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Exploring the association between magnesium deficiency and chronic obstructive pulmonary diseases in NHANES 2005–2018

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Chronic Obstructive Pulmonary Disease (COPD) significantly impacts patients' quality of life and burdens healthcare systems. Magnesium is crucial for lung function and reducing respiratory disease risk. This study investigates the association between Magnesium Depletion Score (MDS) and COPD and explores whether inflammatory markers mediate this relationship. A cross-sectional analysis was conducted using data from 30,490 participants in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018. MDS was calculated based on diuretic use, proton pump inhibitors, renal function, and alcohol consumption. Univariable and multivariable logistic regression analyses were performed to assess the association between MDS and COPD, adjusting for potential confounders. Mediation analysis was used to examine the roles of neutrophils, serum albumin, and the Systemic Immune-Inflammation Index (SII). In the univariable logistic model, higher MDS was significantly associated with increased COPD risk. Specifically, compared to MDS = 0, the odds ratios (OR) for COPD were 2.50, 4.12, 6.13, 8.53, and 7.81 for MDS = 1, 2, 3, 4, and 5, respectively (all $P < 0.001$). In the multivariable model, the ORs were 1.79, 2.25, 2.71, and 3.44 for MDS = 1, 2, 3, and 4, respectively (all $P < 0.001$). Higher neutrophil levels and SII were positively associated with increased COPD risk, while higher serum albumin levels were inversely associated. Mediation analysis indicated that neutrophils, serum albumin, and SII significantly mediated the MDS-COPD relationship. Higher MDS is significantly associated with increased COPD risk, mediated by systemic inflammation markers. Improving magnesium levels could potentially reduce COPD risk, warranting further research on magnesium supplementation in COPD prevention and management.

Keywords Chronic obstructive pulmonary disease (COPD)$_1$, Magnesium depletion score (MDS)$_2$, Inflammation$_3$, Public health strategies$_4$, NHANES$_5$

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent and debilitating respiratory condition characterized by persistent airflow limitation and a range of associated comorbidities, significantly impacting patients' quality of life and posing a substantial burden on healthcare systems globally[1]. The etiology of COPD is multifactorial, with smoking being the primary risk factor, although environmental pollutants, occupational exposures, and genetic predispositions also contribute to its development[2,3].

Previous research has highlighted the importance of magnesium in maintaining lung function and reducing the risk of respiratory diseases[4]. Magnesium deficiency has been shown to be associated with airway hyperreactivity and increased bronchoconstriction, which are key factors in the development of COPD[5]. To assess an individual's overall magnesium status, the Magnesium Depletion Score (MDS) has been developed. This scoring system considers four factors: the use of diuretics, proton pump inhibitors, renal function, and alcohol consumption. Higher MDS scores indicate a greater likelihood of magnesium depletion[6]. However, the relationship between MDS and COPD has not been fully elucidated.

Recent studies have highlighted the importance of systemic inflammation in the pathogenesis and progression of COPD[7]. Inflammatory markers such as neutrophils, serum albumin, and the systemic immune-inflammation index (SII) have been proposed as potential biomarkers for COPD diagnosis and prognosis[8,9]. The systemic

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immune-inflammation index, calculated as (platelet count × neutrophil count)/lymphocyte count, has been particularly noted for its predictive value in various inflammatory conditions[10].

Emerging evidence suggests that magnesium status may influence systemic inflammation[11]. Magnesium depletion has been linked to elevated levels of inflammatory markers, indicating that individuals with higher MDS scores may also exhibit greater systemic inflammation[11]. Understanding this relationship is crucial, as systemic inflammation plays a significant role in the pathogenesis of COPD and other chronic diseases. Therefore, investigating the interplay between MDS and inflammatory markers such as neutrophils, serum albumin, and SII could provide valuable insights into the underlying mechanisms linking magnesium status, systemic inflammation, and respiratory health.

This study aims to investigate the association between MDS and COPD in a representative sample of the U.S. population, utilizing data from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018. Additionally, we seek to elucidate whether neutrophils, serum albumin, and SII mediate this relationship, thereby providing insights into the underlying mechanisms linking diet, inflammation, and respiratory health.

Methods

Study populations

The data for this study were sourced from the NHANES (2005–2018). NHANES is an ongoing, biennial cross-sectional survey aimed at assessing the nutritional and health status of adults and children in the United States. Information from participants was collected through questionnaire interviews and mobile examination centers, including data on demographics, diet, physical measurements, and laboratory tests. The NHANES survey has been approved by the National Center for Health Statistics Ethics Review Board, and all participants provided written informed consent. All methods of this study were performed in accordance with the relevant guidelines and regulations. For more details about NHANES, please visit the official website at https://www.cdc.gov/nchs/nhanes/index.htm.

