


BMJ Open Association between magnesium depletion score and chronic obstructive pulmonary disease risk: a secondary data analysis from NHANES

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ABSTRACT

Background and objective The association between magnesium depletion score (MDS) and the risk of chronic obstructive pulmonary disease (COPD) has not been examined to date. Meanwhile, the potential impact of dietary magnesium intake on this association remains unclear. This study aimed to investigate the influence of dietary magnesium intake on the association between MDS and COPD incidence.

Methods In this cross-sectional study using the National Health and Nutrition Examination Survey database, we analysed the relationship between MDS and COPD, while also exploring the role of dietary magnesium.

Results A total of 39 852 participants, including 1762 patients with COPD and 38 090 patients with non-COPD, were included in the analysis. After adjusting for confounding factors, our results demonstrated a significant association between higher MDS and increased COPD incidence (OR=1.48, 95% CI: 1.10 to 1.99). Furthermore, it was observed that dietary magnesium intake did not significantly impact this association.

Conclusion This study highlights a significant positive correlation between MDS and the incidence of COPD. Nonetheless, no significant alteration in this association was observed with dietary magnesium intake.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent and significant respiratory disorder, emerging as a major global health concern.¹ Epidemiological studies indicate a global prevalence of COPD estimated at 10% and rising with age.² Moreover, the WHO predicts that by 2030, COPD will rank as the third leading cause of disability-adjusted life-years lost.³ Given its high prevalence along with severe morbidity and mortality rates, the need to enhance our understanding and management of COPD cannot be overstated. COPD's aetiology and pathogenesis involve a complex interplay of genetic predisposition and exposure to environmental risk factors, such as tobacco smoke, air pollution and occupational hazards.⁴ Yet, despite progress in understanding COPD,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study leverages the comprehensive National Health and Nutrition Examination Survey (NHANES) database which provides a nationally representative sample enhancing the generalisability of findings.
- ⇒ We used the validated magnesium depletion score which allows for a more nuanced assessment of magnesium deficiency as compared with serum magnesium levels alone.
- ⇒ Despite adjusting for a broad range of covariates, residual confounding by unmeasured factors within the NHANES database could have influenced our results.
- ⇒ The reliance on self-reported dietary intake may introduce recall bias and underestimate nutrient consumption.

several knowledge gaps and controversies still surround this disease.

Magnesium is an essential mineral that plays a crucial role in various physiological processes, including smooth muscle relaxation, bronchodilation and immunomodulation.⁵⁻⁶ However, previous studies have focused on the effects of dietary magnesium and serum magnesium on the respiratory system, which do not respond well to magnesium deficiency.⁷⁻⁹ Recently, the magnesium depletion score (MDS) has been developed as a system for assessing magnesium status and has been shown to be associated with a variety of diseases and states.¹⁰⁻¹³ In addition, magnesium supplementation through diet has been shown to have a protective effect on the respiratory system, but whether it has a moderating role in magnesium deficiency is unknown.

To fill these knowledge gaps, we analysed the National Health and Nutrition Examination Survey (NHANES) database with the aim of evaluating the relationship between MDS and COPD risk in US adults through

