviewed independently by the second echocardiographer; there was 100% agreement in this group.

Definitions

Participants were stratified by their history of long-term household cooking with clean vs. biomass fuels (i.e., urban vs. rural households). We used dwelling locale as a proxy for chronic exposure biomass to fuel use. Presence of CVD was assessed from as a self-reported history or current medication use for one or more of the following: arrhythmias, angina, myocardial infarction, heart failure, hyperlipidemia or stroke. History of hypertension or

diabetes was assessed as a self-reported history or current medication use for each, respectively. Poverty was defined according to official 2010 Peruvian government guidelines, as a monthly income of less than ~100 USD *per capita* [28]. We used the standard definition for Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR), i.e., the product of fasting glucose (mmol/L) and fasting insulin ($\mu\text{U/mL}$)/22.5. Lean mass was defined as total body weight minus body fat weight in kilograms.

Biostatistical methods

The primary outcome of our study was to determine if either NT-pro-BNP or PASP were independently elevated in participants who lived in households in which biomass fuels were used daily for cooking vs. participants who lived in households in which clean fuels were used. We used t-tests to compare continuous variables between groups if normally distributed and Mann-Whitney U tests if non-normally distributed. We used chi-square or Fisher exact tests when appropriate, if categorical variables. NT-pro-BNP was log-transformed for regression analyses. We fitted a multivariable linear regression with either log NT-pro-BNP or PASP as the outcome factor of type of fuel group (biomass vs. clean fuels), age, sex, height, BMI, log hs-CRP, hemoglobin, ratio of LDL to HDL (LDL/HDL), log HOMA-IR, post-bronchodilator FEV₁/FVC%, completed high school, use of anti-hypertensive medications, and a history of hypertension, cardiovascular disease, diabetes or asthma. Statistical analyses were performed using R (www.r-project.org).

Results

Participant characteristics

We did not find differences in age ($p=0.64$), location ($p=0.23$) or socioeconomic status ($p=0.55$) between the 519 participants enrolled in this ancillary study and the remaining participants of the cohort; however, there was a greater proportion of males in this ancillary study (54% vs. 44%; $p<0.001$). Participant characteristics stratified by fuel type are shown in Table 1. All participants in the clean fuel group were from urban areas where liquid-propane gas was used as fuel in 98% of households. In contrast, participants who used biomass fuels were from rural areas where wood, dung and agricultural crop waste were used as fuel in 94% of households. In the subset of 86 households (27 urban and 59 rural) in which indoor air pollution was measured from March 2011 to December 2011, participants in rural households had greater indoor environmental exposures than in urban households. Specifically, median 24-hour indoor PM_{2.5}-equivalent and CO concentrations were 130 vs. 22 $\mu\text{g}/\text{m}^3$ ($p<0.001$) and 5.8 vs. 0.4 ppm ($p<0.001$) in biomass vs. clean fuel households, respectively. Mean 24-hour indoor PM_{2.5}-equivalent concentrations were 178 vs. 27 $\mu\text{g}/\text{m}^3$ ($p<0.001$) in biomass vs. clean fuel households. Furthermore, monthly urban outdoor 24-hour average PM_{2.5}-equivalent concentrations ranged from 18 $\mu\text{g}/\text{m}^3$ (March 2011) to 29 $\mu\text{g}/\text{m}^3$ (June 2011), with an overall median of 23 $\mu\text{g}/\text{m}^3$ during the study period. No differences were found in the prevalence of self-reported history of diabetes, asthma, hypertension and CVD between fuel types. Participants who used biomass fuels for cooking had higher NT-pro-BNP levels, higher LDL/HDL ratio and higher hs-CRP levels, but had lower HOMA-IR, lower BMI, lower SBP and a lower socioeconomic status compared to those who used clean fuels (Table 1).

Determinants of NT-pro-BNP

In Figure 2, we display relationships between multiple variables and NT-pro-BNP. In single variable analysis, age, female sex and SBP were directly associated with NT-pro-BNP, whereas BMI, % lean body mass, hemoglobin, LDL/HDL ratio, HOMA-IR and post-bronchodilator FEV₁/FVC had an negative relationship with NT-pro-BNP (Table 2). In multivariable analysis, we found that age, hs-CRP, being male and SBP remained positively associated with NT-pro-BNP levels, whereas BMI, LDL/HDL ratio and HOMA-IR remained negatively associated with NT-pro-BNP levels (Table 2).