This study collected data from 70,190 participants over seven cycles from 2005 to 2018. Among them, 30,023 participants were excluded due to missing data, making COPD diagnosis impossible. An additional 4,457 participants were excluded because their MDS could not be calculated. Furthermore, 5,220 participants were excluded due to missing covariate data. Ultimately, 30,490 participants were included in this study. For more details on the selection process, refer to Fig. 1.

Assessment of MDS

MDS is a novel method for comprehensively assessing systemic magnesium status. The algorithm primarily includes four factors: the use of diuretics, proton pump inhibitors, kidney function assessment, and heavy alcohol consumption. Diuretic use, defined as self-reported use in the past 30 days, is assigned 1 point. Proton pump inhibitor (PPI) use, also defined as self-reported use in the past 30 days, receives 1 point. Kidney function is assessed based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, measuring serum creatinine and calculating estimated glomerular filtration rate (eGFR). Moderate decline in kidney function (eGFR between 60 and 90 mL/min/1.73 m^2) is given 1 point, while chronic kidney disease (eGFR < 60 mL/min/1.73 m^2) receives 2 points. Heavy alcohol consumption is defined as more than 2 drinks per day for men and more than 1 drink per day for women, and it is assigned 1 point[6,12]. For more details, see http://www.health.gov/DietaryGuidelines.

Diagnosis of COPD

In the NHANES database, COPD diagnosis is determined using both objective spirometry criteria and self-reported medical diagnosis. Spirometry was performed by trained technicians according to the guidelines set

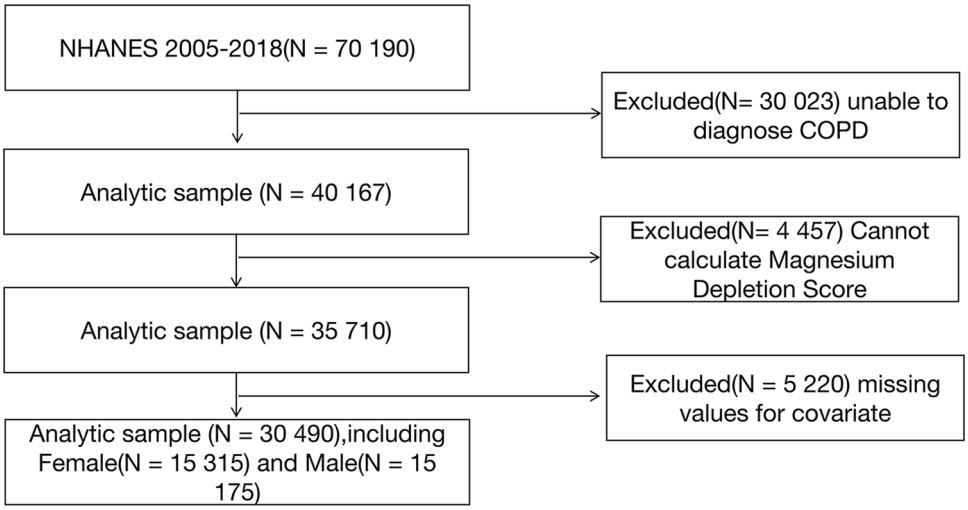

Fig. 1. The flowchart of study and excluded participants, from NHANE 2005–2018.

by the European Respiratory Society (ERS) and the American Thoracic Society (ATS). A post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of less than 0.70 was used as the criterion for airflow limitation. Additionally, participants are classified as having COPD if they report that a doctor or health professional has diagnosed them with emphysema, chronic bronchitis, or COPD based on NHANES interview questions. For our analysis, participants who met either the spirometry-based or the self-reported criteria were categorized as COPD patients[13].

Assessment of serum albumin, neutrophils and SII

In the NHANES database, trained researchers use automated hematology analyzers to measure and record the counts of neutrophils, platelets, and lymphocytes in blood samples, with the SII calculated using the formula: (platelet count × neutrophil count) / lymphocyte count. Serum albumin concentrations are measured using the bromocresol purple dye method. More information on sample collection can be found at https://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals.

