

# Development and Validation of a Multivariable Exercise Adherence Prediction Model for Patients with COPD: A Prospective Cohort Study

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**Purpose:** Pulmonary rehabilitation (PR) is considered a cost-effective method of improving health-related quality of life in patients with chronic obstructive pulmonary disease (COPD). However, increasing demand and increasing costs of supply demands for sustainable and affordable care. One of the possible solutions to keep care affordable is self-management. A challenge here is non-adherence. Understanding who are adherent and who are non-adherent could be helpful to differentiate between patients who need more or less support. Therefore, the aim of this study was to develop and validate a model to predict adherence to PR in patients with COPD.

**Patients and methods:** A multivariable logistic regression model for exercise adherence was developed. Eight candidate predictors, that were prespecified, were obtained in a prospective cohort study from 196 patients with COPD following PR in 53 primary physiotherapy practices in the Netherlands and Belgium, between January 2021 and August 2022. To create a parsimonious model, variable selection using backward selection was performed with a  $p$ -value of  $>0.05$  for elimination. Model performance was assessed by discrimination, calibration and clinical utility. Internal validation was assessed by bootstrapping ( $n = 500$ ).

**Results:** The final model included four predictors: intention, depression, MRC-score and alliance. The optimism-corrected AUC after bootstrap internal validation was 0.79 (95% CI, 0.72–0.85). Calibration plots suggested good calibration and decision curve analysis showed great net benefit in a wide range of risk thresholds.

**Conclusion:** The exercise adherence prediction model has potential for clinical utility to predict adherence in patients with COPD. Information from such a model can be used to manage the patient instead of managing the disease, and thereby to determine the treatment frequency for each individual patient. As a result, healthcare capacity might be better distributed, potentially reducing pressure on healthcare without compromising the effectiveness of PR for the individual patient.

**Keywords:** chronic obstructive pulmonary disease, sustainable healthcare, pulmonary rehabilitation, self-management

## Plain Language Summary

Nowadays, people are getting older, but also face more chronic diseases as a result. Chronic obstructive pulmonary disease, COPD, is one of the most common chronic diseases. Unfortunately, COPD cannot be cured, so people with COPD need a lot of care. In addition to medical treatment, supervised exercise is an effective treatment to manage COPD. But with the increase in the number of people with COPD, and other chronic diseases, care is becoming increasingly expensive and there is a shortage of healthcare providers to support patients. Both people with COPD and healthcare providers would benefit if patients could take more control of their own health. This self-management does require that patients keep the agreements they made with their healthcare provider. But this is not always easy for everyone.



With this study, we examined whether certain people might need more support from a healthcare provider than other people. People who participated in our study, and who suffered more from the following symptoms or problems, need more support from a healthcare provider:

- Depressive symptoms
- Severe shortness of breath
- Poor motivation to exercise
- A poorer relationship with the healthcare provider.

People who do not have these symptoms or problems, or very few, have less difficulty with following the agreements. These people might exercise more independently with regular follow-up. By discussing this together, more personalized care might be given.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide with an economic and social burden that is both substantial and increasing.<sup>1</sup> The prevalence of COPD increased by almost 40% between 1990 and 2017, and by 2017 COPD had become the third leading cause of death globally.<sup>2</sup> In the European Union, the total costs of respiratory disease are estimated to be about 6% of the total annual healthcare budget, with COPD accounting for 56% (38.6 billion euros).<sup>3</sup> In the United States, the costs attributable to COPD are expected to increase over the next 20 years, with projected costs of 800.90 billion dollars.<sup>4</sup> COPD prevalence, morbidity and mortality vary across countries.<sup>5</sup>

Based on demographic trends, the absolute number of patients with COPD is expected to increase by 31% between 2015 and 2040 in the Netherlands.<sup>6</sup> COPD is associated with an increase in disability-adjusted life years and years of life lost across the life course, and with substantial social and economic consequences for both individual patients and health systems.<sup>2</sup> Total healthcare costs for patients with COPD were 400 million euros in 2007 in the Netherlands and will rise to nearly 1.4 billion euros in 2032, being more than three times what it was in 2007 (including a growth in healthcare spending of 2.3% per year).<sup>7</sup>

Pulmonary rehabilitation (PR) aims to reduce the levels of morbidity, to improve functioning, and is currently an integral component of managing COPD.<sup>8</sup> PR is a cost-effective method of improving health-related quality of life in patients with COPD and is recommended in national guidelines.<sup>9</sup> Despite PR being cost-effective, increasing demand by an aging population and increasing costs of supply demands for sustainable and affordable care.<sup>10</sup> In the medium term, the cost of care is rising and a shortage of personnel is looming.<sup>11</sup> Due to the high number of consultations per patient per year (24.7), the cost of PR in primary care is relatively high: nearly 40 million euros in 2007.<sup>7</sup> To keep healthcare affordable and to make PR less labor-intensive, there is a need for more focus on self-management, without compromising on the effectiveness of PR.<sup>12</sup> Self-management programs in primary care may improve health behaviors, health outcomes, and quality of life and, in some cases, have demonstrated effectiveness for reducing health care utilization and the societal cost burden of chronic diseases.<sup>13</sup> One of the biggest challenges here is long-term adherence.<sup>14</sup>

