

The Association Between Dietary Magnesium Intake and Frailty in Patients with Chronic Obstructive Pulmonary Disease: National Health and Nutrition Examination Survey

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Background: Patients with chronic obstructive pulmonary disease (COPD) are at high risk of developing frailty and need to be prevented and managed. This study aims to investigate the relationship between dietary magnesium (Mg) intake and the risk of frailty in patients with COPD.

Methods: We conducted a cross-sectional study from the National Health and Nutrition Examination Survey (NHANES) in the United States, focusing on patients with COPD. We used logistic regression to determine the adjusted odds ratios (OR) and 95% confidence interval (CI). Curve fitting, subgroup analysis, and sensitivity analysis were performed to further assess the relationship between dietary Mg intake and frailty in patients with COPD.

Results: There were 1696 participants in this study, and the mean age was 60.4 ± 0.4 years. Weighted logistic regression and curve fitting showed a linear relationship between dietary Mg intake and frailty in patients with COPD. The risk of frailty decreased by 15% for each 100-unit increase in Mg intake (OR: 0.85, 95% CI: 0.76–0.96). Participants in the highest quartile Q4 of Mg intake had a lower risk of frailty than those in the lowest quartile Q1 (OR: 0.48, 95% CI: 0.32–0.72).

Conclusion: There is a linear relationship between dietary Mg intake and frailty in patients with COPD. Increasing dietary Mg intake is associated with a decreased risk of frailty in COPD.

Keywords: magnesium, chronic obstructive pulmonary disease, frailty, ageing

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the world.¹ Due to its high morbidity and mortality rates, COPD has become a significant factor in the social and economic burden.² COPD is considered a disease of accelerated ageing,³ characterised by increased frailty.⁴ Frailty is a complex clinical syndrome characterized by a decline in the physiological function of multiple organ systems.⁵ Frailty puts individuals at an increased risk of adverse outcomes, including falls, hospitalization, and death.⁶ There is a high prevalence of frailty among patients with COPD,⁷ and it is associated with poor clinical outcomes.⁸ A systematic review has shown that the incidence of frailty in patients with COPD ranges from 6.43% to 71.7%.⁹ Frailty increases the risk of hospital admission

and length of hospital stay in patients with COPD and reduces quality of life.^{10,11} Therefore, it is necessary to strengthen the prevention and management of frailty in patients with COPD.

The assessment of dietary and nutritional status is of great value in the management of COPD¹² and serves as an important predictor of clinical outcome.¹³ Research that included 39,852 participants has shown a significant positive correlation between magnesium depletion scores and the prevalence of COPD, with higher levels of magnesium deficiency increasing the risk of developing COPD.¹⁴ It has also been shown that dietary magnesium (Mg) intake is positively correlated with lung function in the general population, with higher dietary Mg intake associated with higher Forced Expiratory Volume in the first second (FEV1) and Force Validation Committee (FVC).¹⁵ Mg is a common cation in cells, and plays many biological roles, such as energy production, nucleic acid and protein synthesis, regulation of adenylate cyclase, and muscle contraction.^{16,17} Studies have shown magnesium sulphate can effectively treat acute exacerbations of COPD.¹⁶ Additionally a single-blind randomized controlled trial demonstrated that consumption of a whey drink fortified with Mg in participants with COPD reduced levels of inflammatory cytokines and improved skeletal muscle mass.¹⁸ A meta-analysis showed the use of Mg supplements reduced serum C-reactive protein levels.¹⁹ Mg also inhibits aging processes such as telomere structure²⁰ and free radical accumulation.²¹ However, the relationship between dietary Mg intake and the risk of frailty in patients with COPD remains unclear. Therefore, our study aims to investigate the relationship between dietary Mg intake and frailty in patients with COPD using the National Health and Nutrition Examination Survey (NHANES).

