



Effect of low protein intake on acute exacerbations in mild to moderate chronic obstructive pulmonary disease: data from the 2007–2012 KNHANES

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Background: Several researchers have reported that the amount of protein intake is associated with lung function and airflow obstruction. However, few studies have investigated the effect of low protein intake on acute exacerbations of chronic obstructive pulmonary disease. This study aimed to investigate the effect of low protein intake on exacerbations in mild to moderate chronic obstructive pulmonary disease.

Methods: We used data obtained from the Korean National Health and Nutrition Examination Survey (KNHANES) between 2007 and 2012, linked to the National Health Insurance claims data. The clinical outcomes and the rate of exacerbation were retrospectively compared between the low protein intake group and the non-low protein intake group which was stratified by quartile categories of protein intake in 2,069 patients with mild to moderate chronic obstructive pulmonary disease.

Results: The low protein intake group was significantly associated with older age, women, never smoker, low household income, and low education level, compared with the non-low protein intake group. The low protein intake group was significantly associated with increased hospitalization (18.0% *vs.* 10.5%, $P < 0.001$) and emergency department utilization (1.6 ± 1.0 *vs.* 1.1 ± 0.4 , $P = 0.033$) compared with the non-low protein intake group. In multivariate analysis, the low protein intake group was associated with hospitalization (odds ratio 1.46; 95% CI, 1.09–1.96; $P = 0.012$). The multiple linear regression analysis revealed that the amount of protein intake was associated with FVC % predicted ($\beta = 0.048$, $P < 0.001$) and FEV₁ % predicted ($\beta = 0.022$, $P = 0.015$).

Conclusions: Low protein intake was associated with an increased risk of exacerbations in mild to moderate chronic obstructive pulmonary disease. The data are available at the KNHANES website (<https://knhanes.cdc.go.kr>).

Keywords: Chronic obstructive pulmonary disease (COPD); exacerbation; nutrient; protein; pulmonary function

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitations caused by chronic inflammation and remodeling of the airways (1). Systemic disease manifestations and acute exacerbations are associated with increased mortality risk in patients with COPD. Weight loss and muscle wasting are considered signs of terminal progression of the disease process and independent predictors of survival (2,3). These changes are frequently accompanied by reduced exercise capacity and symptoms having a nutritional impact, such as anorexia and early satiety. In fact, 25% to 40% of patients with COPD are in a malnourished status, which is well known to be associated with decreased lung function and exercise intolerance as well as increased risk of acute exacerbations and hospitalization (2,4-7).

As nutritional support in stable COPD patients has been found to be effective in improving both nutritional intake and nutritional status, the role of nutritional assessment in patient management is increasing (6-9). Several animal studies have suggested that protein deficiency induces pulmonary emphysema and impaired lung growth (10,11). In addition, there are reports that the amount of protein intake is associated with forced vital capacity (FVC), vital capacity and airflow obstruction in COPD (12,13). However, few studies have investigated the effect of low protein intake on acute exacerbations of COPD.

In the present study, we investigated the effect of low protein intake on acute exacerbations in patients with mild to moderate COPD. We also investigated the relationship between low protein intake and lung function. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/jtd-20-3433>).

Methods

Study population

The clinical outcomes and the rate of exacerbation were

retrospectively compared between the low protein intake (LPI) group and the non-LPI group which was stratified by quartile categories of protein intake in patients with mild to moderate COPD. We used data obtained from the Korean National Health and Nutrition Examination Survey (KNHANES) between 2007 and 2012, linked to the National Health Insurance (NHI) claims data. The NHI system includes the medical reimbursement records for the entire Korean population. The KNHANES involves a cross-sectional, multistage probability-based sample representing the total non-institutionalized Korean civilian population. This information is available at the KNHANES website (<https://knhanes.cdc.go.kr>). The KNHANES contains de-identified data regarding demographics, underlying diseases, smoking history, spirometry results, laboratory data, and nutritional status. Trained nutritionists conducted interviews of each subject based on 24-hour dietary recall. Nutrient intakes were calculated using Korean food composition tables (14). Unfortunately, we were unable to investigate whether the source of protein was animal or vegetable.