Adherence is a multidimensional construct that is defined as the extent to which a person's behavior in therapeutical interventions corresponds with agreed recommendations from a healthcare provider.<sup>15</sup> Adherence includes behaviors such as attendance at clinic appointments, the extent to which patients follow the prescribed treatment, and the communication with their healthcare provider about their recovery.<sup>16</sup> In supporting patients staying adherent, available resources could be used in ways that are both effective (desired outcomes) and efficient (that do so with the least amount of effort and cost).<sup>17</sup>

Understanding who are adherent and who are non-adherent could be helpful to differentiate between patients who need more or less support during PR (effective and efficient). Therefore, accurate estimates of adherence in patients with COPD might be important to be able to support healthcare providers in their choices of support for the benefit of the individual patient. To predict patient's probability of adherence to PR, a prediction model could be beneficial. Information from such a model can be used to manage the patient instead of managing the disease, as the traditional medical model does.<sup>13</sup> The model would aim to reduce unnecessary intervention and thus reduce pressure on the health system (patients who are adherent might need less

support). By reducing the average number of consultations from 24.7, healthcare costs are directly saved and the pressure on healthcare providers will also be reduced. This person-centered care requires a patient-provider partnership involving collaborative care and education in chronic disease self-management to ensure the best possible health outcomes for the patient<sup>13</sup> and less pressure on the health system.<sup>10</sup> So far, no prediction models for adherence are available.

Therefore, the aim of this study was to develop and validate a model to predict adherence to pulmonary rehabilitation in a cohort of patients with COPD in the Netherlands and Belgium.

## Methods

The study is consistent with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines (Additional file 1).

## Study Design and Population

Participants of this prospective cohort study were Dutch/Flemish-speaking patients aged  $\geq 18$  years from primary physiotherapy practices, and from the COPD patient-organizations from the Netherlands and Belgium. Recruitment commenced in January 2021, and 12-month follow-up assessments were completed in August 2022. Patients ( $\geq 18$  years) with COPD, with airflow limitation stage GOLD II–IV and having rehabilitation sessions for at least once a month, were potentially eligible for inclusion. The exclusion criteria were home-based rehabilitation and insufficient mastery of the Dutch/Flemish language to complete the questionnaires.

Physiotherapy practices were approached by e-mail and social media for participation, and patients were recruited by their attending physiotherapist. Physiotherapy practices could receive a financial compensation of €20 per participating patient, at the time of study completion as a token of appreciation. Patients who were willing to participate were contacted by the researcher per email for further information on their participation, and to obtain informed consent. For patients without an e-mail address, this was done by their physiotherapist during their visit to the physiotherapy practice. Patients were also recruited via the COPD patient-organization in the Netherlands and Belgium who, in turn, invited their physiotherapist for participation (no financial compensation was offered to the physiotherapists).

## Procedures

After signing informed consent and inclusion, patients completed an online (Qualtrics) or paper form on their demographic characteristics: age (years), gender (male/female), country (the Netherlands/Belgium), education (low/middle/higher), smoking status (never smoked/quit smoking/still smoking) and medication adherence (yes/no). About simultaneously, the physiotherapist provided information on the characteristics of the disease of the patient: classification of severity of airflow limitation (GOLD classification) (GOLD II/III/IV), degree of baseline functional disability due to dyspnea (MRC-score) (0/1/2/3/4/5), duration of COPD since diagnosis (years), and duration of physiotherapy (years).

Both patients and physiotherapists provided information at baseline and 12 months after inclusion. Patients provided additional information three months after inclusion. Characteristics of the participating physiotherapists are summarized in Additional file 2.

## Data Collection

All questionnaires for both patients and physiotherapists were prepared in Qualtrics (online survey software).<sup>18</sup> The questionnaires were sent by the researcher from Qualtrics to the participants at the different measurement moments. Answers to the questionnaires were automatically collected in Qualtrics. If a questionnaire was not completed after two weeks, an automatic reminder was sent. The researcher entered the responses of patients who completed a paper questionnaire into Qualtrics to obtain a complete data file of all participants. Prior to data analysis, the raw data file was checked by the researcher for any input errors. If input errors were found, the researcher contacted the respective participant (patient and/or physiotherapist), if possible. In this way, the raw data file was made technically correct and

consistent. Data were anonymized by deleting the e-mail addresses and adding a PID number. Based on the PID number measurements of all measurement moments could be merged.

## Candidate Predictors

To construct a prespecified model (to limit selection bias and overfitting), candidate predictors were identified through: pre-existing knowledge, fundamental mechanisms, and specified criteria for selection.

### Pre-Existing Knowledge

A previous performed systematic review and meta-analysis of prognostic factors of adherence to home-based exercise therapy in patients with chronic diseases<sup>19</sup> formed the basis. According to this systematic review and meta-analysis higher exercise adherence was predicted by self-efficacy, exercise history, motivation, education, physical health, comorbidities, depression, fatigue, and support from a healthcare provider.<sup>19</sup>

Further, in paramedical professions, it is widely accepted that the treatment regimen alone cannot fully account for patient outcome.<sup>20</sup> The relationship between patient and therapist (therapeutic alliance) has been viewed as an important determinant of treatment outcome and is considered central to the therapeutic process.<sup>21</sup>

### Fundamental Mechanism

To model the fundamental psychological determination of behavior, the theory of planned behavior (TPB) was used. TPB supposes that a person's intention to perform a behavior is the major determinant of that behavior.<sup>22</sup> Furthermore, a person's intention is determined by three theoretically independent variables: a person's attitude, subjective norm, and perceived behavioral control (PBC).<sup>22</sup>

### Other Criteria for Selection

The process of prespecifying predictors takes into account the prevalence (between 20% and 80%) of the candidate predictors in the dataset. Further, it has been taken into account that prediction models tend to include predictors that are quite readily available, not too costly to obtain, and can be measured with reasonable precision.<sup>23</sup> To achieve parsimony and reliability of predictions that are provided by the prediction model, eight candidate predictors could be chosen. The minimum events per variable for obtaining good predictions may be ten.<sup>23</sup> The smallest event category must be assumed (limiting sample size); this was the event "adherent" and included 84 cases. With an EPV rate of at least ten, up to eight predictors can be simultaneously included in the full model for reliable results. For the feasibility of the prediction model, we chose to categorize candidate predictors into five domains: demographic data, disease characteristic data, planned behavior constructs, psychological constructs, and exercise and fitness variables.