Covariates

To more accurately assess the relationship between MDS and COPD, we adjusted for the following confounding factors: sex, age, race/ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Hispanic, Other Race -Including Multi-Racial), education level (less than high school, high school, college or above), poverty income ratio (PIR) (<1, 1–3, ≥ 3), marital status (Divorced, Living with partner, Married, Never married, Separated, Widowed), smoking status ("Former smoker" (smoked more than 100 cigarettes in their lifetime but currently do not smoke), "Never smoker" (smoked fewer than 100 cigarettes in their lifetime and do not currently smoke), "Current smoker" (smoked more than 100 cigarettes in their lifetime and currently smoke every day or some days)), and body mass index (BMI) (<18.5, 18.5–25, ≥ 25), with BMI calculated as weight (kg) divided by the square of height (m^2).

Statistical analyses

Considering the multi-stage, complex, stratified sampling design of the NHANES database, we conducted weighted analyses to generate nationally representative estimates. Continuous variables were expressed as weighted means (± standard deviation) and statistical differences were described using the weighted Student's t-test. Categorical variables were expressed as weighted percentages, and statistical differences were described using the Rao-Scott chi-square test. We constructed univariable and multivariable logistic regression models to evaluate the association between MDS and COPD. The univariable model did not adjust for any confounding factors; the multivariable model adjusted for sex, age, race/ethnicity, education level, PIR, marital status, smoking status, and BMI. Additionally, serum albumin, neutrophils, and SII levels were categorized based on quartiles (Quartile 1 (Q1): < 25th percentile, Quartile 2 (Q2): 25-50th percentile, Quartile 3 (Q3): 50-75th percentile, Quartile 4 (Q4): > 75th percentile), and univariable and multivariable models adjusted for the same factors were used to assess the associations between these biomarkers and COPD. We conducted mediation analyses to determine whether serum albumin, neutrophils, and SII mediated the relationship between MDS and COPD. The total effect (TE) represents the direct relationship between MDS and COPD, unaffected by the mediators. The indirect effect (IE) refers to the impact of serum albumin, neutrophils, and SII on COPD through MDS. The direct effect (DE) represents the impact of MDS on COPD after controlling for serum albumin, neutrophils, and SII levels. A significant IE indicates a notable mediation effect. Additionally, to better control for potential confounders, we performed a multivariable logistic regression analysis to explore the association between MDS and COPD. In this analysis, COPD status was the dependent variable, and magnesium deficiency along with potential confounding variables, including gender (female, male), age, PIR, race, education level, smoking status (yes/no), hypertension (yes/no), hyperlipidemia (yes/no), diabetes (diabetes mellitus (DM), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), no glycemic abnormality), marital status, and BMI, were the independent variables. We also stratified the analysis by these variables and assessed the potential interactions between MDS and COPD across the stratified groups.

All statistical analyses and plotting in this study were performed using R (version 4.3.3), with all tests being two-sided and a p-value <0.05 considered statistically significant.

Results

Baseline characteristics

A total of 30,490 participants were included in this study, comprising 15,175 men and 15,315 women. Participants were categorized into COPD and non-COPD groups based on whether they had COPD. Compared to the non-COPD group, those with COPD were more likely to be over 65 years old, non-Hispanic white, have a high school education or less, be divorced/single, be former or current smokers, have a BMI either below 18.5 or above 25. Additionally, they exhibited higher MDS scores, lower serum albumin levels, higher SII and neutrophil levels, and were more likely to have hypertension, hyperlipidemia, or diabetes. More detailed baseline characteristics of this study can be found in Table 1.

Association between weighted MDS and COPD

As shown in Table 2, in the univariable model, compared to the MDS = 0 group, the risk of COPD increased by 150% (OR 2.50, 95% CI 1.97–3.18, $P<0.001$), 312% (OR 4.12, 95% CI 3.18–5.34, $P<0.001$), 513% (OR 6.13, 95% CI 4.78–7.86, $P<0.001$), 753% (OR 8.53, 95% CI 5.57–13.04, $P<0.001$), and 681% (OR 7.81, 95% CI 1.84–33.09, $P=0.01$) for MDS = 1, 2, 3, 4, and 5 groups, respectively. In the multivariable model, compared to the MDS = 0 group, the risk of COPD increased by 79% (OR 1.79, 95% CI 1.42–2.27, $P<0.001$), 125% (OR 2.25, 95% CI