We screened patients aged 40 years or older who underwent spirometry and the nutrition examination survey (Figure 1). Of these, the clinical outcomes of mild to moderate COPD were retrospectively analyzed by quartile categories of protein intake. Mild to moderate COPD was defined as the ratio of forced expiratory volume in one second (FEV₁) to FVC of less than 0.7 and FEV₁ \geq 50% of the predicted value. Spirometry was performed using equipment that met the American Thoracic Society performance criteria (15). After excluding two patients who consumed extreme amounts of protein which was defined as more than 300 g/day, a total of 2,069 patients were included in the present study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All KNHANES participants signed an informed consent form. In addition, it is open data which is available for everyone. All data were anonymously managed in all stages. Thus, ethical approval was not required, because the present study used data from

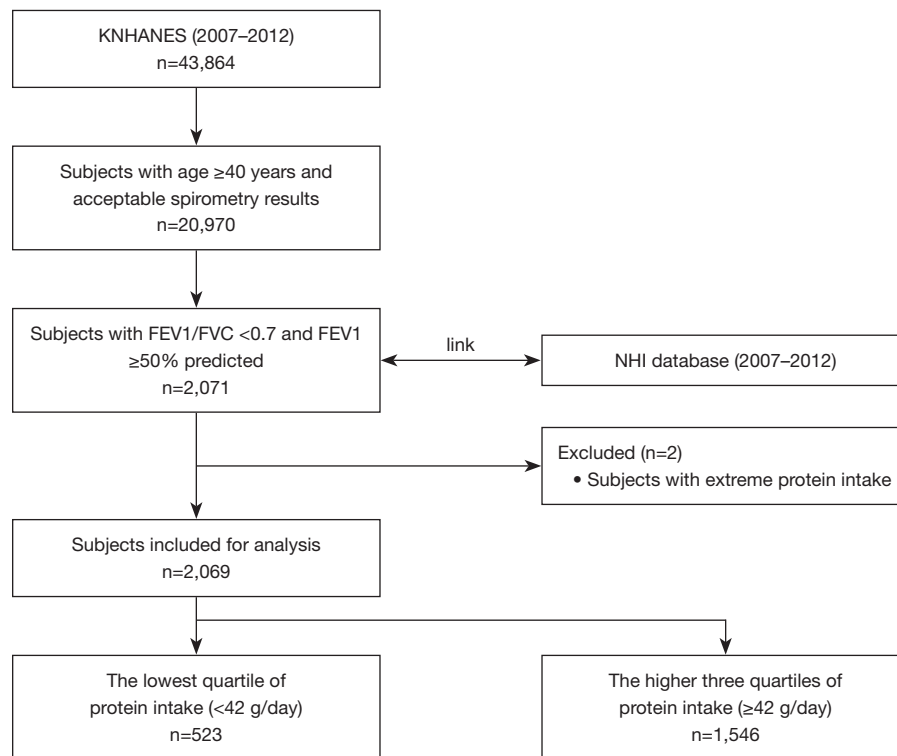


Figure 1 Flow chart of study identification, inclusion, and exclusion criteria. KNHANES, Korean National Health and Nutrition Examination Survey; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NHI, National Health Insurance.

those surveys retrospectively.

Study design and data collection

Patients with mild to moderate COPD were stratified by quartiles of dietary protein intake. The recommended daily protein intake for Korean over the age of 40 is 55–60 g/day for men and 45–50 g/day for women (16). The distribution of protein intake is demonstrated in *Figure 2*. The lowest quartile of protein intake (<42 g/day) was classified as the low protein intake (LPI) group and the higher three quartiles (≥42 g/day) were classified as the non-LPI group. We collected demographic information, spirometry results, and laboratory data from the KNHANES database. To minimize potential over-diagnosis of airway obstruction, we also used the lower limit of normal (LLN) criterion which classifies the bottom 5% of the healthy population as abnormal, based on the normal distribution (17). The LLN of the FEV₁/FVC was calculated using the following prediction equations: $125.77628 - 0.36304 \times \text{age (years)} - 0.17146 \times \text{height (cm)}$ for men and $97.36197 - 0.26015 \times \text{age (years)} - 0.01861 \times \text{height (cm)}$ for women.

Based on the NHI claims data, the patient's hospitalizations, emergency department (ED) visits, intensive care unit (ICU) admissions, and prescription records were analyzed. An acute exacerbation of COPD was determined when patients were hospitalized or visited the ED with claim codes for the International Classification of Disease 10th edition codes J42.X-J44.X and used inhaled short-acting bronchodilators and systemic corticosteroids.