Materials and Methods

Data Source

This cross-sectional study used NHANES data from 1999–2018. The NHANES project is a study based on the entire US population conducted by the Centers for Disease Control and Prevention (CDC).²² Researchers used complex sampling weights to examine the health and nutritional status of the entire US population.²³ All participants signed informed consent. All data is de-identified and made publicly available. The NHANES survey was authorised by the National Centre for Health Statistics (NCHS) Ethics Committee, and therefore no additional informed consent was required for the secondary analysis.²⁴ The Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine exempted us from ethical review with acceptance number 2024-0026 because all data were de-labeled.

Study Population

Adult patients with COPD aged >20 years were included in this study. COPD was diagnosed by meeting any of the following criteria: (1) post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.7 (2) self-reported COPD (3) age >40 years, history of smoking or chronic bronchitis and taking one of the following drugs: leukotriene modifiers, mast cell stabilisers, selective phosphodiesterase-4 inhibitors, or inhaled corticosteroids.²⁵ Data for missing dietary Mg intake and frailty index (FI) were excluded.⁴ All covariates were missing by less than 15%, so data were removed for missing covariates.

Dietary Magnesium Intake

In the NHANES survey, trained interviewers at the Mobile Examination Center (MEC) collect information on the types and amounts of food consumed by respondents during the first 24 hours of the survey. Dietary Mg intake is based on the United States Department of Agriculture (USDA) Food and Nutrition Database for Dietary Studies (FNDDS).⁴

Frailty

Frailty is defined in this study by the FI. The FI was developed by Rockwood et al and is calculated by accumulating cumulative deficits and other geriatric signs and symptoms.²⁶ In this study, a total of 49 deficits covering cognitive function, depression, and comorbidity were selected based on the characteristics of the NHANES database and previous research.^{4,26} As a commonly used diagnosis of frailty in the NHANES database, a higher FI indicates a higher degree of frailty. The FI is calculated as the ratio of the number of deficits to the number of potential deficits. The FI is graded from

0 to 1, with 0 indicating no deficiency and 1 indicating a complete deficiency. $FI \geq 0.21$ is defined as frailty,^{4,27} and $FI < 0.21$ is defined as non-frailty.

Study Covariates

To reduce bias, we collected information including age, gender (male and female), race (white, black, Mexican, and other), education level (high school and below, college and higher), marital status (married and unmarried), family income, smoking status, alcohol use, diabetes, and hypertension. Family income was categorized into two groups based on 130% of the Federal Poverty Level (FPL), which serves as the cut-off point for participation in the Supplementary Nutrition Assistance Program.^{4,28} Hypertension was defined as meeting one of the following conditions: diagnosed by a doctor, having a systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg, and taking antihypertensive medication.^{29,30} Diabetes was defined as meeting any of the following conditions: being diagnosed by a doctor, taking diabetes medication or insulin, fasting glucose ≥ 7.0 mmol/L, two-hour oral glucose tolerance test (OGTT) blood glucose ≥ 11.1 mmol/L and glycohemoglobin $\geq 6.5\%$.³¹

Statistical Analysis

Complex sampling weights were used in the analysis. Data were divided into four groups based on quartiles of dietary Mg intake (Q1: ≤ 182 ; Q2: 182–244.925; Q3: 244.93–340.25; Q4: > 340.25). Categorical variables were described as percentages, and continuous variables were presented as mean \pm standard deviation (SD). To describe differences between groups, comparisons were made using one-way ANOVA for continuous variables and for categorical variables using chi-square tests. We used univariate logistic regression to test the relationship between covariates and frailty. The odds ratios (OR) and 95% confidence intervals (CI) between dietary Mg intake and frailty were determined using multivariate logistic regression. We constructed three models. We select covariates to include in the model for adjustment based on three factors.³² First, we adjusted for a variable if its effect value changed by more than 10% when it was added to the model. Second, we adjusted for variables with P values less than 0.05 in the univariate analyses. Third, we also selected covariates based on clinical significance and previously published literature. Model 1 adjusted for gender, race, and education level; Model 2 was further adjusted for family income and marital status based on Model 1; and Model 3 was further adjusted for alcohol use and hypertension based on Model 2. The selection of confounding factors was based on a combination of baseline character, univariate logistic regression, and clinical experience. We used fitted curves to assess the dose-response relationship between dietary Mg intake and risk of frailty after adjustment for confounders in Model 3. Restricted cubic spline (RCS) regression was performed at the 5th, 35th, 65th, and 95th percentiles of dietary Mg intake. Subgroup analyses were conducted according to different subgroups of BMI (< 25 , ≥ 25), family income ($\leq 130\%$ FPL, $> 130\%$ FPL), marital status (Married, Non-married), smoking, diabetes, and hypertension to assess heterogeneity between subgroups. Interactions between subgroups and dietary Mg intake were examined by likelihood ratio tests. Since all data had a missing value of $< 8\%$, missing data were removed. To assess the robustness of the results, we conducted the following sensitivity analyses. First, we performed multiple interpolation of missing data for covariates. Second, to prevent the year of the survey from influencing the results, we adjusted the year as a confounder in the regression model. All analyses were performed using R software (version 4.2.2) and Free Statistical software (version 1.8). $P < 0.05$ was considered significant.