Level	No COPD	COPD	*P*-value
Sex (%)			
Female	50.97(0.34)	47.93(1.96)	0.15
Male	49.03(0.34)	52.07(1.96)	
Age (%)			
20-65	84.39(0.43)	64.15(1.62)	< 0.001
≥ 65	15.61(0.43)	35.85(1.62)	
Race/ethnicity (%)			
Mexican American	7.68(0.58)	8.50(0.81)	< 0.001
Non-Hispanic Black	11.61(0.69)	8.99(0.66)	
Non-Hispanic White	67.70(1.25)	71.75(1.34)	
Other Hispanic	5.31(0.42)	4.79(0.41)	
Other race - including multi-racial	7.70(0.40)	5.97(0.39)	
Education level (%)			
Low high school	14.27(0.51)	20.18(1.59)	< 0.001
High school	22.43(0.51)	25.36(1.34)	
College school or above	63.30(0.82)	54.47(1.96)	
Poverty income ratio(%)			
<1	13.49(0.48)	15.55(1.64)	0.06
1-3	35.29(0.70)	38.04(1.77)	
≥3	51.22(0.94)	46.40(2.26)	
Marital status (%)			
Divorced	10.28(0.27)	14.75(1.21)	< 0.001
Living with partner	8.13(0.28)	6.50(0.83)	
Married	56.03(0.67)	57.77(1.80)	
Never married	18.02(0.57)	5.58(0.64)	
Separated	2.31(0.12)	3.25(0.59)	
Widowed	5.23(0.16)	12.16(1.02)	
Smoking status (%)			
Former	24.21(0.45)	45.96(1.84)	< 0.001
Never	56.63(0.58)	18.13(1.34)	
Now	19.15(0.43)	35.91(2.01)	
BMI (%)			
<18.5	1.42(0.10)	2.38(0.63)	0.02
18.5-25	28.97(0.51)	24.60(1.65)	
≥25	69.61(0.55)	73.02(1.66)	
MDS (%)			
0	44.79(0.64)	19.34(1.87)	< 0.001
1	35.36(0.46)	39.06(1.85)	
2	14.36(0.37)	25.57(1.55)	
3	4.54(0.15)	12.42(0.88)	
4	0.92(0.07)	3.49(0.60)	
5	0.04(0.01)	0.14(0.09)	
SII (mean (SD))	537.31(3.48)	651.07(10.68)	< 0.001
Neutrophils (mean (SD))	4.27(0.02)	4.71(0.06)	< 0.001
Albumin (mean (SD))	42.74(0.05)	41.68(0.15)	< 0.001
Hypertension (%)			
No	63.50(0.51)	41.39(1.73)	< 0.001
Yes	36.50(0.51)	58.61(1.73)	
Hyperlipidemia (%)			
No	32.09(0.52)	18.21(1.31)	< 0.001
Yes	67.91(0.52)	81.79(1.31)	
Diabetes (%)			
DM	13.12(0.30)	25.04(1.56)	< 0.001
IFG	4.65(0.24)	6.08(0.91)	
IGT	3.32(0.14)	4.07(0.66)	
No	78.90(0.41)	64.81(1.63)	

Table 1. Survey-weighted baseline characteristic of the study population. Notes: For categorical variables, numbers outside parentheses represent weighted counts, and numbers inside represent weighted percentages. For continuous variables, means with standard deviations (SD) are shown in parentheses. BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; MDS, Magnesium Depletion Score; SD, Standard Deviation; SII, Systemic Immune-Inflammation Index; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; No, normal.

	Univariable model		Multivariable model	
	OR(95% CI)	*P*-value	OR (95% CI)	*P*-value
MDS				
0	Reference		Reference	
1	2.50(1.97, 3.18)	< 0.001	1.79(1.42, 2.27)	< 0.001
2	4.12(3.18, 5.34)	< 0.001	2.25(1.72, 2.95)	< 0.001
3	6.13(4.78, 7.86)	< 0.001	2.71(1.99, 3.70)	< 0.001
4	8.53(5.57,13.04)	< 0.001	3.44(2.18, 5.41)	< 0.001
5	7.81(1.84,33.09)	0.010	2.37(0.51,11.11)	0.250

Table 2. Survey-weighted Association Between Magnesium Depletion Score (MDS) and Chronic Obstructive Pulmonary Disease (COPD). Notes: MDS, Magnesium Depletion Score; OR, Odds ratio; CI, confidence interval; Univariable model: No covariates were adjusted. Multivariable model: Adjusted for sex, age, race/ethnicity, education level, poverty income ratio, marital status, smoking status, and body mass index (BMI).

1.72–2.95, $P<0.001$), 171% (OR 2.71, 95% CI 1.99–3.70, $P<0.001$), and 244% (OR 3.44, 95% CI 2.18–5.41, $P<0.001$) for MDS = 1, 2, 3, and 4 groups, respectively.