Statistical analysis

All statistical analyses were performed using SAS ver. 9.2 (SAS Institute, Cary, NC, USA). Data are expressed as means ± standard deviations or numbers (%). Continuous variables were analyzed using either Student's *t*-test or Mann-Whitney tests and categorical variables were analyzed using Pearson's chi-square test. Multiple logistic regression analysis was performed by adjusting for confounding factors to assess the effect of LPI on exacerbations leading to hospitalization. The effect of protein intake on lung function was assessed using multiple linear regression analysis after adjusting for confounding factors. All tests for

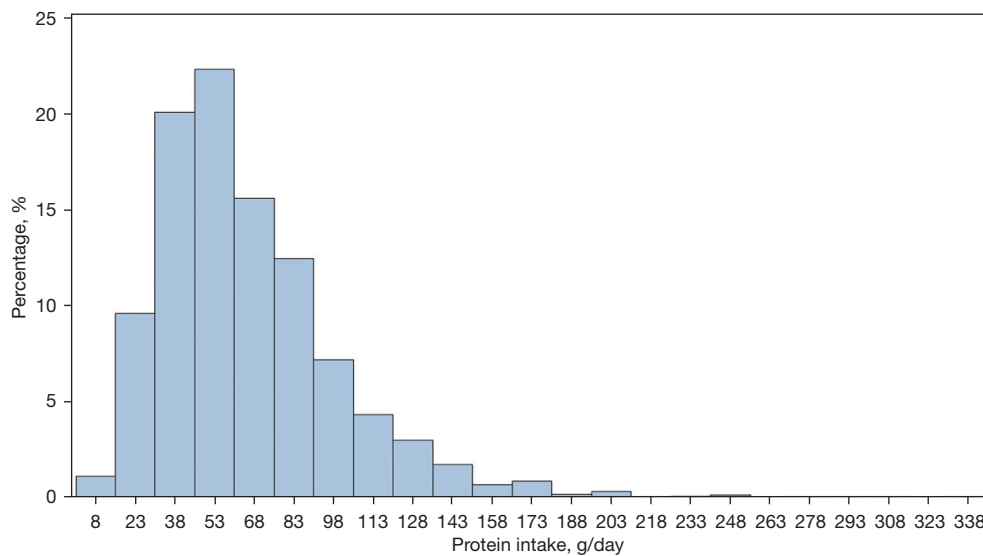


Figure 2 Distribution of protein intake in patients with mild to moderate chronic obstructive pulmonary disease.

significance were two-sided, and all variables with a $P < 0.05$ were considered to be significant.

Results

Patient characteristics

A total of 2,069 patients were included in the present study. The baseline characteristics of the patients are presented in *Table 1*. The mean age of the patients was 65.4 ± 9.8 years old; 1,468 (71.0%) were men. There were several demographic differences between the two groups: the LPI group was associated with older age, women, low body mass index (BMI), never smoker, higher rate of Medical Aid, low household income, low levels of education, and not being married. In addition, the Charlson comorbidity index was significantly higher in the LPI group compared with the non-LPI group (0.5 ± 1.4 vs. 0.2 ± 0.9 , $P < 0.001$). More patients in the LPI group had coronary artery disease and congestive heart failure.

Nutrient intake status

The LPI group was found to have not only low protein intake but also a low intake of other kinds of nutrients, such as carbohydrates, fat, and vitamins, compared with the non-LPI group (*Table 2*). Interestingly, significantly more patients in the non-LPI group reported that they had hyperlipidemia (12.2% vs. 8.6%, $P = 0.024$); however, the

total cholesterol level was actually significantly higher in the LPI group (193.7 ± 37.7 vs. 188.5 ± 36.0 mg/dL, $P = 0.006$).

Pulmonary function

Spirometry results revealed that patients in the LPI group had a lower mean FEV_1/FVC and a higher prevalence of airflow obstruction by the LLN criterion compared with those in the non-LPI group (*Table 3*). However, there were no significant differences in FVC and FEV_1 % predicted between the two groups.