Results

Study Population and Baseline Characteristics

A total of 1696 adult patients with COPD were included in the study, and the exact inclusion-exclusion process is shown in [Figure 1](#). After weighting, these participants represent a population of 7,368,884 in the United States. [Table 1](#) shows the baseline characteristics of participants by quartile of dietary Mg intake. The incidence of participant frailty was 53.1%. The mean age of the participants was 60.4 ± 0.4 years, of which 56.7% were male. Participants with higher intakes of Mg tended to be male; had higher levels of education; were married; had higher family income; drank alcohol; and had a lower incidence of hypertension.

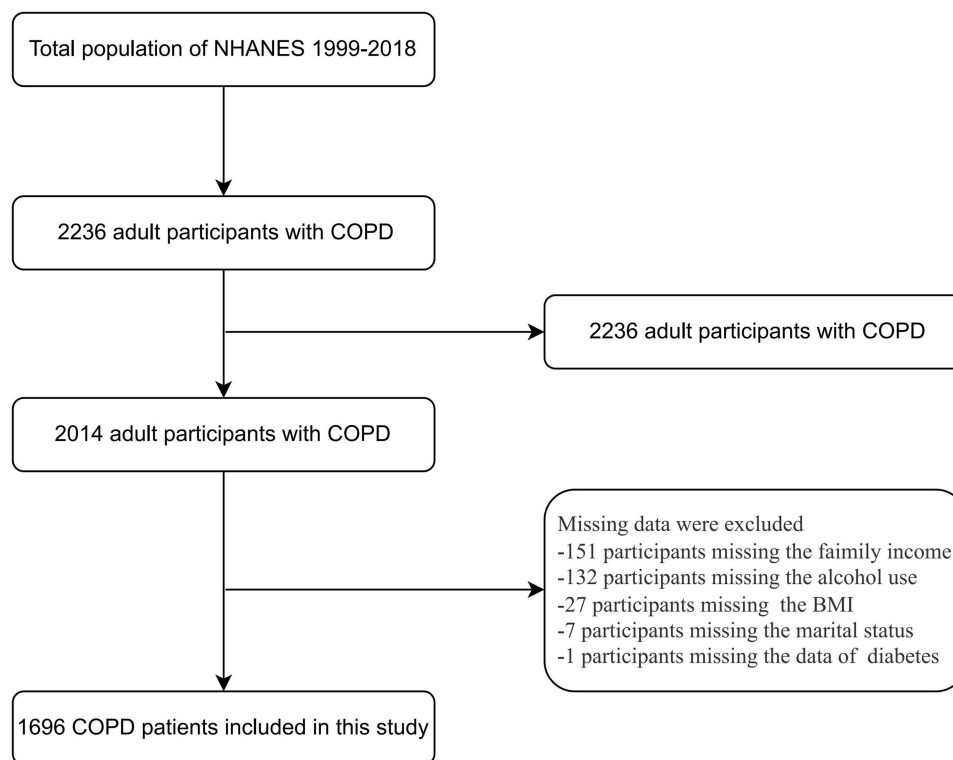


Figure 1 Flowchart of the study participant.