Association of chronic exposure to biomass fuel smoke with NT-pro-BNP and PASP

In unadjusted analysis, we found that NT-pro-BNP and PASP levels were higher in the biomass vs. clean fuel group (Table 1). Higher values for either NT-pro-BNP (Table 2) or PASP ($p=0.31$) were no longer evident in participants who used biomass vs. clean fuels in multivariable regression. In subset analyses, we did not find an association between NT-pro-BNP and chronic exposure to biomass fuel smoke in either women ($p=0.76$) or men ($p=0.51$). PASP was directly associated with log NT-pro-BNP ($\rho=0.25$, 95% CI 0.09–0.39; $p=0.002$; Figure 3). Mean NT-pro-BNP levels were higher in those with PASP>35 mmHg(225 vs. 47 pg/ml; $p=0.08$).

Discussion

In this study, we sought to determine whether chronic exposure to biomass fuel smoke is associated with right ventricular pressure/volume overload and pulmonary hypertension in 519 participants living at high altitude in Puno, Peru. We used NT-pro-BNP levels and echocardiographically-derived PASP as surrogate biomarkers and found no association between either NT-pro-BNP levels or PASP and chronic exposure to biomass fuel smoke.

Prior studies have shown that natriuretic peptides are increased in conditions associated with acute and chronic pulmonary hypertension. As BNP is a neurohormone released by cardiac myocytes in response to stretch, the increase in this hormone is thought to result, among other things, from right ventricular pressure/volume overload. In patients with acute pulmonary embolism, elevated BNP levels predict adverse outcomes including need for thrombolysis and mortality [29-32]. Other studies have assessed the role of BNP in patients with chronic pulmonary hypertension [33-34]. In primary pulmonary hypertension, BNP levels are predictive of adverse outcomes and in those with chronic pulmonary thromboembolism; and, BNP has also been useful to assess efficacy of pulmonary thromboendarterectomy [33-34]. BNP and NT-pro-BNP levels have been used as predictors of morbidity and mortality in clinical trials of pulmonary hypertension [18, 35]. These studies suggest that BNP levels increase proportionally to the degree of right ventricular pressure/volume overload and could serve as a noninvasive surrogate for assessment of pulmonary hypertension.

The use of echocardiography to estimate PASP has been extensively validated as studies have shown that echocardiography-derived PASP measurements correlate closely with values obtained at right heart catheterization [24-26]. We obtained echocardiographically-

derived PASP measurements in 159 (31%) randomly selected subjects, and found a strong, significant correlation between NT-pro-BNP levels and echocardiographically-derived PASP. Furthermore, mean NT-pro-BNP levels were significantly higher in those with abnormally increased PASP (>35 mmHg) compared to those with normal PASP.

Although biomass fuel smoke exposure has been suggested as an important cause of pulmonary hypertension in subjects in LMICs, studies on the association between BNP and biomass fuel smoke exposure are limited [20, 36, 37]. A recent study of 70 subjects, Ermioglu *et al.* showed an association between BNP levels and echocardiographically-determined right ventricular dysfunction in 39 women with long-term household air pollution exposure [20]. In this study 39 Turkish women with respiratory symptoms (cough or dyspnea), chronic exposure to biomass fuel smoke, and living in a rural area were found to have echocardiography-detected abnormalities such as right ventricular enlargement, decreased right ventricular fractional shortening and increased PASP compared to 31 age-, gender- and BMI-matched controls. They also found that right ventricular size and PASP were positively associated with NT-pro-BNP levels among those with biomass fuel exposure. Furthermore they also found abnormalities in left ventricular diastolic function, which are known to increase BNP levels [19]. In contrast with these results, we did not find a relationship between either NT-pro-BNP or PASP and chronic biomass fuel smoke exposure. The apparent discrepant findings between these two studies can be explained by several major differences. First, the study by Emiroglu *et al.* included individuals with respiratory symptoms of cough and dyspnea, raising concerns that the symptoms could arise from pulmonary disease such as COPD, diastolic heart failure and others. Our subjects were community-dwelling individuals and most had minimal or no symptoms. Furthermore, there were no differences in symptoms or other clinical characteristics between those with chronic exposure to biomass fuel smoke and those without such exposure. Second, compared to our study of 519 subjects, the study by Emiroglu *et al.* was relatively small (n=70). Finally and most importantly, our study is a large population-based study; the study by Emiroglu *et al.* was comprised of patients enrolled at a clinic vs. normal volunteers, which may suffer from selection bias.