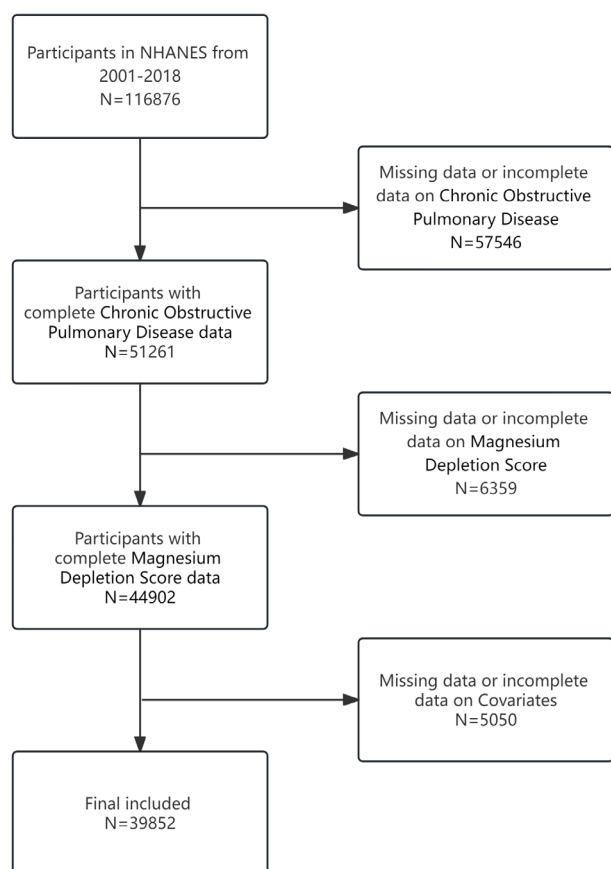


Figure 1 Flow chart of participants inclusion. NHANES, National Health and Nutrition Examination Survey.

a cross-sectional study design and exploring whether dietary magnesium plays a role as an effect modifier.

METHOD

Design

The NHANES database is a notable cross-sectional survey that provides nationally representative data on the health and nutrition of households in the USA.¹⁴ For our research study, we used data from the years 2001 to 2018. Prior to analysis, we excluded 57546 cases with missing or incomplete COPD data, 6359 cases with missing or incomplete MDS data and 5050 cases with missing or incomplete information on other variables. Ultimately, our study included 39852 participants (figure 1).

Patient and public involvement

Patients and the public were not directly involved in the design, recruitment, or conduct of this study due to its retrospective nature using the NHANES database which includes de-identified data. However, we recognise the importance of patient and public involvement in research and plan to disseminate the results of this study through patient advocacy groups, public health outreach programmes and relevant online platforms to ensure that the findings are accessible to the broader community.

MDS

Based on the MDS model developed and validated by Fan *et al*, we quantified MDS using four relatively independent metrics.¹⁰ The first factor assessed was the use of diuretics. One point was attributed to individuals who had used a diuretic within the last 30 days, while those who had not received zero points. The second factor considered was the utilisation of proton pump inhibitors, which was consistent with diuretic use. One point was assigned to individuals using proton pump inhibitors. The third factor taken into account was the estimated glomerular filtration rate (eGFR). Participants were given one point if their eGFR was between 60 and 90, and two points if it fell below 60. Lastly, alcohol abuse was evaluated, and one point was given to male participants consuming more than two drinks per day, or female participants consuming more than one drink per day. We categorised the MDS into four classes: 0, 1, 2 and ≥ 3 .

Dietary magnesium

We extracted data from the NHANES database, specifically using information from two dietary interviews conducted with participants.¹⁵ The first interview took place face-to-face at a Mobile Examination Center (MEC) and aimed to capture dietary intake over the previous 24 hours. Subsequently, a second interview was conducted via telephone within 3–10 days after the MEC visit. To minimise potential errors arising from unusual dietary activities, we calculated the average dietary magnesium (mg) intake for each participant.

COPD

We used the standardised diagnostic criteria recommended by the American Thoracic Society to evaluate the presence of COPD.¹⁶ Specifically, we assessed one-second force expiratory volume (FEV1) and forceful lung volume (FVC). Subsequently, we calculated the FEV1 to FVC ratio and considered an FEV1/FVC ratio of <0.7 , in the presence of bronchodilator usage, as indicative of COPD.

Covariates

In our study, We included demographic data, lifestyle factors, medical history and haematologic marker information as covariates.

1. Demographic data: we considered age, sex, race and body mass index (BMI) as important demographic factors that could influence the association between MDS and COPD incidence.
2. Lifestyle factors: smoking, education and poverty income ratio (PIR) were included as lifestyle factors. These variables have been associated with both MDS and COPD risk, thus warranting consideration in our analysis.
3. Disease history: we assessed hypertension, diabetes and cardiovascular disease (CVD) as important disease history variables. Hypertension was defined as a mean systolic blood pressure of 140 mm Hg or higher, mean diastolic blood pressure of 90 mm Hg or higher,