Association Between Mg Intake and Frailty Risk

After performing a univariate logistic regression ([Supplementary Table S1](#)), three multivariable regression models were constructed to examine the relationship between dietary Mg intake and the risk of frailty. [Table 2](#) shows the ORs and 95% CIs for different models when dietary Mg intake was used as a continuous and categorical variable. When used as a continuous variable, the risk of frailty was reduced by 15% (OR: 0.85, 95% CI: 0.76–0.96) for every 100 units change in Mg intake in model 3. Additionally, the risk of frailty was lower for participants in the highest quartile Q4 of dietary Mg intake than in the lowest quartile Q1 in Model 3 when used as a categorical variable (OR: 0.48, 95% CI: 0.32–0.72). The results of the trend test showed a linear relationship between dietary magnesium intake and frailty in all models (P for trend < 0.001). The curve fitting results in [Figure 2](#) also show a linear relationship between dietary magnesium intake and risk of frailty (P for non-linearity: 0.583). Specifically, The risk of frailty decreased with increasing dietary Mg intake.

Table 1 Weighted Baseline Characteristics by Categories of Dietary Magnesium Intake

Variable	Magnesium Intake, mg/Day					P-value
	Total (n = 1696)	Q1 ≤ 182 (n = 426)	Q2 182–244.9 (n = 422)	Q3 244.9–340.3 (n = 424)	Q4 > 340.3 (n = 424)	
Age (years)	60.4 ± 0.4	60.4 ± 0.9	61.1 ± 0.7	60.9 ± 0.9	59.2 ± 0.9	0.334
Sex (%)						<0.001
Female	734 (43.3)	234 (63.2)	217 (61.6)	163 (39.9)	120 (34.6)	
Male	962 (56.7)	192 (36.8)	205 (38.4)	261 (60.1)	304 (65.4)	
Race (%)						0.008
White	1151 (67.9)	267 (79.2)	287 (83.5)	299 (86.0)	298 (87.2)	
Black	274 (16.2)	92 (10.7)	69 (7.1)	56 (4.8)	57 (4.1)	
Mexican	89 (5.3)	19 (1.2)	22 (1.2)	20 (1.4)	28 (2.4)	

(Continued)

Table 1 (Continued).

Variable	Magnesium Intake, mg/Day					P-value
	Total (n = 1696)	Q1 ≤ 182 (n = 426)	Q2 182–244.9 (n = 422)	Q3 244.9–340.3 (n = 424)	Q4 > 340.3 (n = 424)	
Other	182 (10.7)	48 (8.9)	44 (8.2)	49 (7.8)	41 (6.2)	0.004
Education level (%)						
High school and below	972 (57.3)	289 (56.9)	247 (48.8)	235 (54.2)	201 (40.0)	<0.001
College and higher	724 (42.7)	137 (43.1)	175 (51.2)	189 (45.9)	223 (60.0)	
Marital status (%)						<0.001
Married	866 (51.1)	195 (48.1)	208 (51.8)	220 (56.1)	243 (68.4)	
Non-married	830 (48.9)	231 (51.9)	214 (48.2)	204 (43.9)	181 (31.6)	0.234
BMI (kg/m ²)	29.3 ± 0.3	29.2 ± 0.5	30.4 ± 0.6	28.9 ± 0.5	28.9 ± 0.5	
Family income (%)						< 0.001
≤ 130% FPL	624 (36.8)	194 (39.1)	162 (28.7)	146 (27.4)	122 (18.8)	
> 130% FPL	1072 (63.2)	232 (60.9)	260 (71.3)	278 (72.7)	302 (81.2)	0.957
Smoke (%)						
Yes	1434 (84.6)	357 (84.3)	360 (82.4)	347 (82.9)	370 (83.6)	<0.001
No	262 (15.5)	69 (15.8)	62 (17.7)	77 (17.1)	54 (16.5)	
Alcohol use (%)						0.210
Yes	1575 (92.9)	376 (89.5)	386 (92.5)	400 (94.3)	413 (98.7)	
No	121 (7.1)	50 (10.5)	36 (7.5)	24 (5.7)	11 (1.3)	0.023
Diabetes (%)						
Yes	477 (28.1)	132 (25.4)	130 (26.6)	113 (22.6)	102 (19.4)	0.023
No	1219 (71.9)	294 (74.6)	292 (73.4)	311 (77.4)	322 (80.6)	
Hypertension (%)						<0.001
Yes	1091 (64.3)	294 (64.2)	276 (61.6)	273 (56.0)	248 (50.3)	
No	605 (35.7)	132 (35.8)	146 (38.4)	151 (44.0)	176 (49.7)	<0.001
Frailty (%)						
Yes	901 (53.1)	279 (60.7)	237 (51.0)	219 (44.0)	166 (32.9)	<0.001
No	795 (46.9)	147 (39.3)	185 (49.0)	205 (56.0)	258 (67.2)	

