**SUPPLEMENTARY INFORMATION**

**TITLE: The impact of COPD exacerbations in the year following pulmonary rehabilitation: secondary analysis of a randomised controlled trial**

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**Exacerbation definition**

Coding of exacerbations was performed by one researcher (BW) and checked by a second researcher (AH). Data from hospital and pharmacy usage for each participant were first display in chronological order starting from the first day of the 12-month follow-up period. A single exacerbation was counted for 15 days from the start of exacerbation, after this period it was considered as another exacerbation. Exacerbations were considered:

**Moderate exacerbations:** Purchase of prescription medication (oral corticosteroids and/or antibiotics) was considered as moderate exacerbation (Table 1). Collection of inhalers commonly used to treat COPD (ipratropium or inhaled corticosteroids) was not considered as an exacerbation. Medication prescribed repeatedly over the following months was not considered as a new exacerbation (e.g. long-term antibiotics). If antibiotics were collected on the same day as any topical antibiotics it was not registered as exacerbation once it was assumed that the medication was prescribed for reasons other than respiratory.

**Severe exacerbations:** Hospital admission or emergency department visit for a respiratory condition was considered to be a severe exacerbation (Table 1). Antibiotics and/or oral corticosteroids collected during admission were not registered as new exacerbation. If the participant had collected ipratropium or inhaled corticosteroids within 15 days before admission, this was considered to denote a single exacerbation and the exacerbation was counted as severe.

**Table S1-** *Exacerbation definition based on health care usage*

|  |  |
| --- | --- |
| **Severity** | **Exacerbation definition based on health care usage** |
| Moderate | Collected a new prescription for oral corticosteroids and/or antibiotics based on the Pharmaceutical Benefits Scheme (Australia) data. |
| Severe | Respiratory-related admission to hospital or emergency department visit with a primary discharge diagnosis of COPD. |

Legend: Exacerbation definitions are based on the GOLD strategy(1). COPD: chronic obstructive pulmonary disease

1. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary <https://goldcopd.org/>: GOLD; 2020