Based on the results of the systematic review (high and moderate quality evidence), TPB, and the other criteria for selection, the following candidate predictors were included: planned behavior constructs: PBC, attitude, subjective norm, intention; exercise and fitness variables: exercise history; disease characteristics: depression, Medical Research Council dyspnea scale (MRC)-score; and psychological constructs; therapeutic alliance (patient-provider relationship) (Additional file 3).

## Measures

Exercise adherence (the outcome) was assessed by the Dutch version of the Rehabilitation Adherence Measure for Athletic Training (RAdMAT-NL). The RAdMAT-NL has good psychometric properties with an internal consistency reliability of  $\alpha = 0.91$ .<sup>24</sup> The RAdMAT-NL is a 16-item questionnaire that uses a 4-point rating scale (never = 1, occasionally = 2, often = 3, always = 4) to evaluate clinic-based adherence.<sup>24</sup> The RAdMAT-NL consists of 3 subscales: Attendance/participation (items 1–5, range 5–20 points), Communication (items 6–8, range 3–12 points), and Attitude/effort (items 9–16, range 8–32 points). The total scale range is 16–64, a higher score indicates a higher degree of adherence. According to the American College of Sports Medicine guidelines, a score of at least 85% must be achieved to be adherent to the rehabilitation program.<sup>25</sup> This means that a minimum total score of 54 or higher must be achieved on the RAdMAT-NL to be adherent. The RAdMAT-NL was completed at 12 months by the physiotherapist, independent of the patient and not in their presence.

TPB constructs were assessed at baseline. The constructs were measured according to the questions from Ajzen.<sup>22</sup> The four intention items focused on goals and plans for exercise and uses a 5-point rating scale (totally disagree = 1, disagree = 2, do not disagree/do not agree = 3, agree = 4, totally agree = 5). The total scale range is 4–20, a higher score indicates a higher degree of intention. Attitude was measured using seven bipolar adjective scales (5-point rating scales) that asked about both instrumental (eg, useful–useless, bad–good) and affective (eg, enjoyable–unenjoyable, boring–interesting) attitude. The total scale range is 7–35, a higher score indicates a more positive attitude. PBC was measured by three questions that asked about aspects of controllability and ease/difficulty and uses a 5-point rating scale. The total scale range is 3–15, a higher score indicates better PBC. Subjective norm was measured by three items that asked about approval and support for exercise and uses a 5-point rating scale (totally disagree = 1, disagree = 2, do not disagree/do not agree = 3, agree = 4, totally agree = 5). The total scale range is 3–15, a higher score indicates more social pressure.

Alliance was assessed after three months by the Working Alliance Inventory (WAI).<sup>21</sup> The patient-provider relationship was measured with 12 questions rated on a 5-point scale (range 12–60) and a higher score indicated a higher level of alliance.

Depression was assessed at baseline by four depression questions of the Four-Dimensional Symptom Questionnaire (4DSQ).<sup>26</sup> The 4DSQ is a self-report questionnaire that has been developed in primary care to distinguish non-specific general distress from depression, anxiety and somatization. All items were rated on a 4-point scale (range 4–16) and a higher score indicated a higher level of depression.

Exercise and fitness variables were collected by self-reports. At baseline, patients were asked about exercise history (yes/no).

## Sample Size

Data were collected for regression modelling, so therefore sample size calculation has been determined for this purpose with the graph of Miles and Shevlin.<sup>27</sup> The graph illustrates the sample size needed to achieve different levels of power, for different effect sizes, as the number of predictors vary. For ten predictors and a medium effect size, a number of 150 participants are needed.

## Statistical Analysis

All statistical analyses were performed in R version 4.0.3 using “mice” for multiple imputation, “rms” for logistic regression modelling, “epi” for calculating the AUC, “cutpointr” for calculation of the “optimal” cut-off value, and “rmda” for decision curve analysis. For all analyses,  $p < 0.05$  was considered statistically significant.

## Missing Data

Following the in-depth considerations of the patterns of missing data, the data were assumed to be missing at random. First, the amount of missingness for each variable was calculated; the difference between the sample size and the number of useable observations. Second, Fisher exact tests were used to analyze differences in baseline characteristics between patients with missing and complete data. Finally, multiple imputation was used to create and analyze five multiple imputed datasets. Incomplete variables were imputed under fully conditional specification. Analyses were done in each imputed dataset and pooled using Rubin’s rules in the primary analysis.

## Baseline Characteristics

Baseline characteristics are presented with appropriate measures of central tendency and dispersion for the overall cohort and for patients who are adherent and are non-adherent.