Notes: Data are presented as the mean ± SD for continues variables or numbers (proportions) for categorical variables.

Abbreviations: BMI, body mass index; FPL, Federal Poverty Level.

Table 2 Weighted Odds Ratios (95% Confidence Intervals) of Frailty and Different Dietary Magnesium Intake in Different Models

Variable	Unadjusted		Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Mg per 100, mg/day	0.77 (0.67–0.87)	< 0.001	0.81 (0.72–0.92)	0.001	0.83 (0.74–0.94)	0.003	0.85 (0.76–0.96)	0.01
Mg quartiles, mg/day								
Q1 (≤182.0)	Ref		Ref		Ref		Ref	
Q2 (182.0–244.9)	0.67 (0.43–1.04)	0.08	0.71 (0.46–1.11)	0.13	0.76 (0.48–1.19)	0.22	0.76 (0.48–1.20)	0.23
Q3 (244.9–340.3)	0.51 (0.34–0.77)	0.001	0.56 (0.37–0.86)	0.01	0.60 (0.40–0.91)	0.02	0.64 (0.41–0.99)	0.04
Q4 (>340.3)	0.32 (0.22–0.46)	<0.001	0.38 (0.26–0.57)	<0.001	0.44 (0.30–0.65)	< 0.001	0.48 (0.32–0.72)	<0.001
P for trend		<0.001		<0.001		< 0.001		<0.001

Notes: Model 1: Adjust for sex, race and education level. Model 2: Adjust for the variables in model 1 plus family income and marital status. Model 3: Adjust for the variables in model 2 plus alcohol use and hypertension.

Abbreviation: Mg, magnesium.

Subgroup Analysis

We conducted subgroup analyses in several groupings and adjusted the covariates in Model 3. The results showed that the protective effect of dietary magnesium intake against frailty was attenuated in the presence of BMI<25 and hypertension ($P>0.05$). Although the 95% CIs for the BMI<25 group and the combined hypertension group were across

