

Online Supplement

Associations Between Muscle Weakness and Clinical Outcomes in Current and Former Smokers

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| | Entire Cohort (n=1,972) | Male (n=976) | Female (n=996) |
|---|------------------------------------|-------------------------|---------------------------|
| Age (y) | 69.0 (8.4) | 68.7 (8.3) | 69.2 (8.6) |
| Caucasian race (n, %) | 1,380 (70%) | 678 (69%) | 702 (70%) |
| BMI (kg/m²) | 29.0 (6.2) | 29.0 (5.6) | 29.0 (6.6) |
| Active smoker (n, %) | 657 (33%) | 329 (33%) | 328 (33%) |
| Total pack-years * | 40 (28-54) | 42 (30-59) | 39 (26-51) |
| Spirometry | | | |
| FEV₁/FVC | 0.66 (0.15) | 0.65 (0.15) | 0.68 (0.15) |
| FEV₁ predicted (%) | 78.4 (25.8) | 77.1 (26.1) | 79.7 (25.6) |
| FVC predicted (%) | 87.8 (19.9) | 86.8 (19.6) | 88.7 (20.2) |
| DLco predicted (%) | 74.4 (22.2) | 76.1 (23.5) | 72.7 (20.7) |
| LAA% below -950 HU | 6.8 (8.8) | 7.6 (9.2) | 6.1 (8.4) |
| CAT score * | 10 (5-17) | 10 (4-16) | 10 (5-17) |
| Comorbidity | | | |
| Cardiovascular disease (n, %) | 358 (18%) | 195 (20%) | 163 (16%) |
| Congestive heart failure (n, %) | 92 (5%) | 48 (5%) | 44 (4%) |
| Chronic kidney disease (n, %) | 91 (5%) | 42 (4%) | 49 (5%) |
| Diabetes mellitus (n, %) | 418 (21%) | 225 (23%) | 193 (19%) |
| Malignancy (n, %) | 297 (15%) | 140 (14%) | 157 (16%) |
| Osteoarthritis (n, %) | 781 (40%) | 310 (32%) | 471 (47%) |
| Joint pain (n, %) | 874 (44%) | 386 (40%) | 488 (49%) |
| STS (repetitions) | 10.7 (4.2) | 10.8 (4.2) | 10.6 (4.1) |
| 6MWD (m) | 392 (123) | 402 (126) | 382 (119) |
| HGS (kg) | 29.0 (9.9) | 35.4 (9.0) | 22.7 (6.1) |
| SGRQ score * | 18 (6-37) | 16 (5-35) | 19 (6-38) |
| SF-36 General Health score * | 67 (47-82) | 67 (47-82) | 67 (50-82) |
| SF-36 Physical Functioning score * | 70 (40-90) | 75 (45-90) | 65 (40-88) |
| History of severe exacerbation (n,%) | 173 (9%) | 87 (9%) | 86 (8%) |
| Prospective severe exacerbation (n, %) | 73 (5%) | 37 (5%) | 36 (4%) |

Supplemental Table 1. Study visit characteristics by gender. Values are listed as mean (standard deviation), unless otherwise specified by *, indicating median (interquartile range).

| Standardized β | | | | | | | | | |
|----------------------|---------------------------|---------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | SGRQ Impact | SGRQ Symptom | SGRQ Active | SF-36 RP | SF-36 RE | SF-36 SF | SF-36 BP | SF-36 VT | SF-36 MH |
| STS | -0.21, <i>p</i> <0.001 | -0.12, <i>p</i> <0.001 | -0.25, <i>p</i> <0.001 | 0.32, <i>p</i> <0.001 | 0.24, <i>p</i> <0.001 | 0.25, <i>p</i> <0.001 | 0.26, <i>p</i> <0.001 | 0.20, <i>p</i> <0.001 | 0.13, <i>p</i> <0.001 |
| HGS | -0.19, <i>p</i> <0.001 | -0.12, <i>p</i> <0.001 | -0.16, <i>p</i> <0.001 | 0.18, <i>p</i> <0.001 | 0.17, <i>p</i> <0.001 | 0.16, <i>p</i> <0.001 | 0.17, <i>p</i> <0.001 | 0.18, <i>p</i> <0.001 | 0.16, <i>p</i> <0.001 |

Supplemental Table 2. There are larger magnitudes of effect sizes for STS than for HGS and clinical

outcomes. Multivariable regression modeling was used to describe standardized coefficient (β) values.