**Table S2-** *Multiple regression analysis - impact of any exacerbation during follow-up on clinical outcomes at 12 months.*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Variable** | | **B** | **95%CI** | **Standardised Beta** | **p** | **R2 for model** |
| CRQ Total |  | |  |  |  |  | 0.18 |
|  | Constant | | 42.197 | 0.324 to 84.070 |  | 0.05 |  |
|  | Exacerbation during follow-up | | -4.680 | -13.639 to 4.279 | -0.091 | 0.30 |  |
|  | Group allocation | | -0.165 | -7.224 to 6.893 | -0.004 | 0.96 |  |
|  | Age | | -0.55 | -0.500 to 0.390 | -0.023 | 0.81 |  |
|  | Gender | | 1.919 | -5.214 to 9.052 | 0.046 | 0.60 |  |
|  | FEV1 | | 4.771 | -1.784 to 11.327 | 0.129 | 0.15 |  |
|  | Smoking status | | -2.830 | -12.179 to 6.520 | -0.053 | 0.55 |  |
|  | Baseline CRQ Total | | -0.406 | -0.603 to -0.208 | -0.375 | <0.001 |  |
| CRQ Dyspnoea |  | |  |  |  |  | 0.18 |
|  | Constant | | 8.529 | -4.365 to 21.423 |  |  |  |
|  | Exacerbation during follow-up | | -0.364 | -3.128 to 2.400 | -0.023 | 0.80 |  |
|  | Group allocation | | -0.10 | -2.207 to 2.186 | -0.001 | 0.99 |  |
|  | Age | | -0.070 | -0.200 to 0.060 | -0.097 | 0.29 |  |
|  | Gender | | 2.559 | 0.364 to 4.754 | 0.199 | 0.02 |  |
|  | FEV1 | | 1.330 | -0.702 to 3.361 | 0.116 | 0.20 |  |
|  | Smoking status | | -1.141 | -4.074 to 1.791 | -0.069 | 0.44 |  |
|  | Baseline CRQ Dyspnoea | | -0.382 | -0.583 to -0.182 | -0.327 | <0.001 |  |
|  |  |
| CRQ Fatigue |  | |  |  |  |  | 0.25 |
|  | Constant | | 9.301 | -1.738 to 20.340 |  | 0.10 |  |
|  | Exacerbation during follow-up | | -1.776 | -4.100 to 0.548 | -0.127 | 0.13 |  |
|  | Group allocation | | 0.283 | -1.562 to 2.128 | 0.025 | 0.76 |  |
|  | Age | | 0.000 | -0.111 to 0.111 | 0.000 | 0.99 |  |
|  | Gender | | 0.028 | -1.849 to 1.905 | 0.003 | 0.98 |  |
|  | FEV1 | | 0.658 | -1.071 to 2.387 | 0.065 | 0.45 |  |
|  | Smoking status | | -0.042 | -2.469 to 2.385 | -0.003 | 0.97 |  |
|  | Baseline CRQ Fatigue | | -0.544 | -0.742 to -0.346 | -0.469 | <0.001 |  |
|  |  |
| CRQ Emotional |  | |  |  |  |  | 0.25 |
|  | Constant | | 15.528 | 0.210 to 30.847 |  | 0.05 |  |
|  | Exacerbation during follow-up | | -1.654 | -4.939 to 1.631 | -0.084 | 0.32 |  |
|  | Group allocation | | -0.182 | -2.761 to 2.417 | -0.011 | 0.89 |  |
|  | Age | | 0.029 | -0.134 to 0.192 | 0.032 | 0.73 |  |
|  | Gender | | -0.914 | -3.540 to 1.711 | -0.058 | 0.49 |  |
|  | FEV1 | | 1.718 | 0.697 to 4.133 | 0.122 | 0.16 |  |
|  | Smoking status | | 0-285 | -3.702 to 3.312 | -0.014 | 0.87 |  |
|  | Baseline CRQ Emotional | | -0.427 | -0.585 to -0.268 | -0.479 | <0.001 |  |
|  |  |
| CRQ Mastery |  | |  |  |  |  | 0.26 |
|  | Constant | | 10.682 | 0.287 to 21.078 |  | 0.04 |  |
|  | Exacerbation during follow-up | | -1.164 | -3.400 to 1.073 | -0.086 | 0.31 |  |
|  | Group allocation | | -0.305 | -2.083 to 1.473 | -0.028 | 0.74 |  |
|  | Age | | 0.035 | -0.076 to 0.145 | 0.056 | 0.53 |  |
|  | Gender | | -0.026 | -1.802 to 1.750 | -0.002 | 0.98 |  |
|  | FEV1 | | 1.040 | -0.633 to 2.713 | 0.107 | 0.22 |  |
|  | Smoking status | | -1.333 | -3.673 to 1.006 | -0.095 | 0.26 |  |
|  | Baseline CRQ Mastery | | -0.516 | -0.687 to -0.344 | -0.516 | <0.001 |  |
|  |  |
| 6MWD |  | |  |  |  |  | 0.05 |
|  | Constant | | 79.674 | -120.165 to 279.514 |  |  |  |
|  | Exacerbation during follow-up | | -12.007 | -51.164 to 27.150 | -0.608 | 0.54 |  |
|  | Group allocation | | 10.908 | -19.821 to 41.636 | 0.069 | 0.48 |  |
|  | Age | | -0.932 | -2.788 to 0.924 | -0.105 | 0.32 |  |
|  | Gender | | 9.972 | -21.385 to 41.328 | 0.063 | 0.53 |  |
|  | FEV1 | | 22.070 | -9.473 to 53.613 | 0.154 | 0.17 |  |
|  | Smoking status | | -9.103 | -49.727 to 31.521 | -0.045 | 0.67 |  |
|  | Baseline 6MWD | | -0.131 | -0.289 to 0.028 | -0.182 | 0.11 |  |
|  |  |
| mMRC |  | |  |  |  |  | 0.19 |
|  | Constant | | 2.537 | 0.024 to 5.051 |  | 0.05 |  |
|  | Exacerbation during follow-up | | 0.213 | -0.321 to 0.747 | 0.070 | 0.43 |  |
|  | Group allocation | | 0.232 | -0.184 to 0.648 | 0.096 | 0.27 |  |
|  | Age | | -0.006 | -0.030 to 0.019 | -0.043 | 0.63 |  |
|  | Gender | | -0.582 | -0.998 to -0.166 | -0.239 | 0.01 |  |
|  | FEV1 | | -0.305 | -0.708 to 0.097 | -0.138 | 0.14 |  |
|  | Smoking status | | -0.038 | -0.583 to 0.507 | -0.012 | 0.89 |  |
|  | Baseline MMRC | | -0.604 | -0.862 to -0.346 | -0.422 | <0.001 |  |
|  |  | |  |  |  |  |  |
| Total MVPA |  | |  |  |  |  | 0.24 |
|  | Constant | | -249.339 | -1571.824 to 1073.146 |  | 0.70 |  |
|  | Exacerbation during follow-up | | -172.798 | -476.660 to 131.064 | -0.222 | 0.25 |  |
|  | Group allocation | | -65.390 | -317.204 to 186.425 | -0.093 | 0.60 |  |
|  | Age | | 1.983 | -12.732 to 16.699 | 0.052 | 0.78 |  |
|  | Gender | | -49.281 | -314.425 to 215.863 | -0.069 | 0.71 |  |
|  | FEV1 | | 16.127 | -257.611 to 289.864 | 0.021 | 0.91 |  |
|  | Smoking status | | 332.715 | 13.351 to 652.079 | 0.398 | 0.04 |  |
|  | Baseline MVPA total | | -0.224 | -0.454 to 0.005 | -0.389 | 0.06 |  |
|  |  |
| Duration MVPA Bouts |  | |  |  |  |  | 0.19 |
|  | Constant | | 358.779 | -332.380 to 1049.938 |  | 0.30 |  |
|  | Exacerbation during follow-up | | -125.083 | -294.759 to 44.593 | -0.305 | 0.14 |  |
|  | Group allocation | | -38.517 | -175.508 to 98.475 | -0.104 | 0.57 |  |
|  | Age | | -2.958 | -10.924 to 5.007 | -0.148 | 0.45 |  |
|  | Gender | | -47.282 | -190.759 to 96.196 | -0.125 | 0.51 |  |
|  | FEV1 | | -60.199 | -208.920 to 88.523 | -0.152 | 0.41 |  |
|  | Smoking status | | 119.502 | -63.504 to 302.508 | 0.271 | 0.19 |  |
|  | Baseline MVPA bouts | | -0.145 | -0.393 to 0.104 | -0.252 | 0.24 |  |
|  |  |
|  |  | |  |  |  |  | 0.27 |
| Total Sedentary time | Constant | | 3520.561 | -1737.077 to 8778.199 |  | 0.18 |  |
|  | Exacerbation during follow-up | | -396.690 | -1596.337 to 802.957 | -0.121 | 0.50 |  |
|  | Group allocation | | -232.550 | -1329.880 to 864.780 | -0.078 | 0.67 |  |
|  | Age | | 16.996 | -55.733 to 89.726 | 0.106 | 0.64 |  |
|  | Gender | | -490.499 | -1647.082 to 666.084 | -0.162 | 0.39 |  |
|  | FEV1 | | 49.520 | -1044.784 to 1143.823 | 0.016 | 0.93 |  |
|  | Smoking status | | -313.326 | -1633.277 to 1006.625 | -0.089 | 0.63 |  |
|  | Baseline sedentary time | | -0.737 | -1.336 to -0.139 | -0.540 | 0.02 |  |
|  |  | |  |  |  |  |  |

