

SUPPLEMENTARY MATERIAL

Note on missing data:

Spirometry (FEV1 and FVC) was performed in all 413 patients at baseline, and further each 6 months in 360, 387, 353, 364, 332 and 334 patients, respectively. 18 patients had only one measurement and were not included in the longitudinal analyses. Median GDF15 was slightly higher in those 18 patients; 0.97 ng/mL vs 0.85 ng/mL ($p=0.11$), and median FEV1% and FVC% were both slightly lower; 41 % vs 50 % ($p=0.06$), and 82 % vs 86 % ($p=0.10$) respectively, compared to patients with two or more measurements.

Bioelectrical impedance measurements (FFMI) was performed in 410 patients at baseline, and further each year in 374, 340 and 338 patients, respectively. 30 patients had only one or none measurements, and were not included in the longitudinal analyses. Median GDF15 was significantly higher in those 30 patients; 1.01 ng/mL vs 0.84 ng/mL ($p=0.01$), and median FFMI was slightly lower; 16.0 vs 16.9 ($p=0.11$) respectively, compared to patients with two or more measurements.

Note on study population:

The population of Western Norway is homogenous, especially among people above 50. Out of 413 patients with measured GDF15, 412 were Caucasians.

Table S1, supplementary data to table 3. The unadjusted and adjusted hazard ratios (95% CI) for death among COPD patients, estimated by cox-regression

| Baseline explanatory variables | Unadjusted HR | (95% CI) | p | Adjusted HR | 95% CI | p |
|---|---------------|----------------|--------|-------------|----------------|--------|
| <i>Sex</i> | | | | | | |
| Women | 1 | | | 1 | | |
| Men | 1.45 | (1.03 to 2.06) | 0.03 | 1.03 | (0.71 to 1.49) | 0.87 |
| <i>Age</i> | | | | | | |
| per 10 years increase | 3.32 | (2.50 to 4.42) | <0.001 | 2.31 | (1.67 to 3.19) | <0.001 |
| <i>Body Composition</i> | | | | | | |
| Normal | 1 | | | 1 | | |
| Cachectic | 2.49 | (1.74 to 3.58) | <0.001 | 1.63 | (1.08 to 2.45) | 0.02 |
| Obese | 1.99 | (1.28 to 3.11) | 0.002 | 1.88 | (1.17 to 3.03) | 0.01 |
| <i>Smoking</i> | | | | | | |
| Ex | 1 | | | 1 | | |
| Current | 0.68 | (0.49 to 0.96) | 0.03 | 0.84 | (0.57 to 1.23) | 0.36 |
| <i>GOLD 2007 classification</i> | | | | | | |
| FEV1 50-80% | 1 | | | 1 | | |
| FEV1 30-50% | 3.27 | (2.20 to 4.85) | <0.001 | 2.73 | (1.80 to 4.16) | <0.001 |
| FEV1 <30% | 5.56 | (3.40 to 9.07) | <0.001 | 5.23 | (2.98 to 9.15) | <0.001 |
| <i>Charlson comorbidity Score</i> | | | | | | |
| 1 | 1 | | | 1 | | |
| 2 | 1.40 | (0.93 to 2.09) | 0.10 | 0.97 | (0.66 to 1.53) | 0.98 |
| 3 | 2.21 | (1.39 to 3.50) | 0.001 | 1.10 | (0.66 to 1.85) | 0.71 |
| 4+ | 3.23 | (0.94 to 5.38) | <0.001 | 2.23 | (1.27 to 3.99) | 0.007 |
| <i>Exacerbations 12 months before inclusion</i> | | | | | | |
| 0-1 | 1 | | | 1 | | |
| 2+ | 1.69 | (1.16 to 2.49) | 0.007 | 0.82 | (0.53 to 1.28) | 0.38 |
| <i>GDF15</i> | | | | | | |
| low levels * | 1 | | | 1 | | |
| high levels | 3.00 | (2.10 to 4.27) | <0.001 | 2.07 | (1.40 to 3.05) | <0.001 |

*cut off median

Table S2. Predictors for yearly change in FEV1, in % of predicted. Estimated by bivariable and multivariable random effects linear regression models.