Covariates include age, BMI, FEV₁% predicted. GH = General Health. PF = Physical Function. RP = Role

Physical Functioning. RE = Role Emotional Functioning. SF = Social Function. BP = Body Pain. VT =

Vitality. MH = Mental Health.

| | Standardized β | | | | OR | | HR |
|--------------------|--------------------------|---------------------------|--------------------------|--------------------------|--|--|---|
| | 6MWD | SGRQ | SF-36 GH | SF-36 PF | History of Severe Exacerbation | Prospective Severe Exacerbation | Mortality |
| STS: Male | 0.44, <i>p</i> <0.001 | -0.18, <i>p</i> <0.001 | 0.15, <i>p</i> <0.001 | 0.31, <i>p</i> <0.001 | 0.99 (0.92-1.06), <i>p</i> =0.68 | 1.06 (0.96-1.17), <i>p</i> =0.25 | 0.91 (0.79-1.04), <i>p</i> =0.18 |
| STS: Female | 0.45, <i>p</i> <0.001 | -0.28, <i>p</i> <0.001 | 0.23, <i>p</i> <0.001 | 0.40, <i>p</i> <0.001 | 0.91 (0.85-0.98), <i>p</i> =0.01 | 0.97 (0.86-1.09), <i>p</i> =0.58 | 0.67 (0.54-0.83), <i>p</i> <0.001 |
| HGS: Male | 0.21, <i>p</i> <0.001 | -0.13, <i>p</i> <0.001 | 0.08, <i>p</i> =0.02 | 0.19, <i>p</i> <0.001 | 0.98 (0.95-1.01), <i>p</i> =0.12 | 0.99 (0.95-1.03), <i>p</i> =0.67 | 0.95 (0.90-1.01), <i>p</i> =0.07 |
| HGS: Female | 0.19, <i>p</i> <0.001 | -0.16, <i>p</i> <0.001 | 0.14, <i>p</i> <0.001 | 0.21, <i>p</i> <0.001 | 0.95 (0.91-1.00), <i>p</i> =0.05 | 0.95 (0.88-1.02), <i>p</i> =0.13 | 0.94 (0.83-1.07), <i>p</i> =0.38 |

Supplemental Table 3. Females have larger magnitude effect sizes between weakness measures and

clinical outcomes compared with males. Multivariable regression modeling was used to describe

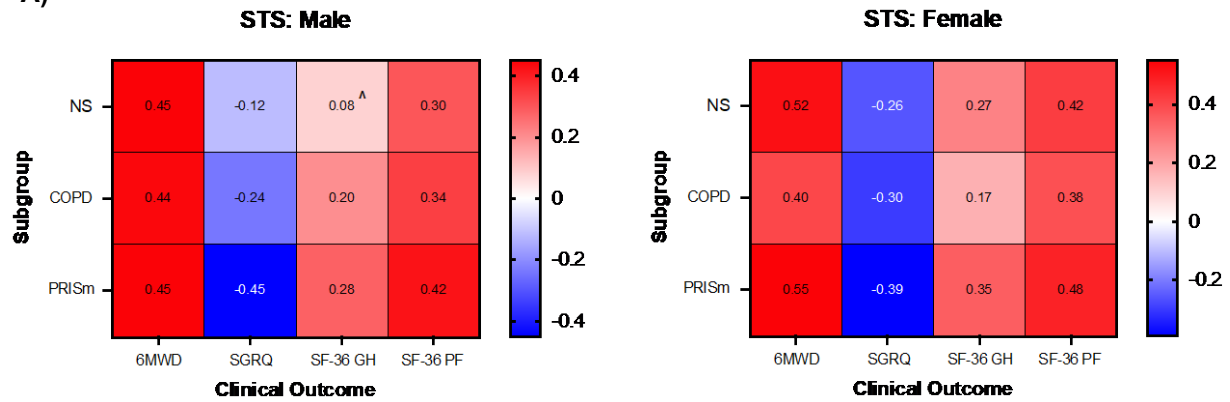
standardized coefficient (β) values, odds ratios (OR), and hazard ratios (HR) with associated 95% confidence

intervals. Covariates include age, BMI, FEV₁% predicted.