Exacerbations

The LPI group was associated with increased hospitalization rates (18.0% vs. 10.5%, $P < 0.001$) and frequent ED visits (1.6 ± 1.0 vs. 1.1 ± 0.4 , $P = 0.033$, *Table 4*). In addition, they were significantly associated with frequent outpatient clinic visits (14.2 ± 22.1 vs. 8.3 ± 15.2 , $P = 0.011$) and increased medical expenses ($2,831 \pm 4,891$ US dollars vs. $1,804 \pm 3,281$ US dollars, $P = 0.015$). However, there were no differences between the groups in the prevalence of ICU admission or lengths of hospital stay. To adjust for confounding factors that may affect exacerbations of COPD, we applied various models in multiple logistic regression analyses (*Figure 3*). The LPI group was independently associated with an increased risk of hospitalization in all models. In model 4, which adjusted for FEV_1 % predicted, weight, smoking pack-years, and

Table 1 Baseline characteristics of study population

Variable	Total, n=2,069	LPI group, n=523	Non-LPI group, n=1,546	P value
Age, years	65.4±9.8	68.5±9.5	64.4±9.7	<0.001
Sex, men	1,468 (71.0)	263 (50.3)	1,205 (77.9)	<0.001
Body mass index, kg/m ²	23.6±2.8	23.3±3.1	23.7±2.7	0.011
<18.5	60 (2.9)	32 (6.1)	28 (1.8)	
≥18.5 and <25	1,419 (68.6)	360 (68.8)	1,059 (68.5)	
≥25	590 (28.5)	131 (25.0)	459 (29.7)	
Weight, kg	62.5±10.2	58.7±10.1	63.7±9.9	<0.001
Height, cm	162.6±8.8	158.6±9.0	163.9±8.3	<0.001
Smoking history				<0.001
Ex-smoker	632 (30.5)	141 (27.0)	491 (31.8)	
Current smoker	781 (37.7)	153 (29.3)	628 (40.6)	
Never-smoker	656 (31.7)	229 (43.8)	427 (27.6)	
Insurance type				<0.001
Health insurance	1,958 (94.6)	465 (88.9)	1,493 (96.6)	
Medical aid	111 (5.4)	58 (11.1)	53 (3.4)	
Urban area	821 (39.7)	192 (36.7)	629 (40.7)	0.108
Household income				<0.001
Lowest	740 (35.8)	271 (51.8)	469 (30.3)	
Low-middle	524 (25.3)	120 (22.9)	404 (26.1)	
Middle-high	394 (19.0)	71 (13.6)	323 (20.9)	
Highest	358 (17.3)	44 (8.4)	314 (20.3)	
Education duration, years				<0.001
≥6 and <9	918 (44.4)	336 (64.2)	582 (37.6)	
≥9 and <12	365 (17.6)	80 (15.3)	285 (18.4)	
≥12 and <16	498 (24.1)	81 (15.5)	417 (27.0)	
≥16	284 (13.7)	23 (4.4)	261 (16.9)	
Marital status				<0.001
Unmarried	17 (0.8)	5 (1.0)	12 (0.8)	
Married	1,696 (82.0)	356 (68.1)	1,340 (86.7)	
Divorced	62 (3.0)	22 (4.2)	40 (2.6)	
Bereavement	290 (14.0)	136 (26.0)	154 (10.0)	
Charlson comorbidity index	0.3±1.0	0.5±1.4	0.2±0.9	<0.001
Diabetes mellitus	812 (39.3)	222 (42.5)	590 (38.2)	0.083
Tuberculosis	261 (12.6)	65 (12.4)	196 (12.7)	0.882
Cerebrovascular disease	932 (45.1)	234 (44.7)	498 (45.2)	0.872

Table 1 (continued)

Table 1 (continued)

Variable	Total, n=2,069	LPI group, n=523	Non-LPI group, n=1,546	P value
Coronary artery disease	498 (24.1)	150 (28.7)	348 (22.5)	0.004
Congestive heart failure	138 (6.7)	51 (9.8)	87 (5.6)	0.001
Chronic kidney disease	35 (1.7)	9 (1.7)	26 (1.7)	0.952

Data are presented as means \pm standard deviations or numbers (%). LPI, low protein intake.