## Model Development

First, the outcome variable was dichotomized: RAdMAT-NL scores  $\leq 54 = 0$  (non-adherent),  $> 54 = 1$  (adherent). Second, logistic regression modelling was used with all candidate predictors. Continuous variables were handled as they had a linear relationship. The categorical variable MRC score was dichotomized (no limitations: 0–2 = 0; and limitations: 3–5 = 1) because patients with MRC 3–5 have limitations of activity due to dyspnea during daily life and are eligible for PR (MRC 0–2 are not).<sup>28</sup>

To create a parsimonious model that can more efficiently be used in clinical practice, variable selection using backward selection was performed with a  $p$ -value of  $>0.05$  for elimination. Bootstrap samples ( $n = 500$ ) were used in which the backward elimination procedure was repeated to increase the likelihood of selecting variables that are genuinely related to the outcome. Variables that remained in the model in more than half of the bootstrap samples were included in the final prediction model.

## Model Evaluation

Model performance was assessed through discrimination (how well predictions differentiated participants who experienced the outcome from those who did not), quantified as the area under the receiver operating characteristic curve (AUROC), calibration (agreement between predicted and observed risk, assessed using calibration slopes, calibration-in-the-large, and calibration plots), and clinical utility (assessed using decision curve analysis and quantified as net benefit).<sup>29</sup> An ideal calibration slope is 1, while calibration-in-the-large should be 0 if the number of observed outcome events matches the number predicted.<sup>29</sup> Decision curve analysis was used to calculate the clinical “net benefit” for the prediction model in comparison to default strategies of “treating” all or no patients.<sup>30</sup> In this study, the benefit of the model is that it correctly identifies which patients are adherent and who are non-adherent. Preference refers to how healthcare providers value different outcomes for a given patient, a decision that is often influenced by a discussion between the healthcare provider and that patient.<sup>30</sup>

Validity was assessed via bootstrapping ( $n = 500$ ) to quantify any optimism in model performance. Adjustment for overoptimism of the overall performance enabled to better approximate the expected model performance in novel samples. Bootstrapping also estimated a uniform shrinkage factor to enable adjustment of the estimated regression coefficients for over-fitting.<sup>31</sup> When poorly calibrated predictions at validation were found, algorithm updating was considered to provide more accurate predictions for new patients.<sup>32</sup> An intercept adjustment was protocolled if the calibration intercept was not close to 0. Finally, the “optimal” cut-off value for the prediction model was calculated.

The study was approved by the Ethical Committee Psychology of the University of Groningen (PSY-1920-S-0504).

## Results

### Participants

From January 2021 until August 2022, patients from 53 different physiotherapy practices participated in the study. Out of 199 patients who gave informed consent, data from 196 patients were analyzed. The percentage of missing values across all 83 variables throughout the main study varied between 13.7% and 22.9%. In total 151–169 out of 196 patients had a complete data set. There was no association between participants with missing data and the pattern of baseline characteristics. Reasons for missing data were leaving the study; three patients died, three patients stopped physiotherapy because they were diagnosed with cancer or other medical reason, six patients stopped physiotherapy for an unknown reason, and the remaining missing data concerned patients who indicated that they did not have to perform homework exercises.

Table 1 summarizes the demographic and disease characteristics of the patients. Table 2 presents the baseline TPB, exercise and fitness, and psychological variables. Both tables also present the  $p$ -values for differences between adherent and non-adherent patients.  $P$ -values  $<0.05$  are considered statistically significant.

### Model Development

In the backward elimination procedure (including bootstrapping), variables that remained in the model in more than half of the bootstrap samples ( $p < 0.05$ ) were included in the final prediction model. Four predictors were remained and entered the model: intention, MRC-score, depression and alliance. Excluded were attitude, subjective norm, PBC, and exercise history, because they did not have a significant ( $p > 0.05$ ) relation with adherence.

The logistic regression analysis results of the four included variables are listed in Table 3.



**Table 1** Patient Demographic and Disease Characteristics

Variable	Overall (n = 196)	Adherent (n = 84)	Non-Adherent (n = 112)	p-value
<b>Demographic data</b>				
Male gender (%)	51.5	50.0	52.7	0.36
Median age in years (IQR)	68.0 (64.0–73.0)	67.0 (64.0–72.0)	68.5 (65.0–74.0)	0.32
Resident of the Netherlands (%)	58.7	64.3	54.5	0.23
Education (%)				0.00*
• Low	21.4	16.7	25.0	
• Middle	53.1	45.2	58.9	
• Higher	25.5	38.1	16.1	
Smoking status (%)				0.08
• Never smoked	1.5	2.4	0.9	
• Quit smoking	84.7	90.5	80.4	
• Still smoking	13.8	7.1	18.7	
Adherent to medication (%)	88.8	94.0	84.8	0.25
<b>Disease characteristic data</b>				
GOLD classification (%)				0.68
• GOLD II	27.6	38.1	19.6	
• GOLD III	36.2	26.2	43.8	
• GOLD IV	36.2	35.7	36.6	
MRC-score (%)				0.01*
• 0	0.5	-	0.9	
• 1	5.1	11.9	-	
• 2	18.4	23.8	14.3	
• 3	36.7	36.9	36.6	
• 4	27.0	19.1	33.0	
• 5	12.3	8.3	15.2	
Median time in years since diagnose (IQR)	10.0 (5.0–14.0)	8.0 (5.0–13.3)	10.0 (6.0–14.0)	0.13
Median depression (IQR)	6.0 (4.0–8.0)	5.0 (4.0–7.0)	6.0 (5.0–10.0)	0.00*

**Notes:** \* $p < 0.05$ ; meaning a significant difference between adherent and non-adherent patients. The GOLD guidelines classify patients into four different categories: GOLD 1 (mild), GOLD 2 (moderate), GOLD 3 (severe), or GOLD 4 (very severe) based on their level of airflow limitation; MRC-score: Medical Research Council dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease.