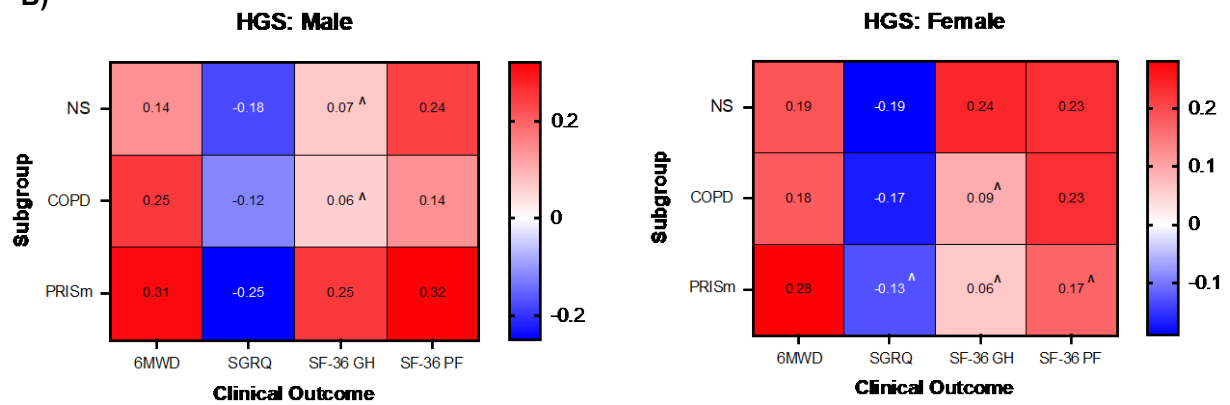
| | PRISm Quartile 1 (n=59) | PRISm Quartile 2 (n=58) | PRISm Quartile 3 (n=59) | PRISm Quartile 4 (n=58) |
|---|--|--|--|--|
| Age (y) | 64.1 (6.6) | 65.0 (7.2) | 65.2 (7.9) | 66.9 (7.5) |
| Male sex (n, %) | 33 (56%) | 30 (52%) | 23 (39%) | 23 (40%) |
| Caucasian race (n, %) | 26 (44%) | 26 (45%) | 31 (53%) | 35 (60%) |
| BMI (kg/m²) | 34.0 (8.0) | 31.9 (5.9) | 31.6 (6.5) | 31.5 (5.9) |
| Active smoker (n, %) | 26 (44%) | 26 (45%) | 30 (51%) | 23 (40%) |
| Total pack-years * | 40 (29-64) | 36 (27-52) | 38 (28-48) | 36 (23-47) |
| Spirometry | | | | |
| FEV₁/FVC | 0.76 (0.05) | 0.76 (0.05) | 0.76 (0.05) | 0.76 (0.04) |
| FEV₁ predicted (%) | 57.3 (6.2) | 68.3 (2.0) | 73.7 (1.4) | 78.3 (1.1) |
| FVC predicted (%) | 57.8 (7.4) | 69.2 (5.1) | 74.5 (5.3) | 78.2 (4.6) |
| DLco predicted (%) | 74.4 (19.7) | 68.9 (19.0) | 77.7 (17.4) | 77.6 (19.0) |
| Supplemental oxygen (n, %) | 243 (12%) | 223 (24%) | 9 (1%) | 11 (5%) |
| % Emphysema (LAA% -950 HU) | 2.0 (3.7) | 1.9 (3.6) | 1.6 (2.0) | 2.6 (2.8) |
| CAT score * | 11 (5-18) | 11 (5-18) | 12 (7-19) | 9 (5-16) |
| Comorbidity | | | | |
| Cardiovascular disease (n, %) | 358 (18%) | 198 (21%) | 116 (14%) | 44 (19%) |
| Congestive heart failure (n, %) | 92 (5%) | 61 (7%) | 17 (2%) | 14 (6%) |
| Chronic kidney disease (n, %) | 91 (5%) | 45 (5%) | 32 (4%) | 14 (6%) |
| Diabetes mellitus (n, %) | 418 (21%) | 175 (19%) | 160 (20%) | 83 (35%) |
| Malignancy (n, %) | 297 (15%) | 173 (19%) | 95 (12%) | 29 (12%) |
| Osteoarthritis (n, %) | 18 (31%) | 22 (38%) | 27 (46%) | 28 (48%) |
| Joint pain (n, %) | 26 (44%) | 29 (50%) | 33 (56%) | 30 (52%) |
| STS (repetitions) | 8.9 (3.5) | 9.5 (4.4) | 9.0 (3.8) | 10.6 (3.8) |
| 6MWD (m) | 349 (107) | 363 (121) | 365 (112) | 407 (123) |
| HGS (kg) | 29.1 (9.6) | 27.5 (8.7) | 28.7 (9.6) | 28.4 (9.7) |
| SGRQ score * | 31 (12-45) | 22 (9-38) | 23 (10-40) | 16 (5-27) |
| SF-36 General Health score * | 57 (35-77) | 59 (40-75) | 57 (42-77) | 67 (47-82) |
| SF-36 Physical Functioning score * | 60 (35-85) | 58 (30-75) | 55 (35-80) | 65 (40-85) |
| History of severe exacerbation (n,%) | 6 (10%) | 4 (7%) | 3 (5%) | 5 (9%) |
| Prospective severe exacerbation (n, %) | 1 (3%) | 4 (9%) | 0 (0%) | 0 (0%) |

Supplemental Table 4. Participants with PRISm in the lowest FEV₁% quartile have greater clinical symptom burden than participants with PRISm in the highest FEV₁% quartile. Quartile 1 represents FEV₁% predicted values in lowest 25% and quartile 4 represents FEV₁% predicted values in the highest 25%. Values are listed as mean (standard deviation), unless otherwise specified by *, indicating median (interquartile range).

A)



B)



Supplemental Figure 1. Females have larger magnitude effect sizes between weakness measures and clinical outcomes compared with males. Heatmap characterizing standardized coefficient (β) values for correlations between subgroup (normal spirometry, COPD, PRISm) and clinical outcomes (6MWD, SGRQ, SF-36 scores). All β values were associated with $p < 0.01$, unless otherwise specified by ^A. Covariates include age, sex, BMI, FEV₁% predicted. NS = normal spirometry.