Association between weighted neutrophils, Albumin, SII and COPD

As shown in Table 3, neutrophil levels were significantly positively associated with the risk of developing COPD. In the univariable model, compared to the Q1 group of neutrophil levels, the risk of developing COPD increased by 42% (OR 1.42, 95% CI 1.13–1.76, $P=0.002$) and 112% (OR 2.12, 95% CI 1.72–2.61, $P<0.001$) in the Q3 and Q4 groups, respectively. In the adjusted multivariable model, compared to the Q1 group, the risk of developing COPD increased by 34% (OR 1.34, 95% CI 1.08–1.66, $P=0.01$) in the Q4 group. In the univariable model, compared to the Q1 group of serum albumin, the risk of developing COPD decreased by 22% (OR 0.78, 95% CI 0.61–0.98, $P=0.03$), 36% (OR 0.64, 95% CI 0.53–0.79, $P<0.001$), and 57% (OR 0.43, 95% CI 0.32–0.58, $P<0.001$) in the Q2, Q3, and Q4 groups, respectively. In the adjusted multivariable model, compared to the Q1 group, the risk of developing COPD decreased by 27% (OR 0.73, 95% CI 0.58–0.92, $P=0.01$) and 42% (OR 0.58, 95% CI 0.42–0.79, $P<0.001$) in the Q3 and Q4 groups, respectively. In the univariable model, compared to the Q1 group of SII, the risk of developing COPD increased by 86% (OR 1.86, 95% CI 1.48–2.34, $P<0.001$) in the Q4 group. In the adjusted multivariable model, the risk of developing COPD increased by 40% (OR 1.40, 95% CI 1.12–1.76, $P=0.004$) in the Q4 group.

Mediation analysis

To assess whether neutrophil, albumin, and SII levels mediate the relationship between MDS and COPD, we conducted a mediation analysis. As shown in Fig. 2, in this mediation model, MDS was the independent variable, COPD was the dependent variable, and neutrophil, albumin, and SII levels were the mediating variables. As shown in Fig. 2A, neutrophils had a significant mediating effect on the relationship between MDS and COPD, explaining 1.06% of the total association, with an indirect effect (IE) of 0.0001 (95% CI: 0.0000 to 0.0002). As shown in Fig. 2B, serum albumin levels had a significant mediating effect on the relationship between MDS and COPD, explaining 4.35% of the total association, with an IE of 0.0004 (95% CI: 0.0002 to 0.0006). As shown in Fig. 2C, SII had a significant mediating effect on the relationship between MDS and COPD, explaining 3.62% of the total association, with an IE of 0.0005 (95% CI: 0.0003 to 0.0008).

Subgroup analysis

Figure 3 presents the regression model results for the interaction between MDS and sex, age, PIR, race, education level, smoking status, hypertension, hyperlipidemia, diabetes, marital status, and BMI on the association between MDS and COPD. The results indicate significant interactions between MDS and age, hypertension, hyperlipidemia, and marital status (P for interaction < 0.05). The positive association between MDS and COPD was particularly significant among those aged 20–65 years, with a PIR between 1 and 3, Mexican Americans, those with a college education, smokers, those without hypertension, hyperlipidemia, or diabetes, those living with a partner, and those with a BMI over 25.

Discussion

The primary objective of this study was to investigate the association between MDS and the prevalence of COPD using data from the NHANES database. Our analysis included 30,490 participants, with a balanced representation of both genders. The study revealed a significant positive correlation between higher MDS and increased risk of COPD. Specifically, as the MDS increased from 0 to 5, the risk of developing COPD escalated markedly, even after adjusting for potential confounders such as gender, age, race/ethnicity, education level, and smoking status. These findings underscore the critical role of magnesium status in respiratory health and suggest that MDS could serve as a valuable tool for identifying individuals at higher risk for COPD.

The observed association between MDS and COPD can be attributed to several underlying mechanisms. Magnesium plays a crucial role in various physiological processes, including muscle function, inflammation modulation, and immune response. A deficiency in magnesium may lead to impaired respiratory muscle function, increased airway hyperreactivity, and heightened inflammatory responses, all of which are key factors in the pathogenesis of COPD[14].

Our mediation analysis further elucidated the pathways through which MDS influences COPD risk. Neutrophils, serum albumin, and the SII were identified as significant mediators in the MDS-COPD relationship. Elevated neutrophil levels, indicative of an inflammatory state, were positively associated with higher MDS and increased COPD risk[15]. Similarly, lower serum albumin levels, reflecting poor nutritional status and systemic inflammation, were linked to higher MDS and greater COPD prevalence[16]. The SII, a composite marker of systemic inflammation, also mediated the relationship between MDS and COPD, highlighting the role of chronic inflammation in this association[10].