**Abbreviation:** GOLD, Global Initiative for Chronic Obstructive Lung Disease.

**Table 2** Descriptive Statistics for the Theory of Planned Behavior, Psychological and Exercise and Fitness Constructs (n = 196)

Variable	Overall	Adherent	Non-Adherent	p-value
<b>Planned behavior</b>				
Median intention (IQR)	16.0 (14.0–17.0)	16.0 (15.0–18.0)	15.0 (13.0–16.0)	0.00*
Median Perceived Behavioral Control (IQR)	11.0 (9.0–11.3)	11.0 (10.8–12.0)	10.0 (9.0–11.0)	0.00*
Median attitude (IQR)	26.0 (20.0–30.0)	27.0 (22.8–30.3)	24.0 (20.0–28.0)	0.00*

(Continued)

**Table 2** (Continued).

Variable	Overall	Adherent	Non-Adherent	p-value
Median subjective norm (IQR)	10.0 (8.0–11.0)	10.0 (8.0–11.0)	10.0 (8.0–11.0)	0.81
<b>Psychological constructs</b>				
Median alliance (IQR)	47.0 (39.8–50.0)	48.0 (44.8–52.3)	44.5 (37.0–49.0)	0.00*
<b>Exercise and fitness</b>				
Exercise history (yes) (%)	62.2	74.1	53.2	0.00*
Years of physiotherapy (%)				0.77
• 0–3 months	14.8	15.3	14.4	
• 3–6 months	7.7	8.2	7.2	
• 6–12 months	6.6	5.9	7.2	
• 1–5 years	30.6	31.8	29.7	
• >5 years	40.3	38.8	41.5	

**Notes:** \* $p < 0.05$ ; meaning a significant difference between adherent and non-adherent patients.

**Table 3** Logistic Regression Analysis of Predictors for Adherence in Patients with COPD

Intercept and Variables	$\beta$ Coefficients	p-value	Odds Ratio (95% CI)	Shrunk $\beta$ Coefficients*
Intercept	–4.996			–4.108**
Intention	0.238	0.001	1.276 (1.109–1.469)	0.203
Depression	–0.171	0.001	0.839 (0.738–0.952)	–0.147
MRC	–1.107	0.004	0.321 (0.148–0.695)	–0.950
Alliance	0.064	0.008	1.068 (1.017–1.120)	0.055

**Notes:** \*Result of bootstrapping technique used to correct for overoptimistic estimation of model. \*\*After intercept adjustment; adding the calibration intercept (–1.015) to the model intercept (–5.123). MRC: Medical Research Council dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease.

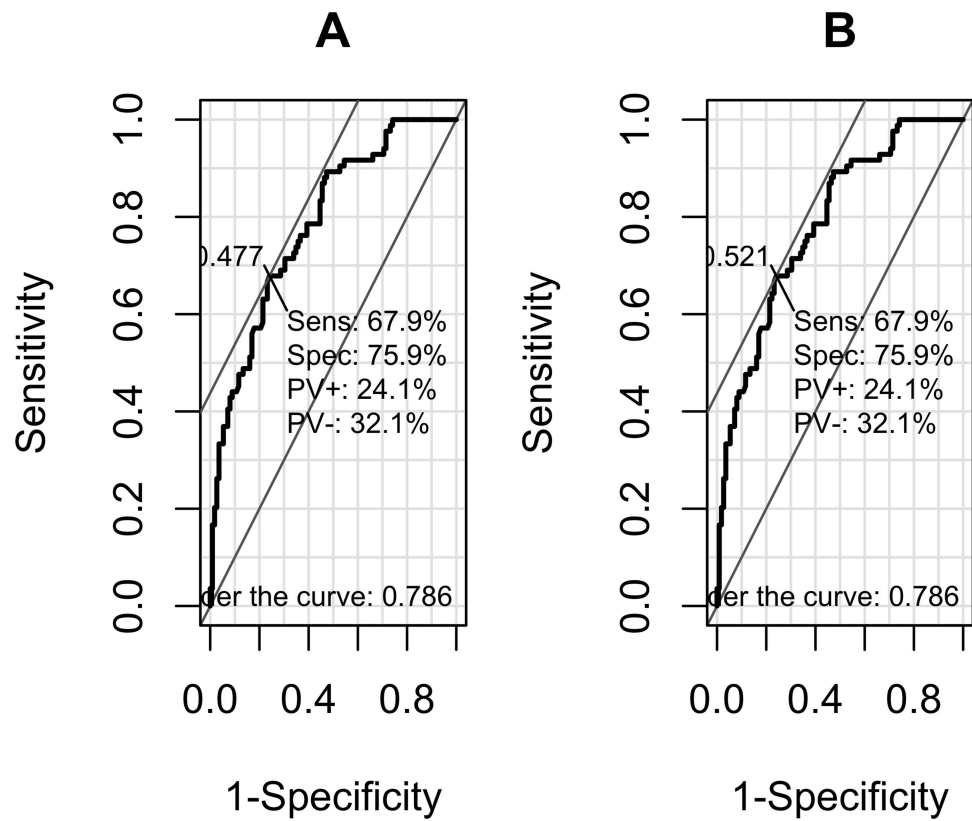
## Model Evaluation

The AUC in the primary model was 0.79 (95% CI, 0.72–0.85);  $p = 0.00$  (Figure 1A). After bootstrap internal validation, the optimism-corrected AUC was the same; 0.79 (95% CI, 0.72–0.85);  $p = 0.00$ , suggesting good discrimination (Figure 1B).

