

## Brief Report

### Severe Obesity and Alpha-1 Antitrypsin Deficiency-Associated COPD: A Dual Burden on Health and Quality of Life

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#### **Running Head: Severe Obesity in AATD-Associated COPD**

**Keywords:** alpha-1 antitrypsin deficiency; COPD; severe obesity

**Abbreviations:** COPD=chronic obstructive pulmonary disease; BMI=body mass index; HRQoL=health-related quality of life; AATD=alpha-1 antitrypsin deficiency; SGRQ=St. George's Respiratory Questionnaire; CCI=Charlson Comorbidity Index

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and obesity are two major public health challenges, each contributing substantially to morbidity, healthcare utilization, and mortality. In COPD, obesity is commonly associated with greater symptom burden and impaired health status. As COPD progresses to more advanced stages, underweight status becomes more prevalent and is independently associated with worsened outcomes, including increased mortality risk. These trends underscore the complex and dynamic relationship between body weight and COPD progression.

Although the clinical implications of weight extremes in COPD are increasingly recognized, key knowledge gaps persist regarding how body mass index (BMI) influences symptoms and health-related quality of life (HRQoL). These gaps are particularly pronounced in the context of alpha-1 antitrypsin deficiency (AATD)-associated COPD, a genetically defined type of COPD characterized by earlier onset.

Campos et al. recently reported high rates of overweight and obese individuals in a historical cohort with AATD, associating elevated BMI with poorer clinical outcomes and reduced HRQoL.<sup>1</sup> The current study expands on this work, examining the associations between BMI and clinical, demographic, and behavioral characteristics in a large cohort of individuals with AATD-associated COPD. We aimed to determine whether the findings reported by Campos et al. are replicated in this expanded and current dataset and to further explain the role of body weight in shaping disease presentation and patient-centered outcomes in AATD-related COPD.

## METHODS

We performed a cross-sectional analysis of data from AlphaNet participants enrolled between 2008 and 2019. AlphaNet is a US-based health management organization supporting individuals with AATD and lung disease through regular telephone calls to provide education and support and collect research data.<sup>2</sup> Participants with lung disease and available self-reported weight and height data were included in these analyses. BMI was classified per CDC guidelines into underweight ( $<18.5$  kg/m<sup>2</sup>), healthy weight ( $18.5$ - $<25$  kg/m<sup>2</sup>), overweight ( $25$ - $<30$  kg/m<sup>2</sup>), obese ( $30$ - $<40$  kg/m<sup>2</sup>), and severely obese ( $\geq 40$  kg/m<sup>2</sup>).<sup>3</sup> Demographic and clinical characteristics (exacerbations, oxygen use, dyspnea severity), HRQoL (measured using St. George's Respiratory Questionnaire [SGRQ] and SF-36), and self-reported exercise behavior were examined. Charlson Comorbidity Index scores were calculated using the established weights<sup>4</sup> and categorized as 1, 2, and 3 or more. Since the study population has COPD, which contributes 1 point to the index, the 0 category was not applicable and therefore omitted.

Continuous variables were summarized as means (SD) and compared across BMI groups using ANOVA with Bonferroni-adjusted pairwise comparisons. Categorical variables were analyzed via chi-square tests with false discovery rate adjustments (Benjamini-Hochberg).<sup>5</sup> A multivariable linear regression model was fit with SGRQ Total score as the outcome, adjusted for covariates selected *a priori* based on clinical relevance and prior research, including age, sex, smoking history, CCI, and exacerbation frequency.

Analyses were conducted using SAS version 9.4. The study was approved by the University of Kentucky Institutional Review Board (#43435).

## RESULTS

Of 8,154 participants (mean age  $57.6 \pm 11.2$  years), BMI distribution was: underweight 4.7%, healthy weight 35.6%, overweight 30.1%, obese 23.9%, and severely obese 5.8% (Table 1).

Overall, 56.8% reported  $\geq 2$  exacerbations in the past year, and 28% had mMRC grade 4 dyspnea. Less than 1% ( $n=87$ ) had lung transplants and 7 individuals had liver transplants.