| Baseline explanatory variables | Unadjusted | | | Adjusted | | |
|---|------------|------------------|---------|----------|------------------|---------|
| | coeff. | 95 % CI | p-value | coeff. | 95 % CI | p-value |
| <i>Constant</i> | 51.7 | | | 66.9 | | |
| <i>Time</i> | -0.65 | (-1.01 to -0.28) | | -3.32 | (-6.02 to -0.63) | 0.02 |
| <i>GDF15[#]</i> | | | | | | |
| high levels | -4.49 | (-7.21 to -1.78) | 0.001 | -1.02 | (-2.39 to 0.35) | 0.14 |
| high levels * time | -0.93 | (-1.46 to -0.41) | <0.001 | -1.06 | (-1.62 to -0.50) | <0.001 |
| <i>Sex</i> | | | | | | |
| Women | 0 | | | 0 | | |
| Men | -0.57 | (-1.11 to -0.04) | 0.04 | -0.65 | (-1.20 to -0.11) | 0.02 |
| <i>Age</i> | | | | | | |
| per 10 years increase | 0.22 | (-0.16 to 0.60) | 0.26 | 0.50 | (0.07 to 0.94) | 0.02 |
| <i>Body Composition</i> | | | | | | |
| Normal | 0 | | | 0 | | |
| Cachectic | -0.72 | (-1.33 to -0.11) | 0.02 | -0.67 | (-1.33 to -0.02) | 0.05 |
| Obese | -0.33 | (-1.06 to 0.41) | 0.38 | -0.49 | (-1.25 to 0.26) | 0.20 |
| <i>Smoking</i> | | | | | | |
| Ex | 0 | | | 0 | | |
| Current | -0.66 | (-1.19 to -0.13) | 0.01 | -0.27 | (-0.85 to 0.31) | 0.36 |
| <i>GOLD 2007 classification</i> | | | | | | |
| FEV1 50-80% | 0 | | | 0 | | |
| FEV1 30-50% | 0.26 | (-0.29 to 0.82) | 0.36 | 0.31 | (-0.25 to 0.86) | 0.28 |
| FEV1 <30% | -0.12 | (-1.06 to 0.81) | 0.79 | 0.16 | (-0.79 to 1.11) | 0.74 |
| <i>Charlson comorbidity Score</i> | | | | | | |
| 1 | 0 | | | 0 | | |
| 2 | 0.40 | (-0.23 to 1.04) | 0.21 | 0.47 | (-0.17 to 1.11) | 0.15 |
| 3 | 0.29 | (-0.55 to 1.13) | 0.50 | 0.55 | (-0.33 to 1.44) | 0.22 |
| 4+ | -0.36 | (-1.47 to 0.74) | 0.52 | -0.24 | (-1.37 to 0.90) | 0.68 |
| <i>Exacerbations 12 months before inclusion</i> | | | | | | |
| 0-1 | 0 | | | 0 | | |
| 2+ | 0.09 | (-0.61 to 0.80) | 0.79 | 0.22 | (-0.51 to 0.95) | 0.56 |

[#] GDF15 is shown as both as a coefficient for GDF15 levels at baseline, and as a GDF15/time-interaction variable, all other variables are only shown as time-interaction variables

Table S3. Predictors for yearly change in FVC, in % of predicted. Estimated by bivariable and multivariable random effects linear regression models.

| Baseline explanatory variables | Unadjusted | | | Adjusted | | |
|---|------------|------------------|---------|----------|------------------|---------|
| | coeff. | 95 % CI | p-value | coeff. | 95 % CI | p-value |
| <i>Constant</i> | 87.3 | | | 94.5 | | |
| <i>Time</i> | -1.44 | (-1.89 to -0.29) | | -1.79 | (-5.89 to 2.31) | 0.39 |
| <i>GDF15[#]</i> | | | | | | |
| high levels | -3.37 | (-6.44 to -0.29) | 0.03 | -0.37 | (-3.13 to 2.40) | 0.79 |
| high levels * time | -1.09 | (-1.86 to -0.29) | 0.01 | -1.29 | (-2.14 to -0.43) | 0.003 |
| <i>Sex</i> | | | | | | |
| Women | 0 | | | 0 | | |
| Men | -0.64 | (-1.45 to 0.18) | 0.13 | -0.49 | (-1.32 to 0.35) | 0.25 |
| <i>Age</i> | | | | | | |
| per 10 years increase | -0.30 | (-0.88 to 0.28) | 0.31 | 0.074 | (-0.58 to 0.73) | 0.82 |
| <i>Body Composition</i> | | | | | | |
| Normal | 0 | | | 0 | | |
| Cachectic | -0.64 | (-1.60 to 0.30) | 0.18 | -0.28 | (-1.28 to 0.73) | 0.59 |
| Obese | 0.01 | (-1.11 to 1.14) | 0.98 | -0.25 | (-1.40 to 0.90) | 0.67 |
| <i>Smoking</i> | | | | | | |
| Ex | 0 | | | 0 | | |
| Current | 0.09 | (-0.72 to 0.90) | 0.83 | 0.31 | (-0.57 to 1.19) | 0.49 |
| <i>GOLD 2007 classification</i> | | | | | | |
| FEV1 50-80% | 0 | | | 0 | | |
| FEV1 30-50% | -0.50 | (-1.34 to 0.33) | | -0.46 | (-1.31 to 0.39) | 0.29 |
| FEV1 <30% | -1.29 | (-2.69 to 0.11) | 0.07 | -1.35 | (-2.82 to 0.13) | 0.07 |
| <i>Charlson comorbidity Score</i> | | | | | | |
| 1 | 0 | | | 0 | | |
| 2 | 0.11 | (0.15 to 2.07) | 0.02 | 1.26 | (0.29 to 2.24) | 0.01 |
| 3 | 0.20 | (-1.08 to 1.47) | 0.76 | 0.84 | (-0.51 to 2.19) | 0.22 |
| 4+ | -0.20 | (-1.86 to 1.47) | 0.82 | 0.19 | (-1.54 to 1.91) | 0.83 |
| <i>Exacerbations 12 months before inclusion</i> | | | | | | |
| 0-1 | 0 | | | 0 | | |
| 2+ | 0.63 | (-0.44 to 1.70) | 0.25 | 0.97 | (-0.14 to 2.08) | 0.09 |

