

Development of the Galaxy Chronic Obstructive Pulmonary Disease (COPD) Model Using Data from ECLIPSE: Internal Validation of a Linked Equations Cohort Model

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ABSTRACT

Background. *The recent ISPOR-SMDM Modeling Good Research Practices Task Force on Modeling emphasized the importance of conceptualizing and validating models. We report a new model of chronic obstructive pulmonary disease (COPD) that was part of the Galaxy project. It is founded on a conceptual model, implemented using a novel linked-equation approach, and internally validated.*

Methods. *An expert panel developed a conceptual model including causal relationships between disease attributes, progression, and final outcomes. Risk equations describing these relationships were estimated using data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, with costs estimated using data from the TOwards a Revolution in COPD Health (TORCH) study. Implementation as a linked-equation model enabled direct estimation of health service costs and quality adjusted life-years (QALY) for COPD patients over their lifetimes. Internal validation compared three years of predicted cohort experience with ECLIPSE results.*

Results. *At three years, the Galaxy COPD model predicted annual exacerbation rate, and annual decline in forced expiratory volume in one second, all fell within the ECLIPSE data confidence limits, although overall survival was outside the observed confidence limits at three years. Projections of the risk equations over time permitted extrapolation to patient lifetimes. Averaging the predicted cost and QALY outcomes for the different patients within the ECLIPSE cohort gives an estimated lifetime cost of £25,214 (undiscounted)/£20,318 (discounted) and lifetime QALY of 6.45 (undiscounted)/5.24 (discounted) per patient in ECLIPSE.*

Conclusions. *A new form of model for COPD was conceptualized, implemented, and internally validated, based on a series of linked equations using epidemiological data from ECLIPSE and cost data from TORCH. This Galaxy model may predict COPD outcomes from treatment effects on disease attributes such as lung function, exacerbations, symptoms or exercise capacity; however, further external validation is required.*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by airflow obstruction, leading to shortness of breath, acute exacerbations, and death [1]. Globally, COPD is the fourth leading cause of death [2]. In England, more than 860,000 individuals were diagnosed with COPD in 2009–2010, corresponding to a prevalence of 1.6% [3]. However, it is estimated that most cases remain undiagnosed and that the true prevalence of COPD is much higher, potentially affecting more than 3 million people [1]. Smoking is the primary risk factor for developing COPD, and exposure to noxious fumes, dust, and gas are also risk factors [4]. The economic burden of COPD is high; it is one of the most costly inpatient conditions treated by the National Health Service in the United Kingdom, with an estimated direct cost of £810–930 million per year [1].

A number of models of COPD exist, which have been used for economic analysis for Health Technology Assessment (HTA). The majority of these are structured around disease ‘states’ that are usually defined using threshold values of % predicted forced expiratory volume in one second (FEV_1), adjusted for patients according to age, gender, and height [5,6]. However, recent prognostic modeling has shown that other aspects of the disease, such as symptoms and exercise capacity, are also important factors for survival [7-9], and clinical guidelines are beginning to acknowledge the multifaceted nature of COPD [2], such that there is inherent heterogeneity in health outcomes for COPD patients that depends on more than just FEV_1 [8].

The Galaxy project was undertaken to develop a new disease/economic model for COPD, accounting for recent developments in the understanding of COPD as a multifaceted disease. The aim was to develop a model with sufficient flexibility to reflect different patient groups, based on an understanding of relationships between disease characteristics, risk factors, biomarkers, and surrogates, on relevant clinical outcomes and disease progression over time. This allows for a better capture of the inherent heterogeneity and corresponding adjustments made for different COPD patient populations, which facilitates comparisons of disease progression between different COPD subgroups. The development of the new Galaxy COPD model has adhered as closely as possible to best practice guidelines for medical decision modeling [10], which emphasize the importance of conceptual modeling [11]. The modeling and analysis we report in this paper was founded upon a conceptual model designed by a panel of experts prior to data analysis [12] and a series of linked risk equations that were

developed from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) data-set based on the relationships from the conceptual modeling exercise [13]. This paper brings the previous work together in a cohesive whole and internally validates the model using the same data that were used to generate model parameters. The model will also enable estimation of the cost effectiveness of a wide range of treatment interventions, acting through different mechanisms, used for the management of COPD.