Legend: Dependent variables are change from baseline to 12 months following pulmonary rehabilitation. 6MWD, 6-minute walk distance; CI, confidence interval for B; CRQ, Chronic Respiratory Questionnaire; FEV1, forced expiratory volume in one second; MVPA, moderate to vigorous intensity physical activity.

Severe exacerbation during follow-up is coded as 0 = no, 1 = yes; Pulmonary rehabilitation group is coded as 1 = home-based, 2 = centre-based; Age is measured in years; FEV1 is measured in litres; Smoking status is coded as 0 = never smoked or quit, 1 = current smoking. Significant results in bold.

**Table S3-** *Response to pulmonary rehabilitation (change from baseline to 8 weeks) for participants with and without exacerbations during follow-up.*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **ANY EXACERBATION** | |  | | **SEVERE EXACERBATION** | |  | |
|  | **Exacerbation** | | **No exacerbation** | | **p value** | **Severe exacerbation** | **No exacerbation or moderate exacerbation** | | **p value** |
|  |  | |  | |  |  |  | |  |
| 6MWD, m | 17 [-5 to 46] | | 31 [-3 to 52] | | 0.45 | 10 [-18 to 42] | 23 [-1 to 53] | | 0.12 |
| CRQ Dyspnoea | 4 [-0.5 to 8] | | 2.5 [-2 to 7] | | 0.28 | 4 [1 to 10] | 3 [-1 to 8] | | 0.23 |
| CRQ Fatigue | 2 [-1 to 4] | | 2.5 [0 to 4] | | 0.18 | 1 [-2 to 4] | 2 [-1 to 4] | | 0.16 |
| CRQ Emotional Function | 2 [-3 to 7] | | 2 [0 to 6] | | 0.55 | 0 [-5 to 5] | 3 [-1 to 7] | | 0.05 |
| CRQ Mastery | 2 [-1 to 5.5] | | 2 [0 to 5] | | 0.49 | 2 [-2 to 6] | 2 [-1 to 5] | | 0.55 |
| CRQ Total | 7 [-5 to 19] | | 9 [-10 to 18] | | 0.99 | 4 [-8 to 17] | 9 [-3 to 20] | | 0.16 |
| mMRC | 0 [-1 to 0] | | 0 [-1 to 0] | | 0.72 | 0 [-1 to 1] | 0 [-1 to 0] | | 0.11 |
| Total MVPA, min/day | 4 [-149 to 231] | | 29 [-303 to 196] | | 0.69 | -83 [-199 to 145] | 64 [-70 to 219] | | 0.17 |
| Duration MVPA in bouts, min/day | 27 [-12 to 90] | | 17 [-114 to 107] | | 0.56 | 0 [-72 to 70] | 29 [-6 to 111] | | 0.12 |
| Sedentary awake time, min/day | -569 [-1358 to 157] | | -285 [-566 to 137] | | 0.42 | -259 [-1225 to 223] | -492 [-1400 to 82] | | 0.47 |

Table legend: Data are median and interquartile range for change from baseline to end rehabilitation (8 weeks); p value represents comparison between those with and without exacerbations.

6MWD, 6 min walk distance; CRQ, Chronic Respiratory Questionnaire; mMRC, modified Medical Research Council scale; MVPA, moderate to vigorous physical activity; Duration MVPA bouts: duration of physical activity when in bouts of at least 10 min.