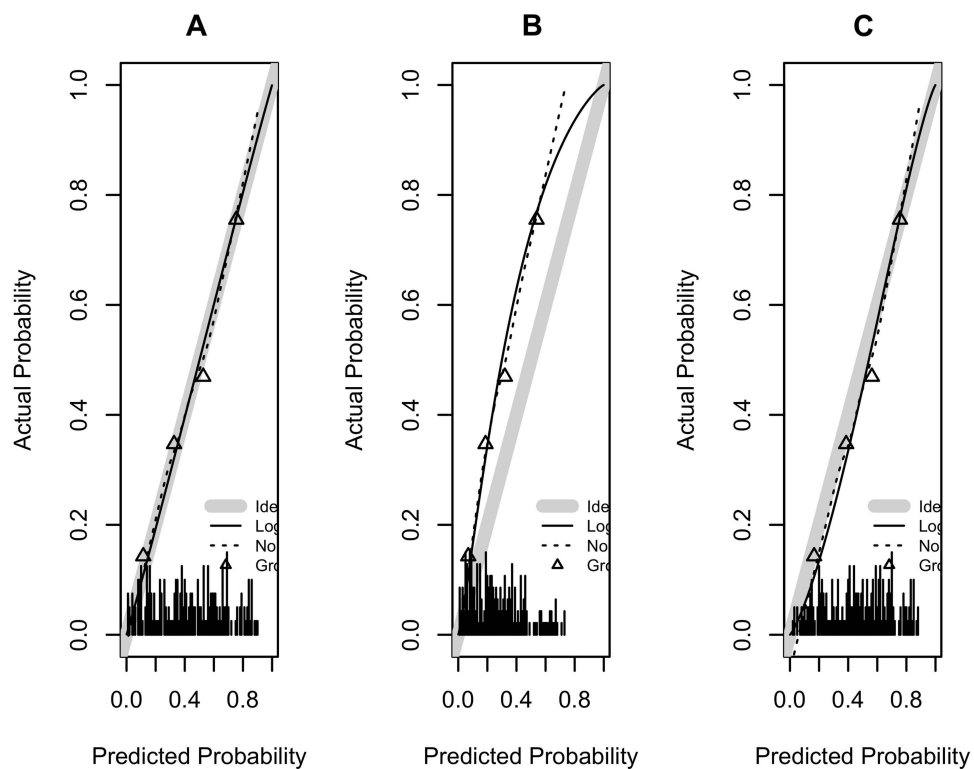
The prevalence of adherence was 42.9% (84/196). The average estimated probability of adherence given by the prediction model was 41.9%, which indicates good estimations. The calibration slope and calibration-in-the-large were respectively 1.026 and –0.007 in the primary model (Figure 2A). After internal validation the probability of adherence given by the shrunk model was 24.4%, which indicates that there is a tendency to give underestimated scores for adherence. The new calibration slope was 1.198 and calibration-in-the-large was 1.015 (Figure 2B). So, after internal validation poorly calibrated predictions were found, with a calibration intercept far from 0. Intercept adjustment was performed by adding the calibration intercept (1.015) to the model intercept (–5.123). After this intercept update, the calibration curve of the intercept-adjusted model was close to the diagonal reference line of perfect moderate calibration (Figure 2C). The average estimated probability of adherence given by this updated model was 47.0% (slightly overestimated score).

Decision curve analysis was performed for the model. In Figure 3, the net benefit of offering an intervention (less support for patients) for all or none of the patients, which are two extreme situations, is represented by the grey line and the horizontal black line, respectively. In a wide range of risk thresholds, the model outperformed the two extreme

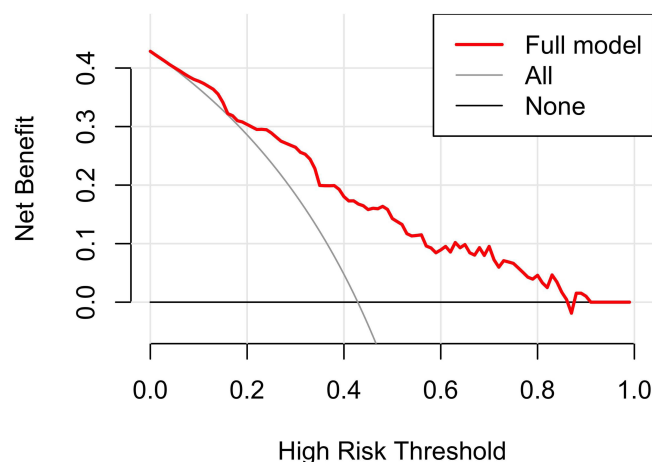




**Figure 1** Area under the receiver operating curve. (A) ROC curve in the primary model. (B) ROC curve after internal validation.