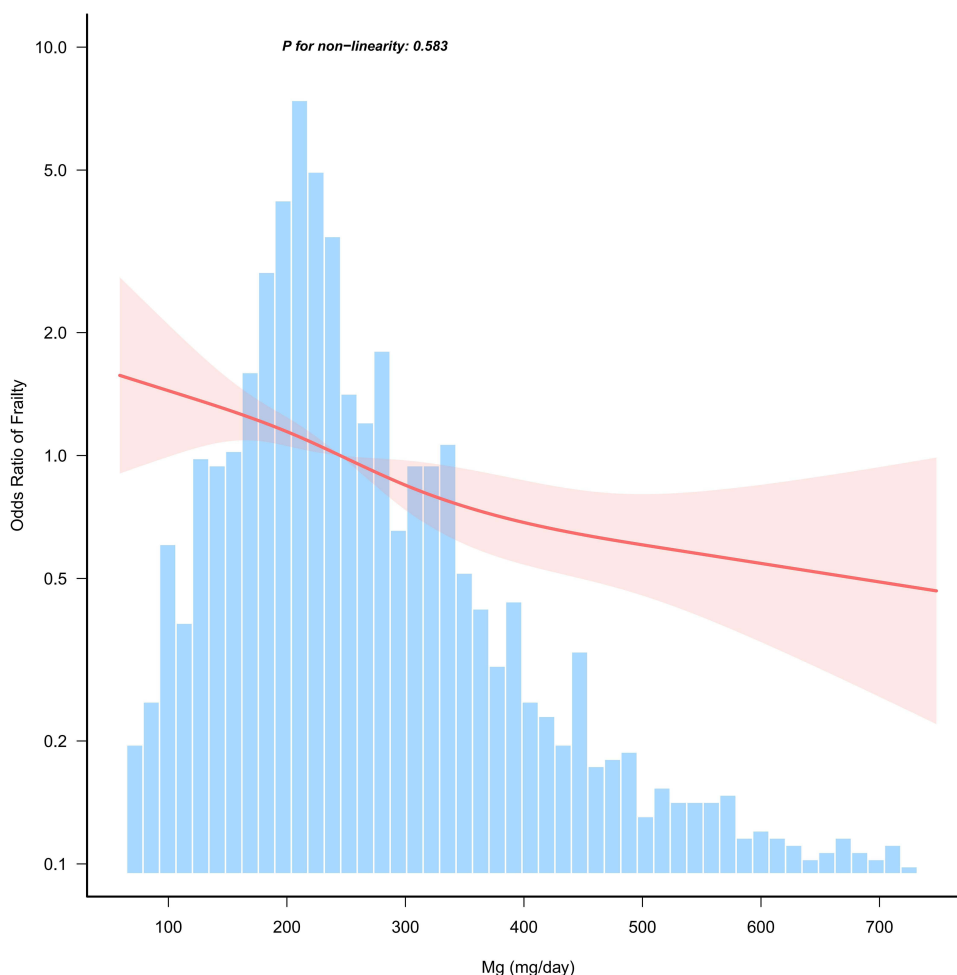


Figure 2 Curve fitting of the Mg intake and the risk of frailty in patients with COPD.

1, their ORs were <1 and both P for interaction were greater than 0.05. This suggests that there is a negative correlation between dietary magnesium intake and frailty, and that there were no significant between-group differences between the subgroups. The results of the remaining subgroup analyses for each group remained stable and no significant interactions were found (Figure 3).

Sensitivity Analyses

In Figure 1, we have removed the missing data. In order to prevent bias caused by the deletion of missing data, we retained the missing data in the sensitivity analysis and performed multiple interpolation. In Supplementary Table S2, 2014 patients with COPD were included in the study. The risk of frailty was reduced by 14% (OR: 0.86, 95% CI: 0.80–0.92) for every 100 units change in Mg intake. Participants in the highest quartile Q4 of dietary Mg intake had a lower risk of frailty than those in the lowest quartile Q1 (OR: 0.51, 95% CI: 0.39–0.68). The relationship between dietary Mg intake and risk of frailty in patients with COPD remained stable after the survey years was included as a covariate in the regression model (Supplementary Table S3). To prevent an effect of the intake of other dietary elements, we also included iron, copper, zinc and, vitamin C intake as covariates in the study. The results showed a 13% (OR: 0.87, 95% CI: 0.76–1.00) reduction in the risk of frailty for each 100-unit increase in dietary Mg intake. (Supplementary Table S4). There were 47.6% of patients with comorbid asthma, which we included in the model for further adjustment. Results showed that participants in the highest quartile of dietary Mg intake had a 51% (OR: 0.49, 95% CI: 0.35–0.67) lower risk of frailty than those in the lowest quartile (Supplementary Table S5).