Table 2 Nutrient intake status and laboratory findings depending on the amount of protein intake in patients with mild to moderate chronic obstructive pulmonary disease

Variable	Total, n=2,069	LPI group, n=523	Non-LPI group, n=1,546	P value
Nutrient intake status				
Caloric intake, gram	1,322 \pm 750	740 \pm 354	1,518 \pm 747	<0.001
Energy, Kcal	1,913 \pm 772	1,207 \pm 351	2,152 \pm 728	<0.001
Protein, gram	65.2 \pm 34.6	30.7 \pm 7.8	76.8 \pm 32.3	<0.001
Fat, gram	30.0 \pm 27.1	10.9 \pm 7.2	36.4 \pm 28.3	<0.001
Carbohydrate, gram	325.6 \pm 116.4	237.2 \pm 76.1	355.5 \pm 112.4	<0.001
Fiber, gram	7.8 \pm 5.7	4.5 \pm 3.0	8.9 \pm 6.0	<0.001
Calcium, mg	483 \pm 359	237 \pm 161	567 \pm 369	<0.001
Phosphate, mg	1,138 \pm 500	628 \pm 179	1,311 \pm 453	<0.001
Iron, mg	14.9 \pm 11.7	7.6 \pm 6.1	17.4 \pm 12.1	<0.001
Carotene, μ g	3,857 \pm 4,523	2,089 \pm 2,762	4,456 \pm 4,836	<0.001
Retinol, μ g	76 \pm 387	15 \pm 32	97 \pm 446	<0.001
Vitamin B1, mg	1.2 \pm 0.7	0.6 \pm 0.3	1.4 \pm 0.7	<0.001
Vitamin B2, mg	1.0 \pm 0.7	0.5 \pm 0.3	1.2 \pm 0.7	<0.001
Niacin, mg	15.7 \pm 8.9	7.9 \pm 2.6	18.3 \pm 8.7	<0.001
Vitamin C, mg	98.3 \pm 84.5	55.1 \pm 49.5	112.9 \pm 88.8	<0.001
Laboratory findings				
Hemoglobin, g/dL	14.3 \pm 1.5	13.9 \pm 1.4	14.5 \pm 1.5	<0.001
AST, IU/L	24.9 \pm 12.8	24.6 \pm 13.9	25.1 \pm 12.4	0.500
ALT, IU/L	22.0 \pm 13.8	20.5 \pm 12.4	22.5 \pm 14.1	0.003
Alkaline phosphatase, IU/L	245.1 \pm 71.2	250.8 \pm 71.5	243.4 \pm 71.0	0.125
Total cholesterol, mg/dL	189.8 \pm 36.5	193.7 \pm 37.7	188.5 \pm 36.0	0.006
Triglyceride, mg/dL	150.2 \pm 120.4	153.4 \pm 117.0	149.1 \pm 121.5	0.499
HDL-cholesterol, mg/dL	48.3 \pm 12.3	48.2 \pm 12.6	48.3 \pm 12.2	0.887
LDL-cholesterol, mg/dL	112.8 \pm 34.4	119.9 \pm 34.0	111.0 \pm 34.3	0.060
BUN, mg/dL	16.3 \pm 5.1	16.0 \pm 4.9	16.4 \pm 5.2	0.133

Table 2 (continued)

Table 2 (continued)

Variable	Total, n=2,069	LPI group, n=523	Non-LPI group, n=1,546	P value
Creatinine, mg/dL	0.9±0.2	0.9±0.2	0.9±0.2	0.500
HbA1c, %	6.2±1.1	6.3±1.2	6.2±1.0	0.104
Vitamin D, ng/mL	20.1±7.0	19.7±7.5	20.2±6.9	0.237

Data are presented as means ± standard deviations. LPI, low protein intake; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen.

Table 3 Spirometry results depending on the amount of protein intake in patients with mild to moderate chronic obstructive pulmonary disease

Variable	Total, n=2,069	LPI group, n=523	Non-LPI group, n=1,546	P value
FVC % predicted	90.4±13.5	89.9±14.4	90.6±13.2	0.284
FEV ₁ % predicted	78.8±13.7	78.4±14.7	78.9±13.3	0.509
≥80%	943 (45.6)	231 (44.2)	712 (46.1)	0.454
<80% and ≥50%	1,126 (54.4)	292 (55.8)	834 (53.9)	0.454
FEV ₁ /FVC	0.64±0.06	0.63±0.06	0.64±0.06	0.015
FEV ₁ /FVC < LLN (%)	1,203 (58.1)	325 (62.1)	878 (56.8)	0.032