Table 1 Baseline characteristics of subjects in NHANES

	MDS				P value
	0	1	2	≥3	
Participants, N	17 668	13 268	6051	2865	
Age, years	38.51 (0.19)	49.48 (0.23)	59.65 (0.26)	68.10 (0.29)	<0.001
Sex					<0.001
Female	9182 (51.54)	6109 (48.05)	2971 (51.23)	1566 (60.03)	
Male	8486 (48.46)	7159 (51.95)	3080 (48.77)	1299 (39.97)	
Race					<0.001
Mexican American	3922 (12.15)	1817(5.56)	596(3.18)	207(2.26)	
Non-Hispanic black	3871 (12.82)	2665(9.32)	1225(8.96)	589 (10.08)	
Non-Hispanic white	6105 (59.42)	6779 (75.81)	3560 (81.16)	1806 (82.23)	
Other Hispanic	1747 (7.02)	1017 (4.13)	366 (2.80)	148 (2.30)	
Other race	2023 (8.59)	990 (5.19)	304 (3.90)	115 (3.13)	
PIR	2.83 (0.03)	3.24 (0.03)	3.27 (0.04)	2.95 (0.06)	<0.001
Education					<0.001
Below high school	1862 (5.57)	1339 (4.27)	740 (5.65)	396 (7.90)	
High school	6683 (35.05)	4821 (33.14)	2315 (34.24)	1177 (38.34)	
Above high school	9123 (59.38)	7108 (62.59)	2996 (60.12)	1292 (53.76)	
BMI, kg/m ²					<0.001
Normal	5635 (33.80)	3898 (31.05)	1394 (24.26)	521 (18.53)	
Overweight	5510 (30.49)	4615 (34.30)	2099 (35.83)	922 (33.63)	
Obese	6344 (35.72)	4608 (34.66)	2426 (39.91)	1331 (47.84)	
Smoke					<0.001
Never	10 657 (58.64)	6600 (50.86)	2832 (48.81)	1304 (47.68)	Never
Former	3068 (18.65)	3509 (26.02)	2181 (34.78)	1240 (42.46)	
Now	3943 (22.71)	3159 (23.12)	1038 (16.41)	321(9.86)	
Hypertension					<0.001
No	13 207 (77.38)	7337 (61.97)	1788 (37.07)	344 (14.07)	
Yes	4461 (22.62)	5931 (38.03)	4263 (62.93)	2521 (85.93)	
Diabetes					<0.001
No	15 558 (91.09)	11 065 (87.82)	4385 (79.12)	1734 (66.91)	
Yes	2110(8.91)	2203 (12.18)	1666 (20.88)	1131 (33.09)	
CVD					<0.001
No	16978 (96.77)	11 885 (92.30)	4689 (82.52)	1741 (66.22)	
Yes	690(3.23)	1383(7.70)	1362 (17.48)	1124 (33.78)	
COPD					<0.001
No	17 297 (97.97)	12 642 (95.49)	5595 (92.70)	2556 (89.08)	
Yes	371(2.03)	626(4.51)	456(7.30)	309 (10.92)	

Continuous variables: mean (SE); categorical variables: frequency (%).

All results are weighted calculations.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MDS, magnesium depletion score; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio.

current use of hypertension medication or receiving a diagnosis of hypertension from a healthcare professional.¹⁷ Participants were classified as having diabetes if they had a fasting blood glucose level of 126 mg/dL or higher, glycosylated haemoglobin of 6.5% or higher,

were taking insulin or glucose-lowering medications, or had been informed of their diabetes diagnosis.¹⁸ CVD was diagnosed if participants reported having coronary artery disease, heart failure, angina, heart attack or stroke.¹⁹

**Table 2** Multivariate logistic regression of MDS and COPD

	MDS							P for trend
	0	1		2		≥3		
	OR (95% CI)	OR	95% CI	OR	95% CI	OR	95% CI	
Model 1	Ref	2.28	1.86 to 2.78	3.8	3.06 to 4.71	5.91	4.67 to 7.48	<0.001
Model 2	Ref	1.34	1.06 to 1.71	1.55	1.17 to 2.05	1.72	1.27 to 2.33	0.006
Model 3	Ref	1.29	1.02 to 1.63	1.40	1.07 to 1.82	1.48	1.10 to 1.99	0.030

Model 1: no adjusted.