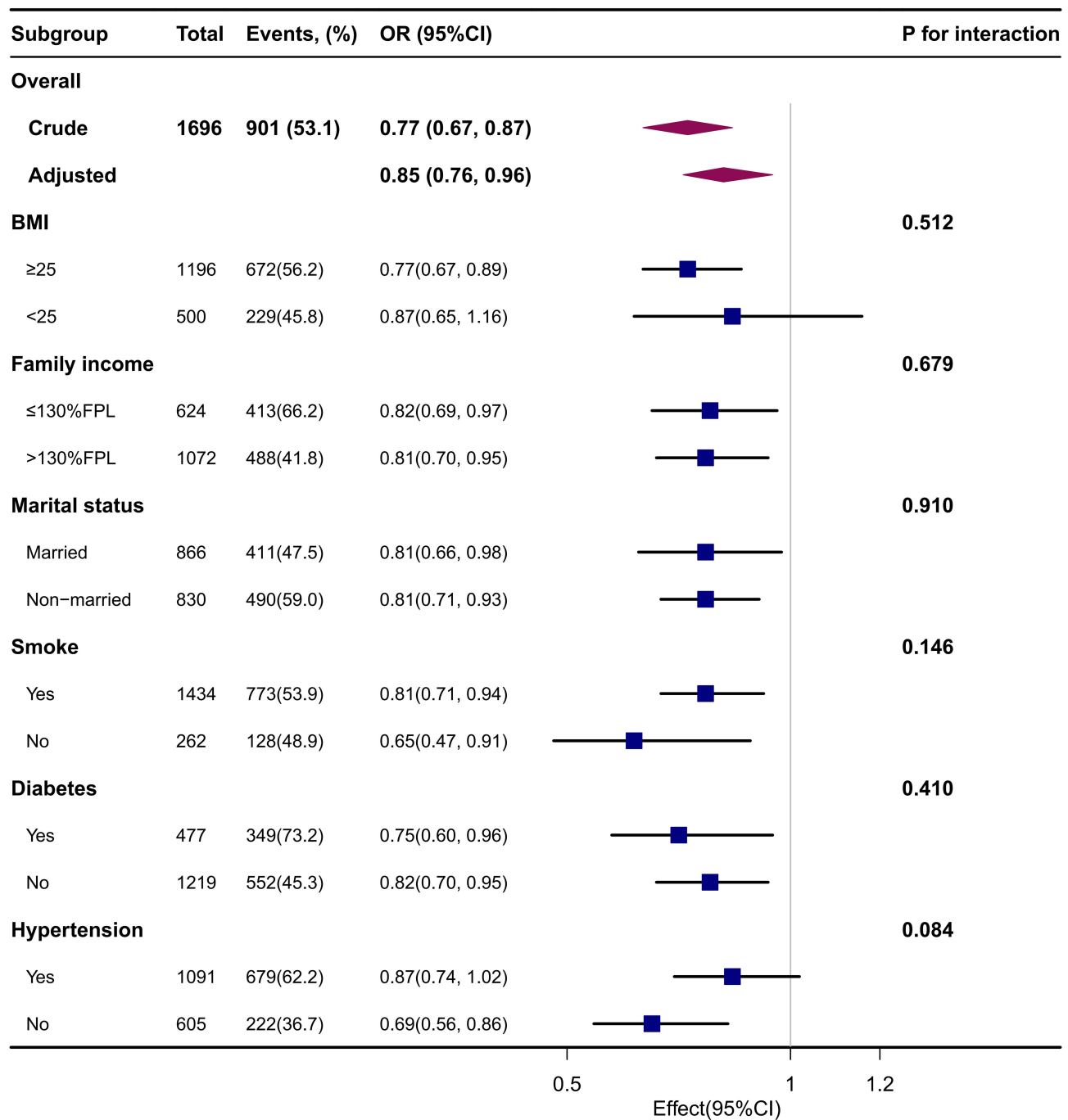


Figure 3 Subgroup analysis of the association between Mg intake and the risk of frailty in patients with COPD.

Discussion

Our study found that dietary Mg intake was associated with the risk of frailty in patients with COPD. Curve fitting analysis demonstrated a linear relationship between Mg intake and risk of frailty indicating that the risk decreases with increasing dietary Mg intake. The risk of frailty was reduced by 15% (OR: 0.85, 95% CI: 0.76–0.96) for each 100 mg increase in dietary Mg intake. Using the lowest quartile of dietary Mg intake Q1 as a reference, participants in the highest quartile Q4 had a 52% lower risk of developing frailty (OR: 0.48, 95% CI: 0.32–0.72). Subgroup and sensitivity analyses further supported the stability of this relationship.