METHODS

Data sources

The ECLIPSE study was a non-interventional, observational, multicenter, three-year study designed to determine mechanisms of disease progression and identify biomarkers that could serve as endpoints to measure progression of COPD [14]. This study included 2164 COPD patients, with an average age of 63.4 years, an average of 0.9 exacerbations in the year prior to study entry, and baseline % predicted FEV₁ of 48.3%. Patients for whom full information on baseline characteristics were available ($n = 1957$) were included in the present model.

The TOwards a Revolution in COPD Health (TORCH) study, was a randomized, double-blind study ($n = 6112$) comparing the effectiveness of salmeterol alone, fluticasone propionate alone, a combination of salmeterol and fluticasone propionate, and placebo, over a three-year period [15]. At baseline, the average age was 65.0 years; patients had an average of 1.0 exacerbation in the year prior to study entry, and baseline % predicted FEV₁ was 44.1%.

Patients included in the model had baseline characteristics that were slightly different from the original published studies, due to small amounts of missing information in the baseline covariates used in the modeling. However, there were no important differences between characteristics of the cohorts analyzed here to the original studies. Summary information for the analysis cohorts is given in the supplementary appendix in Table A1.

Model validation

The conceptualization of the new model of COPD disease progression was reported separately [12], and led to the development of a conceptual model of COPD prognosis. Internal validation of the outputs predicted by the model was conducted by comparing them with published estimates of decline in reported lung function (measured as FEV₁) and exercise capacity (measured as six-minute walking distance [6MWD]) within the ECLIPSE dataset. In addition, we compared the predicted exacerbation count, survival, and HRQoL with the observed data during each of the three years of ECLIPSE. ECLIPSE data were presented as point estimates with associated 95% confidence intervals (CIs) at the relevant time points. Estimated covariance matrices are reported in Appendix B (moderate exacerbations, fixed effects [Table A8]; severe exacerbations, fixed effects [Table A9]; FEV₁, fixed effects [Table A10]; dyspnea, most versus none or several days, fixed effects [Table A11]; dyspnea (none vs most or several days), fixed effects [Table A12]; cough and sputum, fixed effects [Table A13]; 6MWD, fixed effects [Table A14]; SGRQ, fixed effects [Table A15]; mortality, fixed effects [Table A16]; survival, fixed effects [Table A17]; probability of hospitalization [Table A18]; ward days [Table A19]; intensive care unit [Table A20]; emergency room visits [Table A21]; days and nights at home [Table A22]; office visits [Table A13]; outpatient visits [Table A24]).

Structure of the model

The model described the important prognostic factors for COPD disease progression at baseline; the disease progression attributes that evolve over the lifetime of the model, such as exacerbations, lung function, exercise capacity, and symptoms; and the final outcomes of mortality, health-related quality of life (HRQoL), and health service resource use. In particular, lung function and exacerbations were assumed to affect each other in the conceptual model, with lung function affecting symptoms, symptoms affecting exacerbations and all three of these attributes affecting exercise capacity [12]. These relationships from the final conceptual model development were used as the basis for estimating a series of linked statistical equations based on data from ECLIPSE, which formed the epidemiological foundation of the disease model [13].

The statistical equations were brought together to estimate the course of COPD for a patient cohort in terms of the disease progression attributes defined in the conceptual model, through to final health outcomes of (quality adjusted) life expectancy, and health service cost. Observational data from ECLIPSE were used to estimate associations between disease progression attributes, together with mortality and HRQoL (measured by the St George's Respiratory Questionnaire for COPD [SGRQ-C]) [16], while adjusting for prognostic baseline covariates. However, because ECLIPSE did not record health service resource use, the resource use equations were estimated using data from TORCH.