Model 2: adjusted for age, sex, race and PIR.

Model 3: adjusted for age, sex, race, PIR, education, BMI, smoke, hypertension, diabetes and CVD.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MDS, magnesium depletion score; PIR, poverty income ratio.

4. Haematologic markers: we included high-density lipoproteins and low-density lipoproteins as haematologic markers. These markers provide valuable information regarding participants' lipid profile.

Statistical analysis

In our analysis, categorical variables were presented as frequencies and percentages, while continuous variables were reported as means and SD. Analysis of Variance

Table 3 Stratified analysis between MDS and COPD

	MDS				P for trend	P for interaction
	0	1	2	≥3		
Age, years						<0.001
<60	Ref	1.69 (1.29 to 2.22)	2.55 (1.76 to 3.69)	3.72 (2.13 to 6.51)	<0.001	
≥60	Ref	1.17 (0.86 to 1.59)	1.26 (0.90 to 1.77)	1.48 (1.08 to 2.04)	0.780	
Sex						0.498
Female	Ref	1.93 (1.48 to 2.52)	2.41 (1.71 to 3.41)	2.98 (1.96 to 4.51)	<0.001	
Male	Ref	1.38 (1.03 to 1.84)	1.64 (1.15 to 2.35)	1.63 (1.16 to 2.29)	0.002	
Race						0.398
Non-Hispanic white	Ref	1.60 (1.27 to 2.03)	2.03 (1.53 to 2.68)	2.38 (1.71 to 3.31)	<0.001	
Non-Hispanic black	Ref	1.25 (0.90 to 1.75)	1.57 (1.03 to 2.38)	1.37 (0.79 to 2.36)	0.307	
Mexican American	Ref	2.12 (0.91 to 4.95)	3.17 (1.07 to 9.39)	3.43 (1.13 to 10.34)	0.463	
Other Hispanic	Ref	2.37 (1.05 to 5.36)	1.24 (0.48 to 3.21)	1.48 (0.48 to 4.56)	0.376	
Other race	Ref	1.90 (0.79 to 4.61)	1.68 (0.61 to 4.63)	0.98 (0.34 to 2.85)	0.342	
BMI, kg/m ²						0.571
Normal	Ref	1.52 (1.06 to 2.18)	1.58 (0.10 to 2.52)	1.93 (1.14 to 3.26)	0.260	
Overweight	Ref	1.42 (0.99 to 2.04)	1.90 (1.22 to 2.94)	1.93 (1.14 to 3.27)	0.819	
Obese	Ref	1.90 (1.35 to 2.69)	2.35 (1.64 to 3.36)	2.62 (1.72 to 3.99)	<0.001	
Smoke						0.579
Never	Ref	2.32 (1.37 to 3.91)	2.43 (1.50 to 3.92)	3.56 (2.05 to 6.17)	0.006	
Former	Ref	1.37 (0.96 to 1.95)	1.69 (1.13 to 2.53)	1.85 (1.19 to 2.87)	0.801	
Now	Ref	1.59 (1.12 to 2.25)	2.14 (1.14 to 3.27)	2.10 (1.19 to 3.70)	<0.001	
Hypertension						0.029
No	Ref	1.79 (1.37 to 2.35)	2.55 (1.83 to 3.56)	3.04 (1.65 to 5.58)	<0.001	
Yes	Ref	1.34 (0.98 to 1.83)	1.55 (1.13 to 2.14)	1.82 (1.33 to 2.49)	0.288	
Diabetes						0.259
No	Ref	1.70 (1.34 to 2.16)	2.10 (1.56 to 2.83)	2.27 (1.61 to 3.20)	<0.001	
Yes	Ref	1.30 (0.79 to 2.13)	1.55 (0.97 to 2.49)	1.92 (1.11 to 3.32)	0.017	

All variables were adjusted in the model except for the stratified own variable.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MDS, magnesium depletion score.