A prospective 11-year study of a Chinese population found that a dietary pattern based on fresh fruit and protein-rich foods significantly reduced the risk of COPD.³³ A meta-analysis showed that a nitrate-rich beet juice supplement improved exercise and physical activity levels in COPD patients.³⁴ A Cross-sectional study from Iran found that a healthy dietary pattern improves lung function in COPD patients, while an unhealthy dietary pattern increases the risk of depression.³⁵ Higher vitamin E intake was negatively associated with COPD incidence.³⁶ Patients with COPD often suffer from cardiopulmonary insufficiency resulting in impeded feeding, which in turn leads to malnutrition. Scientific nutritional management can improve the functional prognosis and quality of life of COPD patients, so it is crucial to explore the dietary patterns of COPD patients. Mg serves as a cofactor for over 300 enzyme systems that regulate various biochemical reactions in the body, including protein synthesis, muscle and neurotransmission, signal transduction, blood glucose control, and blood pressure regulation.¹⁷ Extensive research has indicated that a positive association between dietary Mg intake and grip strength, skeletal muscle mass indices, as well as a protective effect on bone and skeletal muscle ageing.³⁷ A study conducted in Japan also suggested that Mg may prevent frailty in older Japanese women.³⁸ Additionally as a natural calcium antagonist, Mg can inhibit elastin degradation and vascular calcification in COPD.³⁹ In the general population dietary Mg has been associated with lung function, wheezing, and airway hyperresponsiveness.⁴⁰

Frailty is a multidimensional syndrome characterized by a progressive decline in physiological functions leading to increased vulnerability to health stress and acute illness.⁴¹ Frailty is an important clinical manifestation of population ageing.⁴² In addition, frailty increases the risk of adverse outcomes, including falls, delirium, and disability.⁴² A Meta-analysis has shown that frailty predicts all-cause mortality in patients with COPD.⁴³ Research from the European Respiratory Society has shown a higher incidence of frailty in patients with COPD compared to those without the condition, which could help identify people at risk of poor outcomes.⁴⁴ As a disease characterized by accelerated ageing,⁴⁵ COPD is all the more reason to improve the management of frailty.

Although the specific mechanisms underlying the negative association between dietary Mg intake and frailty in COPD require further investigation, our findings align with existing biological evidence. Firstly, Mg prevents calcium ions from entering blood vessels and bronchial smooth muscle cells through voltage-dependent calcium channels, so it can act as a vasodilator and prevent vascular calcification.¹⁶ Secondly, Mg has been found to reduce the burst of neutrophils in the inflammatory response, exhibiting some anti-inflammatory effects.⁴⁶ Thirdly, Mg functions as an anticholinergic and antihistamine by inhibiting the release of acetylcholine from cholinergic nerve endings and histamine from mast cells.¹⁶ Lastly, Mg is essential for synthesizing glutathione, an important intracellular antioxidant, and can act as an antioxidant.¹⁷

Our study possesses several strengths. Firstly, we are the first to investigate the relationship between dietary Mg intake and frailty in COPD. Secondly, we employed complex sampling weights to reflect the characteristics of the entire US population. Finally, we conducted subgroup and sensitivity analyses to evaluate the robustness of our results. However, certain limitations must be acknowledged. Firstly, this is a cross-sectional study, and we cannot make causal inferences between dietary Mg intake and frailty in patients with COPD. Nevertheless, we adjusted for possible confounders to ensure the accuracy of the results. Secondly, dietary Mg intake was collected by the 24-hour recall, which may introduce recall bias. Due to the limitations of the database, it was unable to be adjusted for patients with digestive disorders. Therefore, further prospective studies are needed to confirm the relationship between dietary Mg intake and frailty in patients with COPD.

Conclusion

In conclusion, there was a linear relationship between dietary Mg intake and frailty in patients with COPD. The risk of frailty decreases with increased dietary Mg intake. This finding offers a new perspective on the management of patients with COPD.

Data Sharing Statement

In this study, we used publicly available data, which can be obtained at "www.cdc.gov/nchs/nhanes/."

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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