Figure 1a illustrates the links between the statistical risk equations from the baseline prognostic variables through to the disease progression attributes of COPD [13] representing the relationships described in the conceptual model [12] above. Figure 1b shows the associations from the baseline covariates and the disease progression attributes through to the final health outcomes.

The Galaxy COPD model starts with the baseline covariates recorded in ECLIPSE (Appendix Table A1) and then builds on these by predicting how the baseline covariates affect the disease progression attributes of exacerbations, lung function, exercise capacity, and symptoms). Not all baseline variables were used in every equation, though all variables from Table A1 appeared in at least one of the equations. The baseline variables and longitudinal disease progression attributes are then used together to predict the final health outcomes of HRQoL/utility, survival, and health service resource use and cost over lifetime.

Health service resource use and cost. Compared with previously reported statistical analyses [13], the model represented in Figures 1a and 1b includes health service resource use added to the list of final health outcomes. COPD-related health service resource use was based on an analysis of the TORCH data from the following health service resource use categories: hospital bed days (general ward, intensive care unit), emergency room visits, and outpatient visits (hospital, physician office, home day/night). Negative binomial count data models with a log link were used for the resource counts, adjusted for the baseline variables from the TORCH study, and are reported in full in Appendix A. Indicator variables for the treatment arm of the TORCH study were not used, so the intercept of the models (along with the rest of the coefficients) effectively represents a pooling across all treatment arms of TORCH.

Weighting-predicted health service resource use in each category computed using the relevant United Kingdom unit costs for that category [17-19] enabled the annual health service costs associated with the progression of COPD to be calculated, taking into account the baseline factors as well as the central disease attributes on costs. These costs were then discounted at an annual rate of 3.5% [20] to provide the net present value of COPD costs, predicted over the lifetime of each patient who enters the model.

Mapping SGRQ score to EuroQol-5 dimension (EQ-5D) utility. The previously reported statistical equations predict the patient-reported outcome of SGRQ-C, as collected in ECLIPSE [13]. However, for health economic modeling, a cardinal utility measure of HRQoL, such as the EQ-5D, is required as a basis for estimating quality-adjusted life years (QALYs). This was achieved firstly by converting SGRQ-C score to SGRQ Total score, as described previously [13], based on guidance from the user manual [15]. A mapping function, estimated from data available in TORCH where both instruments had been collected, suggested the following relationship between EQ-5D and SGRQ Total score [21]:

$$\text{EQ-5D} = 0.9617 - 0.0013 \times \text{SGRQ} - 0.0001 \times \text{SGRQ}^2 + 0.0231 \times \text{male}$$

The longitudinal survival, lung function, exacerbations, symptoms and exercise capacity equations included a time trend term in the regression models [13]. These equations were projected from the observed three years of the ECLIPSE study to estimate lifetime outcomes. Weighting-predicted survival each year by predicted EQ-5D gave a yearly estimate of quality-adjusted survival. Summing this over the lifetime of the model, and applying a discount rate of 3.5% [20] gave the net present value of estimated QALYs over the lifetime of each patient entering the model.

Cohort estimation and baseline values

In order to generate predicted values for the ECLIPSE cohort (employing the statistical equations reported previously [13] and the resource use equations described above and reported in the Appendix) the baseline characteristics of each of the 1957 patients forming the estimation sample of ECLIPSE were entered into the model. Not all equations include all baseline characteristics as covariates, but the set of baseline characteristics reported indicate that they were important predictors of outcome in at least one of the statistical

equations (see [13] for full details). The resulting predictions of lifetime health service resource use cost and QALYs for each patient were estimated based on the predicted symptoms, exacerbations, lung function, and exercise capacity as presented in Figures 1A and B. The distribution of costs and QALYs gave an indication of the heterogeneity of outcomes predicted by the model, for cohort members with different characteristics. Averaging these estimates gave the predicted average lifetime costs and QALYs for the entire ECLIPSE cohort. There has been much interest in the role of past exacerbations as a predictor of future exacerbations [22]. Therefore the importance of exacerbation history in the model is also explored as a prognostic variable.