Severely obese participants were the youngest group (mean age  $54.0 \pm 11.1$  years) and had the highest prevalence of self-reported asthma (47.5%) and  $\geq 2$  exacerbations (71.4%). Nearly half (49.5%) of all participants used oxygen, and 44.4% reported productive cough, with no significant differences across BMI categories.

Dyspnea severity was greatest among underweight and severely obese individuals. Only 19% of those in the severely obese group reported regular exercise, while over half (52.5%) reported no exercise at all, significantly worse than other groups (Table 1 and Figure 1).

HRQoL measures were significantly impaired in the severely obese group. SF-36 Physical Component Summary scores were lower than in all other groups except the underweight, indicating poor physical health in these groups. Mental Component Summary scores were also impaired. SGRQ total scores were high in the severely obese group indicating poor HRQoL, however not significantly different from the underweight or obese groups (Figures 2A and 2B). SGRQ subscale scores were similarly poor among underweight, obese, and severely obese individuals, with the greatest impairments in the activity domain.

In the multivariable model adjusting for age, sex, smoking, comorbidity burden (CCI), and exacerbation frequency, both underweight and severe obesity remained independently associated with worse SGRQ Total scores ( $p < 0.001$ ), indicating that the relationship between BMI extremes

and impaired respiratory health is not fully attributable to studied comorbidities or measured clinical confounders (Table 2).

## DISCUSSION

In this large cohort of individuals with AATD-associated COPD, severe obesity was associated with worse clinical outcomes and poorer HRQoL, extending the findings of prior studies in a broader sample.<sup>1</sup> Notably, severely obese individuals were younger on average, suggesting that excess weight may contribute to earlier or more aggressive disease manifestation in this population.

Our findings suggest a dose-response relationship between BMI and exacerbation frequency, with the highest burden observed among the severely obese, paralleling observations in non-AATD COPD populations.<sup>6</sup> Severely obese individuals also reported the most severe dyspnea and the lowest levels of physical activity, which likely contributes to a cycle of deconditioning, inactivity, and worsening respiratory symptoms.<sup>7</sup>

HRQoL was substantially impaired in both severely obese and underweight participants.

Differences in SGRQ total scores between these groups and normal/overweight participants exceeded the minimum clinically important difference (MCID) of 4 points, indicating a meaningful impact on perceived health status. Similarly, both physical and mental HRQoL assessed via SF-36 were significantly reduced in these extreme weight groups, reinforcing the detrimental effects of both obesity and underweight in AATD-associated COPD. Our multivariable analyses adjusting for age, sex, smoking history, CCI, and exacerbation frequency demonstrate that both underweight and severe obesity were significantly associated with worse

SGRQ Total scores. These findings suggest that low or high BMI contributes to poor respiratory quality of life in AATD, independent of comorbidities or demographic factors.

Self-reported exercise patterns provide additional insight into behavioral contributors to disease burden. Only 1 in 5 severely obese individuals in our study reported regular exercise, while more than half reported no exercise at all. Barriers such as dyspnea, fatigue, and musculoskeletal limitations likely play a role. Nonetheless, this finding highlights the need for tailored, feasible physical activity interventions. Sedentary behavior is a known risk factor for adverse metabolic and cardiovascular outcomes,<sup>8</sup> and growing evidence suggests that obesity may accelerate aging processes through chronic inflammation and physiologic stress.<sup>9</sup>

These results underscore the importance of a comprehensive, individualized approach to weight and activity management in AATD-associated COPD. While nutritional and exercise interventions are central to non-AATD COPD care, specific guidance for the AATD population remains limited.<sup>10</sup> However, our previous work and that of others support the effectiveness of tailored interventions in improving BMI and exercise tolerance in individuals with AATD.<sup>11,12</sup>

It is important to note that the literature on obesity and COPD remains mixed.<sup>13</sup> Some studies have found that higher BMI is associated with worse outcomes, including greater dyspnea, reduced HRQoL, and increased hospitalizations.<sup>6</sup> Conversely, other reports suggest that higher BMI may be linked to lower exacerbation rates.<sup>14</sup> This conflicting evidence has been described as the “obesity paradox,”<sup>13</sup> highlighting the complexity of BMI as a surrogate for adiposity and health risk, particularly in individuals with high muscle mass. These nuances underscore the need for more precise and individualized measures of body composition in future research and clinical care.