Table 4 Interaction between dietary magnesium intake and MDS on COPD

	MDS				P for trend	P for interaction
	0	1	2	≥3		
Dietary magnesium intake (mg)						0.477
<264.5 mg	Ref	1.85 (1.41 to 2.44)	2.13 (1.54 to 2.96)	2.60 (1.82 to 3.72)	<0.001	
≥264.5 mg	Ref	1.50 (1.08 to 2.08)	2.09 (1.42 to 3.08)	1.87 (1.19 to 2.94)	0.049	

Adjusted for age, sex, race, education, PIR, BMI, smoke, hypertension, diabetes and CVD.
 BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MDS, magnesium depletion score; PIR, poverty income ratio.

(ANOVA) was used to analyse continuous variables and χ^2 test was used to analyse categorical variables.

The association between various variables and the risk of COPD was assessed using one-way logistic regression. We calculated the OR of MDS with COPD and their corresponding 95% CI through several adjusted models. To examine the robustness of the association between MDS and COPD risk across different populations, we conducted a stratified analysis. Additionally, we considered dietary magnesium intake and its potential impact on the association between MDS and COPD. Dietary magnesium intake was categorised into high and low groups based on the median value (264.5 mg).

All statistical analyses were performed using the weighting methodology outlined in the NHANES database analysis guidelines. We used R software (V.4.2.1) for the statistical analysis. A p value <0.05 was considered statistically significant.

RESULTS

Characteristics of the participants at baseline

In the final study, a total of 39852 participants were included. **Table 1** provides an overview of the baseline characteristics of the study participants across different MDS quartiles ($p<0.05$). The distribution of covariates, including age, sex, race, PIR, education, BMI, smoking, diabetes, hypertension and CVD, varied across MDS subgroups. Interestingly, a higher proportion of women had high MDS, whereas among men, a higher proportion had low MDS. Additionally, within the normal-weight population, a greater proportion of individuals had low MDS, while within the obese population, a higher proportion had high MDS. In online supplemental table S1, the relationship between all variables and the risk of COPD is presented. The results show that the higher the PIR, the lower the risk of COPD ($p<0.05$). In contrast, age, BMI, smoking, hypertension, diabetes and CVD significantly increased the risk of COPD ($p<0.05$).

Independent association between MDS and COPD

Table 2 presents the results of the weighted multivariate logistic regression analysis, examining the independent association between MDS and COPD. The analysis was adjusted for all confounding factors. Our results indicate that individuals with MDS 1 had a 29% increased risk of COPD compared with those with MDS 0 (OR=1.29, 95% CI: 1.02 to

1.63). Similarly, individuals with MDS 2 had a 40% increased risk (OR=1.40, 95% CI: 1.07 to 1.82), and those with MDS 3 had a 48% increased risk of COPD (OR=1.48, 95% CI: 1.10 to 1.99), compared with participants with MDS 0. Furthermore, our trending study has revealed that this association exhibits a significant difference among diverse subgroups of MDS (P for trend <0.05).

Stratified analysis

Subsequently, we conducted a stratified analysis in **table 3**. After adjusting for other confounding factors, we found that the positive association between MDS and COPD risk remained largely consistent across different subgroups.

However, it is important to note that we observed some variations in the association between MDS and COPD risk in certain subgroups. Specifically, in the non-Hispanic black, other Hispanic and other race populations, the inverse association between MDS and COPD risk was not statistically significant.

Additionally, we explored potential factors that could potentially modify the association between MDS and COPD risk. However, we did not identify any significant factors that significantly influenced the inverse association between MDS and COPD risk in our study (P for interaction >0.05).

Role of dietary magnesium

The results of the interaction analyses are shown in **table 4**. We observed that among individuals with higher dietary magnesium intake, the OR for the association between MDS and COPD was 1.87 (95% CI: 1.19 to 2.94). However, among individuals with lower dietary magnesium intake, the OR increased to 2.60 (95% CI: 1.82 to 3.72). Although this increase in risk was not statistically significant, numerically, it suggests a potential reduction in the risk of COPD (P for interaction >0.05).

DISCUSSION

To the best of our knowledge, the present study is the first to establish an association between magnesium deficiency (MDS) and the risk of COPD, highlighting the importance of magnesium in the pathogenesis of COPD. Additionally, the study findings suggest that dietary magnesium intake does not improve this strong positive association between MDS and COPD risk.