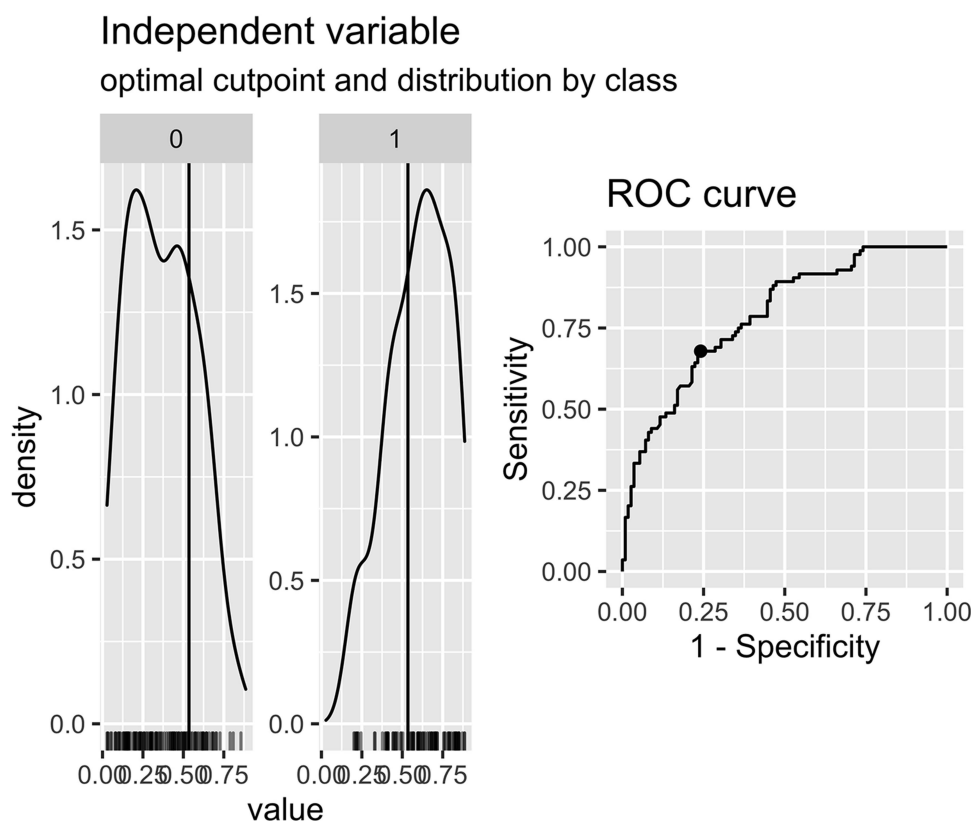
**Figure 2** Calibration plots. (A) Calibration plot primary model. (B) Calibration plot shrunk model. (C) Calibration plot intercept-adjusted model.



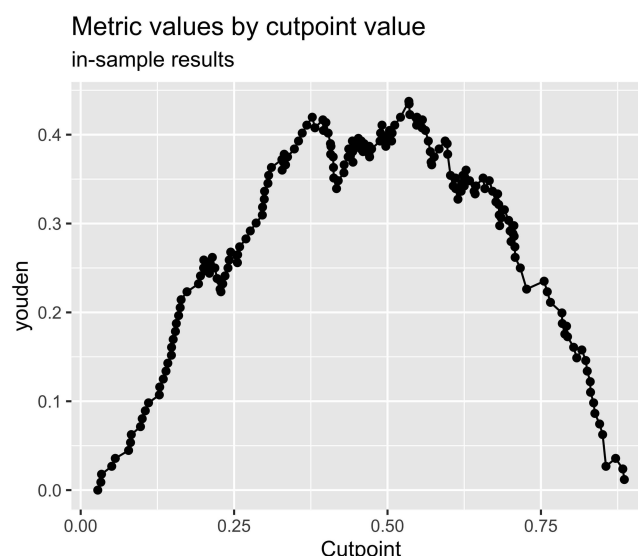
**Figure 3** Decision curve analysis of risk prediction model for adherence. The black solid line represents the assumption that none of the patients get an intervention, and the grey solid line represents the assumption that all of the patients get an intervention. The red line represents the result of the prediction model.

strategies with a much higher net benefit. For example, if a risk threshold of 0.5 is used to determine whether a patient needs less supervision/support according to the model, after weighing the benefit and cost, there is a net benefit for 30 out of every 100 patients.

To make the prediction model easy to use in practice, a calculator is available (<https://derzis.nu/Calculator/>) (screen-shot in Additional file 4). Users can enter the individual patient variables in the calculator to obtain the probability of adherence. The optimal cut-off point for the calculator is based on maximizing the sum of sensitivity and specificity.<sup>33</sup> Based on the cohort of this study, a threshold of 53.5% is suggested as the optimal cut-off value to define adherent patients (Figures 4 and 5).



**Figure 4** Optimal cut-off value and distribution by class; 0 = non-adherent, 1 = adherent.



**Figure 5** Values per cut-off point.

Additional file 5 provides an explanation of how to use the calculator and examples of what interventions might be considered for use to improve exercise adherence.

## Discussion

We developed and validated a model to predict exercise adherence in patients with COPD following PR in a primary physiotherapy practice in the Netherlands and Belgium. The final model integrates four easily available predictors (intention, depression, MRC-score, alliance) and is intended for use in the population of COPD patients following PR for at least one month. Internal validation showed good discrimination, calibration, and net benefit. The calculator provides a probability output that indicates the chance that the patient under evaluation is adherent. These predictions will enable healthcare providers to objectively determine which patients are adherent and might be able to exercise more by themselves. Patients who are non-adherent might need more support than patients who are adherent. As a result, healthcare capacity might be better distributed, potentially reducing pressure on healthcare without compromising the effectiveness of PR for the individual patient.