Strengths of our study include the large, well-characterized cohort of individuals with AATD-associated COPD and the inclusion of both disease-specific and generic HRQoL measures. The availability of exercise behaviors data also adds a valuable patient-centered dimension. However, several limitations should be noted. All data were self-reported, which may introduce recall or reporting bias, particularly related to physical activity. Additionally, the cross-sectional design precludes causal inference and limits the ability to assess temporal changes in BMI or outcomes. BMI also does not account for differences in body composition or fat distribution, which may affect the interpretation of obesity-related risk. Although liver involvement is an important aspect of AATD, the small number of participants with liver disease or liver transplantation precluded meaningful interpretation. Finally, information on potential treatment-related confounders, including pulmonary rehabilitation, airway clearance, statins, GLP1 inhibitors, or surgical procedures for weight control, was not routinely collected in the AlphaNet dataset and could not be incorporated into the analyses.

## CONCLUSION

In this large cohort of individuals with AATD-associated COPD, severe obesity was associated with younger age, higher exacerbation frequency, greater dyspnea, and worse HRQoL, mirroring the clinical burden observed in underweight individuals. These findings underscore the dual vulnerability posed by both obesity and underweight in this population and highlight the importance of addressing weight and activity through individualized clinical and behavioral interventions.

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**Declaration of interest:**

RC reports research support from AlphaNet. KEH receives consulting income from AlphaNet. CS is a paid AlphaNet medical director. DMM reports consulting income from AstraZeneca, GlaxoSmithKline, AmGen, Genentech, Roche, Regeneron, Sanofi, Lilly, Chiesi, Up to Date, and the COPD Foundation. RAS is a paid AlphaNet medical director.

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Table 1. Demographic and clinical characteristics of the study participants in the overall cohort and by five BMI categories, n=8154

	Overall cohort	Underweight n (%)	Healthy weight n (%)	Overweight n (%)	Obesity n (%)	Severe obesity n (%)	Global P-value <sup>d</sup>
	n=8154	381 (4.7%)	2899 (35.6%)	2454 (30.1%)	1950 (23.9%)	470 (5.8%)	
Age at baseline, mean (SD)	57.6 (11.2)	56.7 (11.0)	58.4 (11.5)	58.3 (11.1)	56.6 (10.9)	54.0 (11.1) <sup>a</sup>	<0.0001
Female (n=7873)	4239 (53.8)	254 (67.9)	1492 (53.4)	1093 (46.2)	1069 (56.6)	331 (73.7) <sup>b</sup>	<0.0001
Ever smoked (n=6507)	4849 (74.5)	247 (81.8)	1753 (74.8)	1470 (74.2)	1151 (74.9)	228 (66.1) <sup>a</sup>	0.0002
Exacerbation frequency in the past year (n=6192)							<0.0001
0	1389 (22.4)	53 (18.5)	520 (23.1)	467 (25.2)	301 (20.5)	48 (14.5) <sup>a</sup>	
1	1285 (20.8)	71 (24.8)	510 (22.6)	378 (20.4)	279 (19.0)	47 (14.2) <sup>a</sup>	
2 or more	35.18 (56.8)	162 (56.6)	1223 (54.3)	1007 (54.4)	889 (60.5)	237 (71.4) <sup>a</sup>	
mMRC grade (n=6404)							<0.0001
0	672 (10.5)	23 (7.8)	282 (12.2)	224 (11.5)	125 (8.3)	18 (5.3) <sup>b</sup>	
1	1434 (22.4)	40 (13.6)	606 (26.2)	469 (24.1)	283 (18.8)	36 (10.6) <sup>b</sup>	
2	1208 (18.9)	50 (17.0)	430 (18.6)	412 (21.2)	265 (17.6)	51 (15.0) <sup>b</sup>	
3	1304 (20.4)	55 (18.7)	438 (18.9)	384 (19.7)	339 (22.5)	88 (26.0) <sup>b</sup>	
4	1786 (27.89)	126 (42.86)	561 (24.2)	459 (23.6)	494 (32.8)	146 (43.1) <sup>b</sup>	
Regular use of oxygen (n=6357)	3146 (49.5)	182 (61.5)	1142 (49.5)	878 (46.2)	753 (50.1)	191 (55.2)	0.5776
Daily productive cough <sup>e</sup> (n=6145)	2730 (44.4)	148 (52.7)	976 (43.8)	800 (43.2)	633 (43.5)	173 (53.1)	0.7782
Self-reported asthma (n=6623)	2315 (35.0)	72 (24.2)	720 (30.4)	688 (34.2)	661 (41.9)	174 (47.5) <sup>a</sup>	<0.0001
CCI categories (n=7087)							<0.0001
1	3885 (54.8)	184 (57.5)	1516 (61.2)	1216 (57.7)	809 (46.1)	160 (37.7)	