[#] GDF15 is shown as both as a coefficient for GDF15 levels at baseline, and as a GDF15/time-interaction variable, all other variables are only shown as time-interaction variables

Table S4. Predictors for yearly change in FFMI in kg/m2. Estimated by bivariable and multivariable random effects linear regression models.

| Baseline explanatory variables | Unadjusted | | | Adjusted | | |
|---|------------|-------------------|---------|----------|------------------|---------|
| | coeff. | 95 % CI | p-value | coeff. | 95 % CI | p-value |
| Constant | 17.6 | | | 19.4 | | |
| Time | -0.05 | (-0.10 to 0.01) | 0.11 | 0.38 | (-0.3 to 0.80) | 0.07 |
| <i>GDF15</i> [#] | | | | | | |
| high levels | -1.15 | (-1.76 to 0.53) | <0.001 | -0.40 | (-0.72 to -0.08) | 0.01 |
| high levels * time | -0.03 | (-0.11 to 0.06) | 0.51 | 0.01 | (-0.07 to 0.10) | 0.77 |
| Sex | | | | | | |
| Women | 0 | | | 0 | | |
| Men | -0.004 | (-0.09 to 0.08) | 0.92 | 0.01 | (-0.07 to 0.10) | 0.76 |
| Age | | | | | | |
| per 10 years increase | -0.009 | (-0.01 to -0.003) | 0.005 | -0.07 | (-0.14 to 0.003) | 0.04 |
| <i>Body Composition</i> | | | | | | |
| Normal | 0 | | | 0 | | |
| Cachectic | -0.06 | (-0.15 to 0.04) | 0.23 | -0.03 | (-0.13 to 0.08) | 0.61 |
| Obese | 0.20 | (0.08 to 0.31) | 0.001 | 0.20 | (0.08 to 0.32) | 0.001 |
| <i>Smoking</i> | | | | | | |
| Ex | 0 | | | 0 | | |
| Current | 0.03 | (-0.05 to 0.12) | 0.43 | 0.02 | (-0.07 to 0.11) | 0.66 |
| <i>GOLD 2007 classification</i> | | | | | | |
| FEV1 50-80% | 0 | | | 0 | | |
| FEV1 30-50% | -0.11 | (-0.20 to -0.03) | 0.01 | -0.09 | (-0.18 to -0.01) | 0.03 |
| FEV1 <30% | -0.19 | (-0.34 to -0.05) | 0.01 | -0.16 | (-0.31 to -0.01) | 0.03 |
| <i>Charlson comorbidity Score</i> | | | | | | |
| 1 | 0 | | | 0 | | |
| 2 | 0.008 | (-0.09 to 0.11) | 0.87 | -0.001 | (-0.10 to -0.10) | 0.98 |
| 3 | 0.10 | (-0.03 to 0.24) | 0.13 | 0.09 | (-0.05 to -0.23) | 0.22 |
| 4+ | -0.05 | (-0.23 to 0.13) | 0.57 | -0.08 | (-0.27 to -0.10) | 0.37 |
| <i>Exacerbations 12 months before inclusion</i> | | | | | | |
| 0-1 | 0 | | | 0 | | |
| 2+ | -0.02 | (-0.13 to 0.10) | 0.76 | 0.01 | (-0.10 to 0.13) | 0.82 |

[#] GDF15 is shown as a both as a coefficient for GDF15 levels at baseline, and as a GDF15/time-interaction variable, all other variables are only shown as time-interaction variables