Serum magnesium is a widely studied biomarker. Previous studies have confirmed that hypomagnesemia, or low serum magnesium levels, is an important risk factor for respiratory diseases.^{20 21} In a small cohort study, serum magnesium levels were identified as the most significant predictor of the frequency of acute episodes of COPD.²² Furthermore, there is growing evidence from numerous studies conducted during the COVID-19 pandemic that supports the association between disrupted magnesium levels and COVID-19. These studies consistently highlight the potential role of magnesium in the pathogenesis and clinical outcomes of COVID-19.²³

However, serum magnesium is not a reliable method for assessing magnesium deficiency status due to its highly variable reference range and representation of only a small amount of magnesium in the body.^{24 25} In this challenging context, the MDS system was developed to assess the body's magnesium deficiency status.¹⁰ The MDS is not only simple and easy to operate but has also been proven to effectively map magnesium deficiency status using the Magnesium Tolerance Test (MTT) method. In our study, higher MDS was found to be associated with an increased incidence of COPD. At the same time, this correlation is present in a variety of diseases, including diabetic retinopathy, CVD and kidney disease.^{10 13 26 27} Taken together, these results suggest that we should always pay attention to our magnesium status.

Indeed, magnesium has garnered significant attention from researchers due to its unique antioxidant and anti-inflammatory properties, which have been implicated in various diseases.²⁸ Previous research has demonstrated that increased dietary magnesium intake is associated with reduced levels of serum C reactive protein, a marker of inflammation.²⁹ Furthermore, higher dietary magnesium intake has been linked to disease severity and prognosis in patients with COVID-19. These promising findings have prompted us to explore the interaction of dietary magnesium and MDS on COPD risk. However, our results confirmed that dietary magnesium did not modulate the strong correlation between MDS and COPD incidence. This outcome is not surprising, as a previous study had also demonstrated that dietary magnesium has less significant effects on the association between MDS and congestive heart failure.²⁷ This result emphasises that for reducing the risk of COPD, we should focus more on the overall magnesium status, because when the overall magnesium status is poor, it is not possible to pin the hope of reducing COPD on increasing the intake of dietary magnesium.

Although our study yielded an association between MDS and COPD, however, our paper still has some unavoidable limitations. First, as NHANES is a national cross-sectional design survey, we were unable to infer a causal association between MDS and COPD in our study. Second, although the regression model has incorporated a wide range of covariates affecting the onset of COPD, there are still some unmeasured confounders from the NHANES database that may have played a role in interfering with the results. Finally, although our results

suggest that dietary magnesium intake does not modulate the association between MDS and the risk of COPD, the question of whether dietary magnesium intake and dietary magnesium supplementation can reduce the risk of COPD was not taken into account in the study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of Chongqing Liangjiang New Area People's Hospital (protocol Number: L20230031). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available from the NHANES database (<https://wwwn.cdc.gov/nchs/nhanes/Default.aspx>).

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Table S1. Univariate logistic regression for COPD

	OR	95% CI
Age, years	1.05	(1.05, 1.05)
Sex		
female	ref	ref
male	1.09	(0.95, 1.26)
Race		
Mexican American	ref	ref
Non-Hispanic Black	3.13	(2.27, 4.34)
Non-Hispanic White	6.13	(4.58, 8.20)
Other Hispanic	2.01	(1.30, 3.13)
Other Race	4.43	(3.03, 6.48)
PIR	0.91	(0.87, 0.96)
Education		
below high school	ref	ref
high school	0.85	(0.69, 1.05)
above high school	0.63	(0.50, 0.79)
BMI, kg/m ²		
normal	ref	ref
overweight	1.08	1.08(0.90,1.29)
obese	1.22	1.22(1.02,1.45)
Smoke		
former	ref	ref
never	6.08	(5.09,7.26)
now	5.34	(4.41,6.46)
Hypertension		
no	ref	ref
yes	2.47	(2.18, 2.80)
Diabetes		
no	ref	ref
yes	2.18	(1.89, 2.51)
CVD		
no	ref	ref
yes	4.3	(3.74, 4.94)

PIR: poverty income ratio; BMI: body mass index; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval; All results are weighted calculations.