2	1380 (19.5)	49 (15.3)	410 (16.5)	390 (18.5)	423 (24.1)	108 (25.5)	
≥3	1822 (25.7)	87 (27.2)	553 (22.3)	503 (23.9)	523 (29.8)	156 (36.8)	
Exercise routine (n=6552)							<0.0001
Don't exercise at all	2235 (34.1)	133 (43.6)	708 (30.0)	594 (29.9)	618 (39.8)	182 (52.5) <sup>a</sup>	
Exercise irregularly	2067 (31.6)	83 (27.2)	708 (30.0)	670 (33.8)	508 (32.7)	98 (28.2) <sup>a</sup>	
Exercise regularly	2250 (34.3)	89 (29.2)	947 (40.1)	721 (36.3)	426 (27.5)	67 (19.3) <sup>a</sup>	
SGRQ Total, mean (SD) (n=6216)	44.06 (19.7)	50.5 (20.0)	42.5 (19.8)	42.6 (19.3)	46.1 (19.4)	49.0 (19.6) <sup>c</sup>	<0.0001
SGRQ Symptoms, mean (SD)	45.9 (23.5)	49.2 (23.4)	44.6 (23.4)	45.0 (23.2)	47.6 (23.9)	49.7 (23.2) <sup>c</sup>	<0.0001
SGRQ Activity, mean (SD)	62.7 (25.2)	70.2 (24.8)	60.6 (25.9)	60.6 (24.8)	65.7 (24.2)	69.0 (24.7) <sup>c</sup>	<0.0001
SGRQ Impact, mean (SD)	32.82 (19.6)	39.7 (20.8)	31.4 (19.4)	31.6 (19.3)	34.3 (19.6)	37.4 (20.3) <sup>c</sup>	<0.0001
SF-36, mean (SD) (n=5661)							
MCS	51.4 (10.6)	48.9 (11.7)	52 (10.1)	52.0 (10.2)	50.5 (11.1)	49.6 (11.5) <sup>c</sup>	<0.0001
PCS	36.9 (9.9)	34.3 (10.1)	38 (9.8)	38.0 (9.9)	35.2 (9.7)	32.0 (9.5) <sup>b</sup>	<0.0001

Data presented in frequencies and proportions unless otherwise noted.

BMI was classified per CDC guidelines into underweight (<18.5 kg/m<sup>2</sup>), healthy weight (18.5-<25 kg/m<sup>2</sup>), overweight (25-<30 kg/m<sup>2</sup>), obese (30-<40 kg/m<sup>2</sup>), and severely obese (≥40 kg/m<sup>2</sup>)

SGRQ- St. George's Respiratory Questionnaire, lower scores indicate better health; MCID=4 points

SF-36 MCS and PCS-36-Item Short Form Survey Physical Component Summary and a Mental Component Summary; average for the general population 50 (SD=10); higher scores indicate better health