Data are presented as means ± standard deviations or numbers (%). LLN prediction equations: 125.77628 – 0.36304 × age (years) – 0.17146 × height (cm) for men; 97.36197 – 0.26015 × age (years) – 0.01861 × height (cm) for women. LPI, low protein intake; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

household income, the LPI group had an increased risk of hospitalization [odds ratio (OR) 1.46; 95% confidence interval (CI), 1.09–1.96; P=0.012]. Multivariate analysis revealed that low protein intake was a risk factor for frequent ED visits (OR 4.74; 95% CI, 1.36–16.56; P=0.015), but not for ICU admission (OR 1.32; 95% CI, 0.61–2.89, P=0.482, Table S1). We also evaluated patients stratified by quartiles of protein intake by sex. The cut-off value of the lowest quartile of protein intake was 46 g/day in men and 32 g/day in women. As a result, the LPI group was independently associated with an increased risk of hospitalization in both sex subgroups (Table S2). We applied the same adjusted models for multiple linear regression analysis to investigate the relationship between protein intake and lung function (Table 5). In model 4, the amount of daily protein intake was associated with FEV₁ % predicted ($\beta=0.022$, P=0.015), FVC % predicted ($\beta=0.048$, P<0.001) and FEV₁/FVC ($\beta=0.0001$, P=0.008).

Discussion

The present study demonstrated that low protein intake was associated with an increased risk of hospitalization and ED

visits due to exacerbations in patients with mild to moderate COPD. To our knowledge, this is the first study to investigate the effect of low protein intake on exacerbations of COPD using large-scale data of Korean COPD patients.

Involuntary weight loss and muscle wasting in COPD are a consequence of the increased work of breathing, persistent inflammatory processes, and poor dietary intake resulting from anorexia and early satiety. Both metabolic and mechanical inefficiency contribute to the elevated energy expenditure during physical activity, while systemic inflammation increases resting energy expenditure (18–20). A previous study reported that protein synthesis and breakdown were elevated in weight stable COPD patients (21). This is consistent with another study that demonstrated that COPD patients showed decreased total body protein and lean body mass compared with healthy controls even when there were no differences in body weight and BMI (22). This elevated protein turnover is thought to be associated with low-grade inflammation. A negative nitrogen balance causes muscle wasting, which is known to be associated with reduced respiratory muscle strength and muscle mass.

In the present study, we found that the amount of protein intake was associated with FEV₁, FVC, and FEV₁/FVC.

Table 4 Healthcare utilization and prescribed respiratory medicines depending on the amount of protein intake in patients with mild to moderate chronic obstructive pulmonary disease

Variable	Total, n=2,069	LPI group, n=523	Non-LPI group, n=1,546	P value
Hospitalization				<0.001
Never	1,813 (87.6)	429 (82.0)	1,384 (89.5)	
One or more	256 (12.4)	94 (18.0)	162 (10.5)	
Lengths of hospital stay, days	20.4±22.7	23.4±19.9	18.6±24.1	0.087
ICU admission	32 (1.5)	11 (2.1)	21 (1.4)	0.233
Number of ED visit	1.3±0.7	1.6±1.0	1.1±0.4	0.033
Never	1,999 (96.6)	498 (95.2)	1,501 (97.1)	0.041
One or more	70 (3.4)	25 (4.8)	45 (2.9)	
Outpatient clinic visit	10.2±17.9	14.2±22.1	8.3±15.2	0.011
Medical cost, USD [†]				
Total medical cost	2,131±3,892	2,831±4,891	1,804±3,281	0.015
Outpatient visit cost	321±777	494±1,167	241±487	0.028
Admission cost	3,839±4,542	4,345±5,273	3,545±4,046	0.206
Prescribed respiratory medicines				
ICS	41 (2.0)	12 (2.3)	29 (1.9)	0.553
ICS/LABA	86 (4.2)	32 (6.1)	54 (3.5)	0.009
LAMA	76 (3.7)	26 (5.0)	50 (3.2)	0.068
LTRA	66 (3.2)	22 (4.2)	43 (2.8)	0.069
Oral corticosteroids	115 (5.6)	41 (7.8)	74 (4.8)	0.008
Duration, days	51.6±104.8	74.0±123.3	39.2±9.6	0.119
Cumulative dose*	87.7±188.4	143.3±288.3	56.9±84.8	0.067
SAMA	58 (2.8)	17 (3.3)	41 (2.7)	0.474
SABA	106 (5.1)	39 (7.5)	67 (4.3)	0.005
SABA/SAMA	4 (0.2)	2 (0.4)	2 (0.1)	0.255
Systemic bronchodilators	193 (9.3)	56 (10.7)	137 (8.9)	0.210
Theophylline	238 (11.5)	80 (15.3)	158 (10.2)	0.002