Our study's findings align with and extend the current body of literature on the relationship between magnesium status and respiratory health. Previous studies have consistently demonstrated the importance of magnesium in maintaining pulmonary function and reducing the risk of respiratory diseases[5,17]. For instance, a study by Pizzorno et al.[18] highlighted that magnesium deficiency is associated with increased airway hyperreactivity and bronchoconstriction, which are critical factors in the development of COPD. A recent study by Wang et al.[19] similarly evaluated the association between MDS and COPD risk using data from the NHANES. Their findings corroborate our results, demonstrating a significant positive correlation between higher MDS and increased COPD incidence (OR = 1.48, 95%CI: 1.10 to 1.99). However, our research extends beyond the scope of Wang et al.'s study in several important ways. We investigated a broader range of inflammatory and nutritional biomarkers, providing a more comprehensive understanding of the physiological mechanisms underlying the magnesium-COPD relationship.

Furthermore, our study challenges some existing assumptions by demonstrating that the relationship between magnesium status and COPD is not solely attributable to direct effects on lung function. Instead, it highlights the significant mediating role of systemic inflammation and immune response, as evidenced by the mediation effects of neutrophils, serum albumin, and SII. This perspective aligns with the emerging understanding of COPD as a systemic disease with multifactorial etiology, as discussed by Agusti et al.[7,20]. Our findings contribute to the growing body of evidence supporting the critical role of magnesium in respiratory health, while also underscoring the need for further research to explore the potential benefits of magnesium supplementation in preventing and managing COPD, particularly in populations at higher risk of magnesium deficiency.

	Univariable model		Multivariable model	
	OR(95% CI)	P-value	OR (95% CI)	P-value
Neutrophils				
Q1	Reference		Reference	
Q2	1.21(0.95,1.54)	0.12	1.00(0.78,1.28)	1.00
Q3	1.42(1.13,1.76)	0.002	1.02(0.82,1.28)	0.84
Q4	2.12(1.72,2.61)	<0.001	1.34(1.08,1.66)	0.01
Albumin				
Q1	Reference		Reference	
Q2	0.78(0.61,0.98)	0.03	0.82(0.64,1.04)	0.10
Q3	0.64(0.53,0.79)	<0.001	0.73(0.58,0.92)	0.01
Q4	0.43(0.32,0.58)	<0.001	0.58(0.42,0.79)	<0.001
SII				
Q1	Reference		Reference	
Q2	0.87(0.66,1.15)	0.31	0.82(0.62,1.08)	0.15
Q3	1.14(0.89,1.47)	0.28	1.00(0.77,1.30)	>0.9
Q4	1.86(1.48,2.34)	<0.001	1.40(1.12,1.76)	0.004

Table 3. Survey-weighted Association Between Neutrophils, Albumin, Systemic Immune-Inflammation Index (SII) and Chronic Obstructive Pulmonary Disease (COPD). Notes: OR, Odds ratio; CI, confidence interval; SII, Systemic Immune-Inflammation Index; Univariable model: No covariates were adjusted. Multivariable model: Adjusted for sex, age, race/ethnicity, education level, poverty income ratio (PIR), marital status, smoking status, and body mass index (BMI).