Our study is also in agreement with others which found that NT-pro-BNP levels were positively associated with both CRP and blood pressure. Banerjee *et al.* found that participants with exposure to biomass fuel smoke had higher levels of IL-6, IL-8, CRP and TNF- α [38]. A study of 54 patients by Cheung *et al.* found that NT-pro-BNP was correlated with age and systolic blood pressure [39]. We found that biomarkers of the metabolic syndrome, such as HOMA-IR, LDL/HDL ratio and body composition were inversely associated with NT-pro-BNP levels. Several studies have found HbA1C, body mass index and other measurements to be inversely associated with pro-BNP [40-43].

Our study, however, has some potential shortcomings. First, this is a cross-sectional study and thus we cannot address temporality of the association between chronic biomass fuel exposure and markers of right heart function. Second, we did not have indoor environmental exposures in all households to study dose-response relationships between NT-pro-BNP and indoor air pollution. Nonetheless, we measured indoor PM and CO in a representative subset of homes in the study population and confirmed that the biomass fuel exposed populations

had significantly higher levels of indoor environmental exposures than the households who used clean fuels. Moreover, the median indoor 24-hour PM_{2.5}-equivalent concentrations were similar in magnitude to values reported in other studies in Guatemala and China [44, 45]. Maximum concentrations of biomass fuel smoke during cooking in rural households, however, can exceed 1000 µg/m³ [23], a gross environmental exposure by any standard. Third, we do not have information on personal exposure concentrations; however, we sought to compare to subpopulations with distinct levels of exposure and our indoor measurements supported this claim. Fourth, our echocardiographic protocol did not include assessment of pulmonic valve stenosis, making the approximation for pulmonary artery systolic pressure less reliable in those with pulmonary stenosis. Fifth, a limited echocardiographic study was conducted to measure PASP in a small, albeit representative subset of the study population. We found a strong significant correlation between PASP and NT-pro-BNP levels, the two noninvasive surrogate markers used to assess pulmonary hypertension and/or right ventricular pressure/volume overload. Sixth, as BNP levels are also increased in left sided heart condition such as systolic and/or diastolic dysfunction, elevated BNP levels in the present study may not be representative solely of pulmonary hypertension and/or right ventricular pressure/volume overload. However, in 31% of the population there was a strong significant association between NT-pro-BNP levels and PASP measurements. Finally, we did not control for socioeconomic differences other than education. Due to the strong collinearity between socioeconomic status and type of cooking fuel used, separation of effect sizes between these coexistent sociological factors in this population may not be possible.

Conclusions

In this large, population-based study, neither NT-pro-BNP nor echocardiographically-derived PASP levels were associated with chronic exposure to biomass fuel smoke. There is a need for more studies to better understand the role of biomass fuel smoke exposure on cardiac structure and function, and to identify biomarkers that predict cardiovascular risk due to chronic biomass fuel smoke exposure.

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Figure 1. Flowchart of participants in ancillary study of the relationship between pro-BNP and biomass fuel exposure

Figure 2. Single-variable relationships between pro-BNP levels and multiple variables

Figure 3. Association between NT-pro-BNP and echocardiographically-derived pulmonary artery systolic pressure

The black dots represent observed data and the red solid line represents a local weighted polynomial regression fit. Red broken lines represent two standard errors.