Pairwise comparisons were conducted using Bonferroni-adjusted p-values for continuous variables and false discovery rate (FDR) correction for categorical variables, with notation reflecting significant differences between the severely obese group and other BMI categories:

<sup>a</sup> Significantly different from all other BMI groups; <sup>b</sup> Significantly different from all other BMI groups, except the underweight group

<sup>c</sup> Significantly different from all other BMI groups, except the underweight and obese groups; <sup>d</sup> Global P-values represent

comparisons across all levels of each categorical variable by BMI category (5 groups); <sup>e</sup>Over the past 2 years, have you coughed up sputum/mucus from your lungs on a daily basis for at least 3 months each year?

Table 2. Multivariable linear regression of SGRQ Total score by BMI and other covariates, n=4342

	Adjusted effect (SE)	95% Confidence Limits	p-value
Age (per 10 years)	-1.89 (0.27)	-2.42; -1.35	<.0001
0 exacerbations	REF		
1 exacerbation	4.89 (0.84)	3.25; 6.53	<.0001
≥2 exacerbations	12.64 (0.69)	11.28; 14.00	<.0001
CCI group 1	REF		
CCI group 2	1.97 (0.74)	0.53; 3.42	0.0075
CCI group ≥3	4.10 (0.67)	2.78; 5.42	<.0001
Never smoker	REF		
Ever smoker	7.21 (0.65)	5.93; 8.49	<.0001
Male	REF		
Female	0.29 (0.56)	-0.80; 1.39	0.5983
Normal weight	REF		
Underweight	7.20 (1.45)	4.35; 10.04	<.0001
Overweight	-0.26 (0.67)	-1.58; 1.06	0.6973
Obese	2.15 (0.73)	0.73; 3.58	0.0031
Severe obesity	3.89 (1.30)	1.35; 6.43	0.0027

BMI was classified per CDC guidelines into underweight (<18.5 kg/m<sup>2</sup>), healthy weight (18.5- <25 kg/m<sup>2</sup>), overweight (25-<30 kg/m<sup>2</sup>), obese (30-<40 kg/m<sup>2</sup>), and severely obese (≥40 kg/m<sup>2</sup>); CCI- Charlson comorbidity Index; SE- standard error

Figure 1. Self-reported exercise routine by five BMI categories (%)