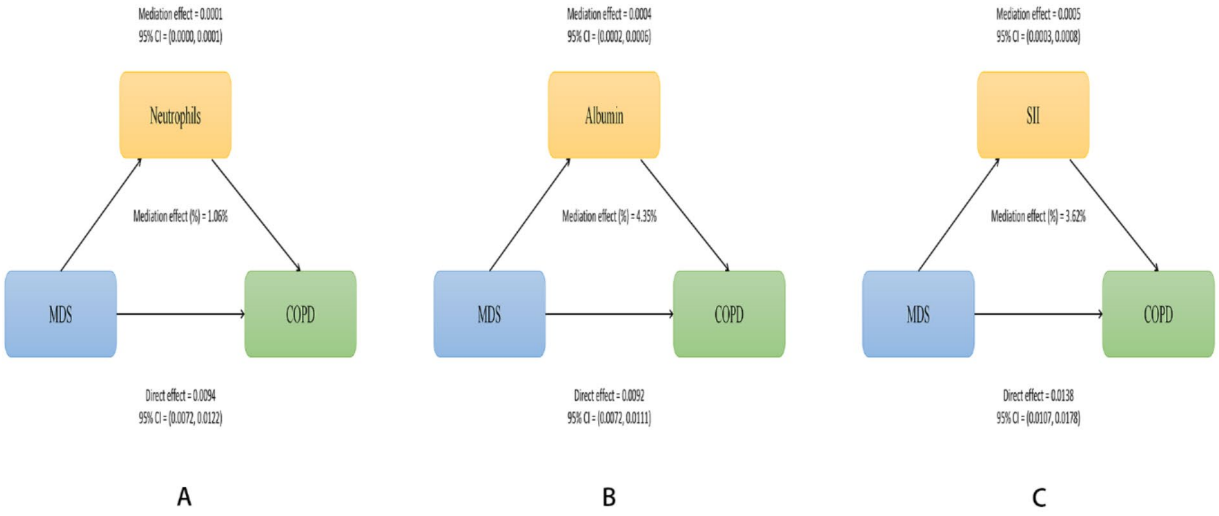

Fig. 2. Path diagram of the mediation analysis models. (**A**) neutrophils; (**B**) serum albumin; (**C**) systemic immune-inflammation index (SII) partially mediates the relationship between Magnesium Depletion Score and Chronic Obstructive Pulmonary Disease.

The biological mechanisms through which magnesium deficiency may influence the development and progression of COPD are multifaceted and complex. Magnesium plays a crucial role in numerous physiological processes, including muscle function, immune response, and inflammation regulation. Its deficiency can lead to a cascade of adverse effects that contribute to respiratory pathologies.

Neutrophils are a key component of the innate immune system and play a significant role in the inflammatory response associated with COPD. This is consistent with findings from Barnes et al.[7], who reported that neutrophilic inflammation is a hallmark of COPD and contributes to airway obstruction and tissue damage. Magnesium deficiency may enhance neutrophil activation and migration to the lungs, thereby increasing the inflammatory burden and accelerating COPD progression. Serum albumin is a marker of nutritional status and systemic inflammation. Low serum albumin levels, which were associated with higher COPD risk in our study, indicate a state of chronic inflammation and poor nutritional status. This aligns with the work of Dial et al.[16] who found that hypoalbuminemia is prevalent in COPD patients and is associated with worse clinical outcomes. Our findings that higher SII levels are associated with increased COPD risk suggest that magnesium deficiency may amplify systemic inflammation. This is supported by the study of Hu et al.[10], which demonstrated that elevated SII is linked to worse prognosis in COPD patients. Magnesium's role in modulating immune cell function and reducing oxidative stress may be critical in mitigating the systemic inflammation observed in COPD.

The MDS, as a comprehensive measure of magnesium status, could serve as an effective tool for early screening and risk stratification in COPD. By identifying individuals with high MDS, clinicians can implement targeted interventions to improve magnesium levels, potentially reducing the risk of COPD development and progression. This approach is supported by the work of Collins et al.[21], who suggested that nutritional interventions, including magnesium supplementation, could improve clinical outcomes in COPD patients.

Several obvious limitations exist in this study. First, the cross-sectional design precludes determining causal relationships between MDS and COPD. Reliance on self-reported data may introduce reporting bias, potentially leading to misclassification. Additionally, the study did not account for all possible confounding factors, such as physical activity levels and other comorbid conditions, which could influence the observed associations.

Future research should focus on verifying the causal relationship between MDS and COPD through longitudinal studies. Interventional studies, such as randomized controlled trials (RCTs), are needed to explore the potential benefits of magnesium supplementation in COPD patients. These studies could provide high-quality evidence on whether correcting magnesium deficiency can improve clinical outcomes and inform clinical guidelines for COPD management. Additionally, exploring the biological mechanisms underlying the association between MDS and COPD could offer insights into potential therapeutic targets.

Conclusion

Using data from NHANES 2005–2018, this cross-sectional study found a significant positive association between higher MDS and increased prevalence of COPD, even after adjusting for confounders. Mediation analysis revealed that inflammatory and nutritional biomarkers partially mediated this relationship. Subgroup analyses showed interactions between MDS and factors like age, hypertension, and marital status, suggesting variability in the MDS-COPD association across different groups. While these findings highlight the potential importance of magnesium status in COPD management, longitudinal and interventional studies are needed to