Data are presented as means ± standard deviations or numbers (%). [†], 1 USD =1,000 won; *, the equivalent dose of prednisone. LPI, low protein intake; ICU, intensive care unit; ED, emergency department; USD, United States dollar; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SAMA, short-acting muscarinic antagonist; SABA, short-acting beta2-agonist.

This is consistent with previous reports that demonstrated that protein intake was associated with lung function, such as FVC, vital capacity, and airway obstruction (12,13). In the present study, patients in the LPI group consumed not only less protein but also fewer total calories, which might act as a confounding factor. However, Yazdanpanah *et al.*

reported that there was no significant correlation between energy intake and lung function (12,13). In addition, several animal experiments have shown that the lungs of protein-deficient rats appeared to be less compliant than those of normal rats, and rats fed a protein-deficient diet from the neonatal period showed abnormal lung development

(11,23,24). Although there are no reports about whether protein supplements improve lung function, it is well known that adequate nutritional supplementation, including protein, improves body weight, muscle mass, muscle length, and lung function (9,25).

A previous prospective study demonstrated that patients with a lower BMI or those who had a weight reduction during the previous year had an increased likelihood of having an exacerbation compared with patients whose weight was either unchanged or increased (26). In addition, there are reports that hypoalbuminemia and hypoproteinemia are independent risk factors of exacerbation (27,28). We could not find any data on the levels of protein, albumin, prealbumin, and retinol-binding protein, which have been considered as markers of visceral protein stores. However, multivariate analysis showed that low protein intake was an independent

risk factor of exacerbation of COPD after adjusting for factors that are well-known risk factors of exacerbation, such as FEV₁ % predicted and household income (29). Snider *et al.* demonstrated that nutritional supplementation was associated with reductions in readmission and length of hospital stay, possibly by reversing the disturbed energy balance in the acute phase of the illness (30). Therefore, a well-designed prospective study is needed to identify whether adequate protein supplementation has clinical benefits on the severity and frequency of exacerbations in COPD.

There are many differences in the baseline characteristics. Among these, older age, male sex, current smokers, less income, and comorbidities are known to be associated with increased risk of COPD exacerbation. Interestingly, the non-LPI group significantly included more men, and current smokers, as well as patients who were younger and earned more income. To adjust these confounding factors, we corrected these in the regression. On the other hands, these characteristics reflect the real world because data were obtained from the KNHANES which involves multistage probability-based sample representing the total non-institutionalized Korean civilian population. Well-verified COPD exacerbation prediction tool needs to be applied to evaluate the quantitative risk affected by various factors other than amount of protein intake.

The present study has several limitations. First, the amount of protein intake was extrapolated from 24-hour dietary recall. This might not reflect long-term dietary pattern of the consumption of protein. If there were data available on the levels of markers of visceral protein stores, it would more correctly reflect any protein deficiency. However, the validity of 24-hour dietary recall has been well established, and the use of large scale data might compensate for any errors (31). Second, other risk factors

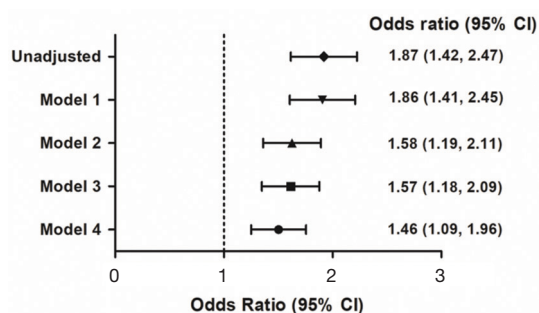


Figure 3 The odds ratio of exacerbation leading to hospitalization of the low protein intake group compared with the non-low protein intake group. Model 1: FEV₁ % predicted-adjusted. Model 2: FEV₁ % predicted and weight-adjusted. Model 3: FEV₁ % predicted, weight, and smoking pack-years-adjusted. Model 4: FEV₁ % predicted, weight, smoking pack-years, and household income-adjusted.