One of the predictors in the final prediction model is not yet available at the time a patient first comes for PR: alliance. Therefore, this prediction model can only be used for patients following PR for at least one month. It is important for healthcare providers to realize, however, that alliance is an important predictor of adherence. So, when a patient follows PR for the first time, there should immediately be invested in alliance (the larger the alliance, the better the adherence). Literature shows that it is widely accepted that the treatment regimen alone cannot fully account for patient outcome.<sup>20</sup> The relationship between patient and therapist has been viewed as an important determinant of treatment outcome and is considered central to the therapeutic process.<sup>21</sup> The construct of alliance in therapeutic situations refers to the sense of collaboration, warmth, and support between the client and therapist.<sup>21</sup> The study of Peiris et al showed that the patient–therapist interaction was more important to the patient than the amount or content of their physiotherapy.<sup>34</sup> In relation with the TPB model, it is shown that patients who experience a positive alliance are more likely to have a stronger self-efficacy and outcome expectations. And self-efficacy and outcome expectations are highly correlated with patient adherence to treatment.<sup>35</sup>

## Strengths and Limitations

The strengths of this study are inclusion of patients from different physiotherapy practices and from patient-organizations in the Netherlands and Belgium. In this way, a representative sample of COPD patients attending PR participated in this study, which enhances the generalizability of the study results regarding other COPD patients already attending PR. The

final variables are easy to obtain and can be entered into the adherence calculator to obtain prognostic estimates. A manual for using the calculator is available, including advice for the healthcare provider how to deal with the probability score (Additional file 5). Another strength is the use of a prespecified model to limit selection bias and overfitting. A recent performed systematic review indicated variables associated with adherence.<sup>19</sup> Further, TPB as the state-of-the-art model to predict adherence behaviors in patients with a chronic disease, was used.<sup>36</sup>

This study also has some limitations. Because we wanted a simple model, and because the sample size was not large enough, we accepted uncertainty about the assumptions; we chose to consider the continuous data as linear (cubic splines would cost too many degrees of freedom, making the model overfit). In terms of handling continuous predictors, researchers strongly advise against converting continuous variables into categorical variables, due to information loss and reduced predictive accuracy.<sup>31</sup> That is why we choose to accept the uncertainty about the assumptions. Therefore, future validation studies in other cohorts should be performed.

In a previous study,<sup>37</sup> we demonstrated that in this cohort of COPD patients adherence was constant over 12 months. Therefore, this prediction model can only be considered valid over this time period. Thereby, the purpose of this prediction model was to better support the current population of COPD patients. Follow-up research should examine whether this prediction model (without alliance) is applicable to patients starting PR, and if this model is valid over a longer period than 12 months. Furthermore, future research might examine whether a reduction in depressive symptoms, an improvement in alliance, intention, and MRC-score actually lead to better exercise adherence in both patients who have had PR for some time and those who are at the beginning of their PR.

Physiotherapy practices were offered a financial compensation if they participated in the full study. The compensation was offered at the end of the study as a token of gratitude and appreciation.<sup>38</sup> This had no impact on the study recruitment as it was given at the end of the study. The financial compensation was too low to influence physiotherapist retention and therefore did not serve as an incentive to prevent a physiotherapist from dropping out of the study.

## Clinical Implications

Adherence is important in many aspects of healthcare as it is related to clinical outcomes and to the (economic) burden for healthcare providers.<sup>39</sup> To keep healthcare affordable and improving patient outcomes, attention must be paid to adherence.<sup>40</sup> Information from this prediction model can be used by healthcare providers to facilitate discussions regarding clinical care and target services to better manage COPD and make more efficient use of health care by patients receiving prolonged (70% of patients in this cohort followed PR for  $\geq 1$  year) pulmonary rehabilitation in a primary physiotherapy practice. Counselling can possibly focus on patients who need it the most, the ones who are non-adherent. Patients who are adherent require less counselling; their self-management ensures stable health outcomes.<sup>37</sup> Both healthcare providers and patients gain substantial benefits; less time and costs spent and placing the patients central to address their needs leading to improved health behaviors, health outcomes, and quality of life.

## Conclusions

In this prospective cohort study, we developed and validated an adherence prediction model with good discrimination and calibration that can be used to estimate the probability of adherence in patients with COPD following PR for at least one month. The final predictors (intention, depression, MRC-score, and alliance) are easily to obtain in clinical practice and can be entered into a calculator to obtain prognostic estimates. These estimates can be used by healthcare providers to manage the patient instead of managing the disease, and thereby to determine the treatment frequency for each individual patient. As a result, healthcare capacity might be better distributed, potentially reducing pressure on healthcare without compromising the effectiveness of PR for the individual patient.

## Abbreviations

4DSQ, Four-Dimensional Symptom Questionnaire; AUC, Area Under the Curve; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, Inter Quartile Range; MRC-score, Medical Research Council dyspnea scale; PBC, Perceived Behavioral Control; PR,

Pulmonary Rehabilitation; RADMAT-NL, Dutch version of the Rehabilitation Adherence Measure for Athletic Training; TPB, Theory of Planned Behavior; WAI, Working Alliance Inventory.

## Data Sharing Statement

Data are available on reasonable request. Data are available on reasonable request through the corresponding author Ellen Ricke, E.Ricke@rug.nl.

## Ethics Approval and Informed Consent

This study complies with the Declaration of Helsinki and is registered with the number METc 2020/392. The METc UMCG has concluded that the study is not clinical research with human subjects as meant in the Medical Research Involving Human Subjects Act (WMO). Also, the study was approved by the Ethical Committee Psychology of the University of Groningen (PSY-1920-S-0504).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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