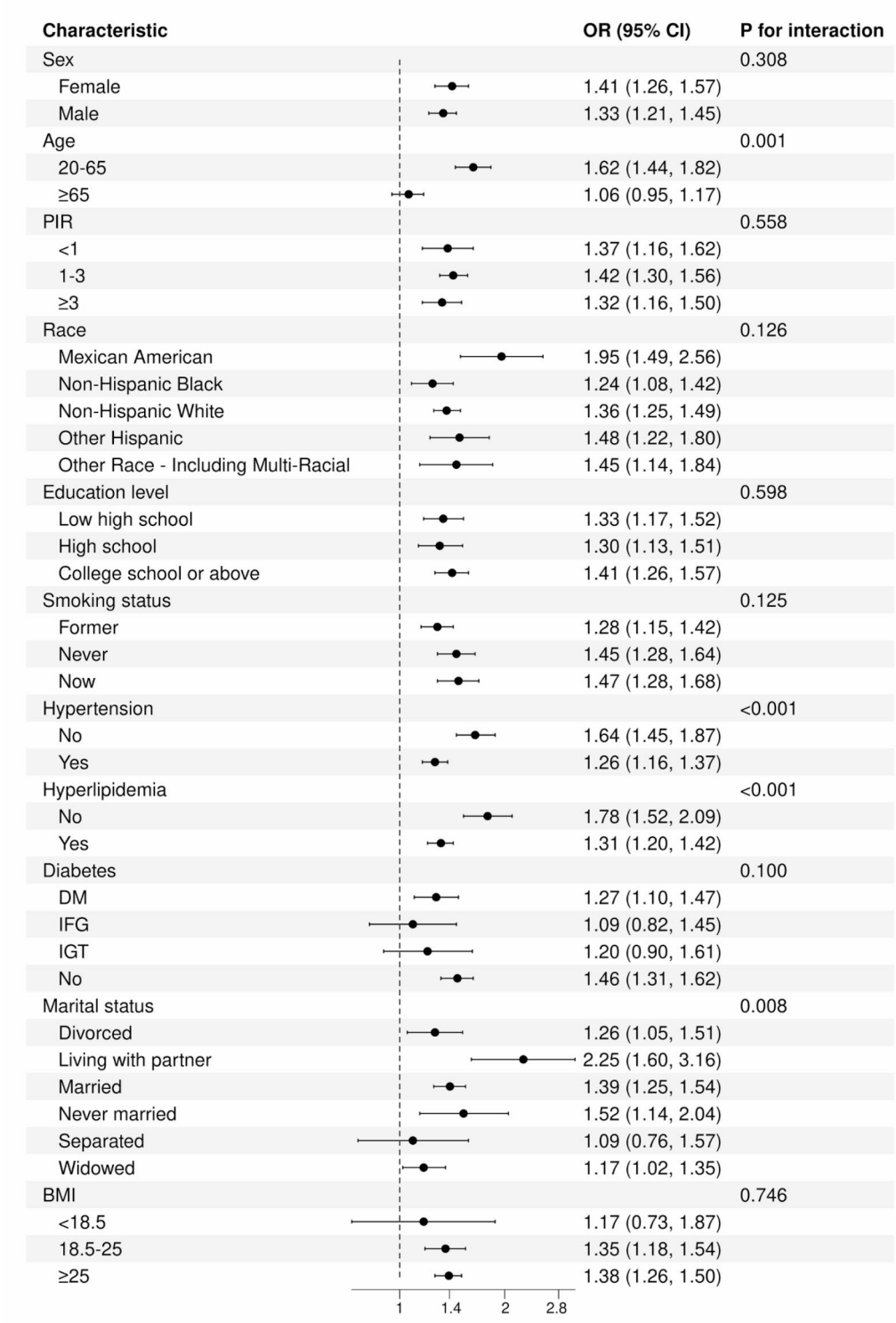

Fig. 3. Subgroup analysis of the association of the MDS and COPD. Each stratifcation was adjusted for sex, age, poverty income ratio, race, education level, smoking status, hypertension, hyperlipidemia, glycemic status, marital status, and BMI. MDS, Magnesium Depletion Score; COPD, Chronic Obstructive Pulmonary Disease.

establish causality and explore the therapeutic benefits of magnesium supplementation. Nonetheless, this study underscores the role of magnesium in chronic respiratory diseases and the need for comprehensive nutritional assessments in COPD care.

Data availability

Sequence data that support the findings of this study can be downloaded here: https://www.cdc.gov/nchs/nhanes/index.htm.

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Author contributions

Yixin Zhao, Hongwei Li and Zhenyu Wang prepared and edited the original draft. Yue Qi, Yu Chang, Yuguang Li, Dongsheng Xu, Xiao Chen were involved in data collation and visualization. Dongsheng Xu and Xiao Chen participated in the drafting of the final article and conceptualization.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The NHANES agreement has been reviewed and approved by the National Center for Health Statistics Research Ethics Committee. All participants provided written informed consent before participating.

Consent for publication

Not Applicable.

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