Table 5 Associations of protein intake and lung function in patients with mild to moderate chronic obstructive pulmonary disease

Model	FEV ₁ % predicted			FVC % predicted			FEV ₁ /FVC		
	β	Exp (β)	P value	β	Exp (β)	P value	β	Exp (β)	P value
Unadjusted	0.016	1.016	0.067	0.034	1.035	<0.001	0.00011	1.0001	0.003
1	0.021	1.022	0.017	0.048	1.049	<0.001	0.00009	1.0001	0.021
2	0.018	1.019	0.035	0.036	1.036	<0.001	0.00014	1.0001	<0.001
3	0.022	1.023	0.013	0.048	1.049	<0.001	0.0001	1.0001	0.006
4	0.022	1.022	0.015	0.048	1.048	<0.001	0.0001	1.0001	0.008

Model 1: weight; Model 2: smoking pack-years; Model 3: weight, smoking pack-years; Model 4: weight, smoking pack-years, household income.

of exacerbation, such as the exacerbation history before the study period, comorbidities, infection, and compliance with medication, were not fully considered. In addition, low protein intake might be associated with low other nutrients intake or reduction in muscle mass which are risk factors for COPD exacerbation. These factors might affect the severity and frequency of exacerbations, and the appetite and protein intake amount. Especially, patients with both congestive heart failure and COPD might have more brittle clinical course because they have increased risk of developing severe ventricular failure, pulmonary congestion mimicking many signs and symptoms of COPD exacerbation, and have more limited pulmonary reserve.

In conclusion, low protein intake was associated with an increased risk of acute exacerbations leading to hospitalizations and ED visits in mild to moderate COPD patients. These findings suggest that encouraging patients to consume adequate protein or to use protein supplements may be important in their management. Further research is needed to clarify the implications of our results on COPD treatment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All KNHANES participants signed an informed consent form. In addition, it is open data which is available for everyone. All data were anonymously managed in all stages. Thus, ethical approval was not required, because the present study used data from those surveys retrospectively.

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Supplementary

Table S1 The odds ratio of intensive care unit admission and emergency department visit of the low protein intake group compared with the non-low protein intake group in mild to moderate chronic obstructive pulmonary disease

Model	ICU admission		ED visit	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Unadjusted	1.56 (0.75, 3.26)	0.236	6.75 (2.07, 22.01)	0.002
1	1.53 (0.73,3.20)	0.258	6.10 (1.86,20.03)	0.003
2	1.23 (0.58,2.63)	0.592	5.14 (1.54,17.15)	0.008
3	1.24 (0.58,2.66)	0.575	5.20 (1.52,17.75)	0.009
4	1.32 (0.61,2.89)	0.482	4.74 (1.36,16.56)	0.015

Model 1: FEV₁ % predicted; Model 2: FEV₁ % predicted, weight; Model 3: FEV₁ % predicted, weight, smoking pack-years; Model 4: FEV₁ % predicted, weight, smoking pack-years, household income. ICU, intensive care unit; ED, emergency department, CI, confidence interval.

Table S2 The odds ratio of exacerbation leading to hospitalization of the low protein intake group compared with the non-low protein intake group in both sex

	Men		Women	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Unadjusted	1.89 (1.33-2.69)	<0.001	1.83 (1.16-2.87)	0.009
Model 1	1.86 (1.31-2.65)	<0.001	1.87 (1.19-2.95)	0.007
Model 2	1.62 (1.13-2.32)	0.009	1.85 (1.18-2.93)	0.008
Model 3	1.62 (1.13-2.33)	0.009	1.83 (1.15-2.90)	0.011
Model 4	1.53 (1.05-2.22)	0.025	1.71 (1.07-2.76)	0.027

Low protein intake was defined as the lowest quartile of protein intake among all men and women, with <46 g/day for men and <32 g/day for women, respectively. Model 1: FEV₁ % predicted; Model 2: FEV₁ % predicted, weight; Model 3: FEV₁ % predicted, weight, smoking pack-years; Model 4: FEV₁ % predicted, weight, smoking pack-years, household income. CI, confidence interval.