Table 1
Population Characteristics

	Biomass fuel group (n=275)	Clean fuel group (n=244)	P
Demographics			
Age, mean (SD)	55.9 (13.2)	54.9 (11.8)	0.32
Sex, % male (n)	48.4% (133)	60.2% (147)	<0.01
Completed high school, % (n)	37.2% (102)	85.7% (209)	<0.001
Monthly salary <100 soles, % (n)	33.2% (91)	2% (5)	<0.001
Clinical Characteristics			
Body mass index in kg/m ² , mean (SD)	25.0 (3.7)	28.5 (4.2)	<0.001
Systolic blood pressure in mmHg, mean (SD)	117.0 (17.2)	113.4 (15.0)	0.01
Height in cm, mean (SD)	155.0 (8.3)	158.7 (9.4)	<0.001
Lean mass in kg, mean (SD)	44.0 (7.3)	48.7 (8.2)	<0.001
Exposure to biomass fuel smoke, % (n)	94.2% (259)	1.2% (3)	<0.001
Years of biomass fuel use, mean (SD)	30.6 (25.5)	10.3 (14.1)	<0.001
Past medical history, % (n)			
Use of anti-hypertensives	2.5% (7)	6.1% (15)	0.05
Hypertension	2.5% (7)	4.9% (12)	0.16
Diabetes	1.5% (4)	2% (5)	0.7
Asthma	0.7% (2)	3.0% (7)	0.09
Cardiovascular disease	0% (0)	2.5% (6)	0.01
Laboratory profile, mean (SD)			
NT-pro-BNP (pg/ml)	101.9 (335.3)	51.0 (77)	<0.001
LDL/HDL	2.8 (1.15)	3.5 (1)	<0.001
C-reactive protein	3.1 (11.4)	2.9 (5.2)	<0.001
Hemoglobin (g/dL)	16.9 (1.7)	17.9 (1.9)	<0.001
HOMA-IR	1.5 (1.6)	2.6 (2.6)	<0.001
Clinical studies, mean (SD)			
Post-bronchodilator FEV ₁ /FVC %	78.0 (6.8)	79.2 (5.8)	0.04
Pulmonary artery systolic pressure (mmHg)	34.2 (7.6)	31.1 (10.2)	0.04

Table 2
Multivariable regression of multiple potential determinants of pro-BNP

Factor	Single variable		Multivariable (n=470)	
	log proBNP (95% CI)	p-value	log proBNP (95% CI)	p-value
Age(per year)	0.034 (0.027,0.041)	<0.001	0.029 (0.021,0.037)	<0.001
Sex(Males are reference)	-0.38 (-0.56,-0.20)	<0.001	-0.66 (-1.00,-0.29)	<0.001
Height(cm)	-0.031 (-0.04,-0.021)	<0.001	-0.026 (-0.05,-0.0026)	0.03
Body mass index(per unit kg/m ²)	-0.053 (-0.074,-0.032)	<0.001	-0.046 (-0.083, -0.0081)	0.02
Systolic blood pressure(per unit mmHg)	0.011 (0.0058,0.017)	<0.001	0.0076 (0.0019, 0.013)	<0.01
log hs-CRP(per unit log increase in hs-CRP)	0.069 (-0.011,0.15)	0.09	0.11 (0.034,0.18)	<0.01
% Lean Mass	-0.038 (-0.049,-0.027)	<0.001	0.039 (0.004, 0.074)	0.03
LDL/HDL	-0.24 (-0.31,-0.16)	<0.001	-0.13 (-0.20,-0.05)	0.001
Hemoglobin(mg/dl)	-0.09 (-0.14,-0.042)	<0.001	-0.011 (-0.056, 0.054)	0.97
Log HOMA-IR(per unit log increase in mmol × μU/L ²)	-0.31 (-0.42,-0.20)	<0.001	-0.21 (-0.35, -0.082)	0.002
Completed high school	0.56 (0.38,0.74)	<0.001	-0.10 (-0.31,0.12)	0.37
Antihypertensive use	0.36 (-0.09,0.82)	0.12	0.75 (-0.29,1.8)	0.16
Hypertension	0.31 (-0.18,0.80)	0.21	-0.48 (-1.6,0.64)	0.40
Cardiovascular disease	-0.062 (-0.92,0.79)	0.89	0.08 (-0.66,0.83)	0.84
Diabetes	0.079 (-0.62,0.78)	0.83	-0.026 (-0.66,0.61)	0.95
Asthma	-0.29 (-0.99,0.42)	0.42	-0.41 (-1.0,0.2)	0.18
Post-bronchodilator FEV ₁ /FVC(%)	-0.024 (-0.039,-0.0095)	0.001	-0.003 (-0.017,0.011)	0.68
Biomass vs. clean fuels	0.38 (0.20,0.56)	<0.001	0.11 (-0.1,0.32)	0.31