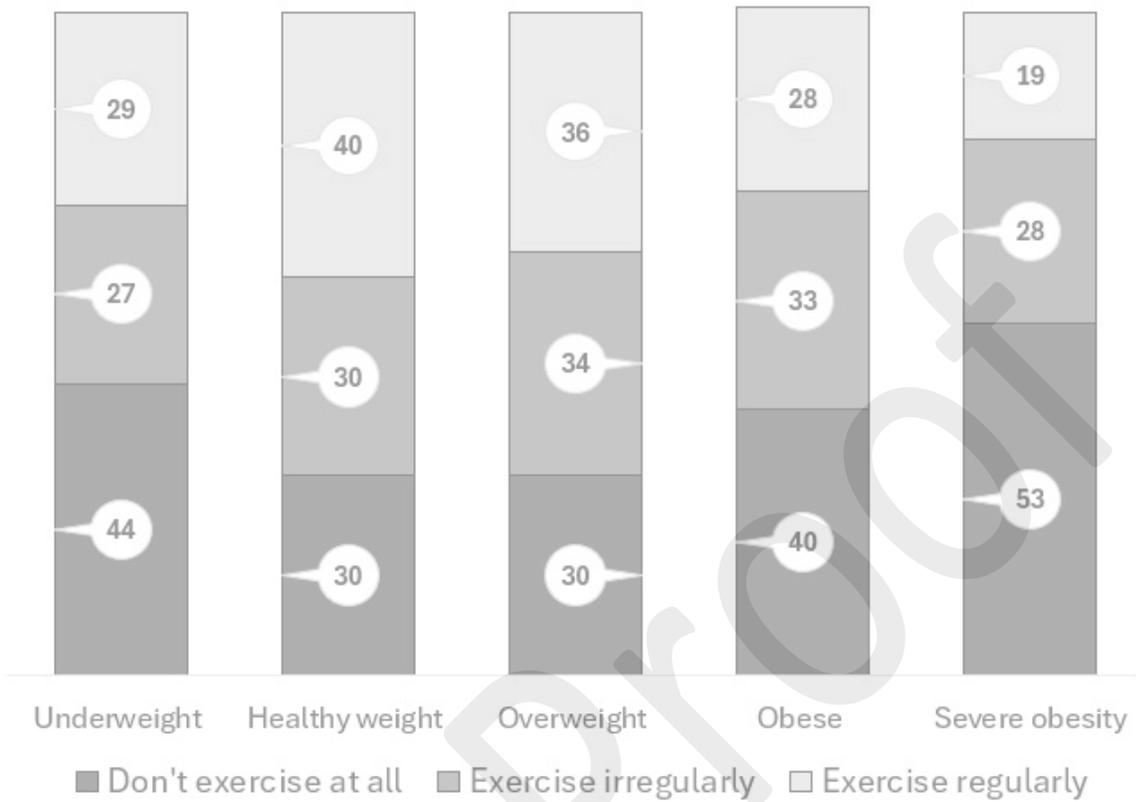
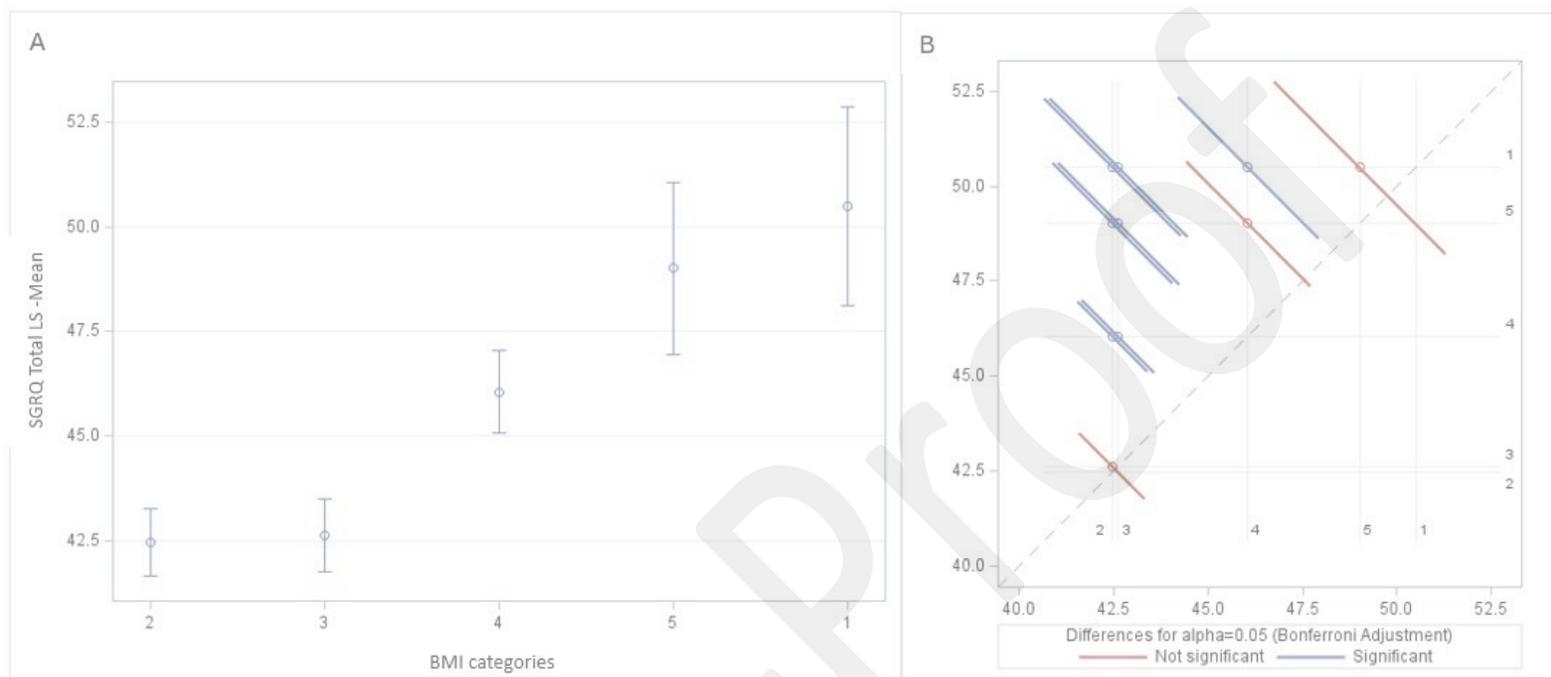
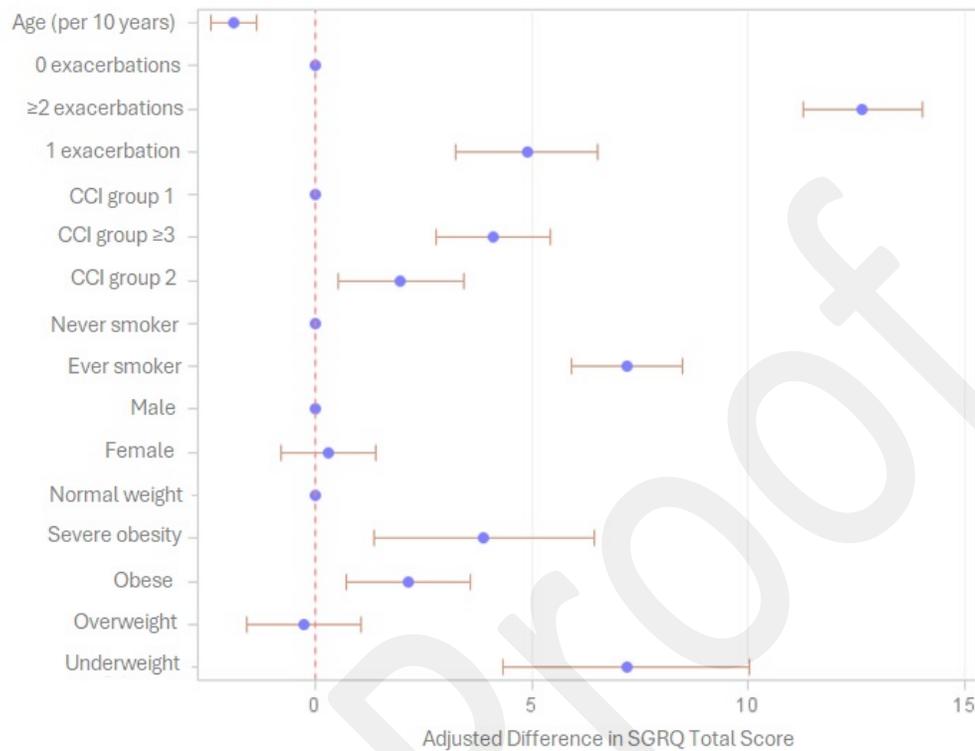


Figure 2. Unadjusted group differences in SGRQ Total scores by BMI category



BMI categories: 1-underweight, 2-normal, 3-overweight, 4-obese, 5-severe obesity; **Figure 2A** - This plot displays the unadjusted least-squares mean SGRQ total scores for each BMI category; **Figure 2B**- The diffogram shows pairwise comparisons of mean SGRQ total scores across BMI categories. Each line represents a comparison; red lines crossing the diagonal reference line indicate non-significant differences, while blue lines that do not cross indicate significant differences between groups. Higher SGRQ scores indicate worse health status.

Figure 3. Forest plot of adjusted associations with SGRQ Total score, n=4342



Adjusted differences in SGRQ Total score by BMI category, controlling for age, sex, smoking history, comorbidity burden, and exacerbation frequency. Higher SGRQ values indicate worse respiratory quality of life. Numerical effect estimates are presented in Table 2. CCI- Charlson Comorbidity Index;