Probabilistic sensitivity analysis

Uncertainty in each of the statistical model equations was represented through the variance covariance matrix of the estimated statistical model. This represents not only the variance of the estimated coefficients, but also their covariance, allowing the probabilistic sensitivity analysis to account for both the parameter uncertainty, and the potential correlation between input parameters. The method of Cholesky decomposition [23] was employed to correlate draws from a multivariate normal distribution of parameter values within each equation. This uncertainty was propagated through the model structure, in order to estimate the uncertainty associated with the lifetime cost and QALY predictions of the model. This estimation of uncertainty is conditional on the individual characteristics of the patient and provides a patient-characteristic specific estimate of uncertainty in the predictions of the model. Heterogeneity is represented by the differing predictions for patients with different characteristics, while uncertainty is estimated given a set of patient characteristics. Uncertainty estimates are therefore nested within the estimated heterogeneity and are handled separately by the model.

RESULTS

Validating model projections at three years

Table 1 shows the predicted results for each of the three years of the model, for overall survival, disease progression attributes, and HRQoL. Figure 5a compares the predicted and observed survival for the three years of ECLIPSE. For FEV₁, the estimated annual decline based on the ECLIPSE study has previously been reported as 33mL (95% CI: 29, 37) [24]. This is a relatively good fit with the estimated 27mL annual decline estimated using the statistical equations that control for changes in other predictors of the disease progression attributes [13], which becomes a 39mL decline once the effects of moderate and severe exacerbations on FEV₁ are taken into account. Figure 5 also shows the observed and predicted values of % predicted FEV₁, moderate and severe exacerbations, symptoms, and HRQoL as measured by SGRQ Total score over the first three years of the model. The annual rate of total and severe exacerbations in the first year was previously reported as 1.21 and 0.22, respectively (CI not reported) [22]. This is comparable with 1.20 and 0.21 total and severe exacerbations per patient as predicted by the model. The annual decline in 6MWD for ECLIPSE patients was previously reported as 5.7m (CIs not reported) [25]. This is comparable with the 7.8m decline estimated using the statistical equation [13], which becomes 6.1m when the effects of lung function, exacerbations and symptoms over time are taken into account. The predicted SGRQ-C values were significantly different from the observed values in years 2 and 3. In general terms, the predictions of lung function and severe exacerbations were closer to the reported values for ECLIPSE than the predicted values for moderate exacerbations, symptoms, mortality, and quality of life.

Heterogeneity of costs and QALYs

Averaging over the predicted cost and QALY outcomes for the different patients within the ECLIPSE cohort gives an estimated lifetime cost of £25,214 (undiscounted) and £20,318 (discounted) and lifetime QALY of 6.45 (undiscounted) and 5.24 (discounted) per patient in the ECLIPSE cohort. As described above, results from the model predictions are individualized based on the characteristics of the patient. However, the average per-patient lifetime costs and QALYs presented above mask the differences in the individual patient predictions. Figure 2 shows the joint distribution of predicted lifetime costs and QALYs for the 1957 patients from ECLIPSE, based on the data for those patients with a full dataset available at baseline. In addition to the joint distribution on the cost-effectiveness plane, the univariate distributions for lifetime cost and QALYs are shown.

As is commonly observed in practice, both health outcomes and costs are predicted to be positively skewed across patients.. The correlation between predicted cost and QALY outcomes was modest, with an estimated correlation coefficient of 0.08, reflecting the competing influences that patients who live longer generally incur more costs, but that those with shorter survival are generally in more advanced stages of disease and cost more.

Lifetime projections by history of exacerbation

Figure 3 shows the projected survival (undiscounted, Figure 3a) and total accumulated cost (discounted, Figure 3b) for an average patient in ECLIPSE within two subgroups: those with no history of exacerbation at study entry, and those with a history of exacerbation at study entry. It is clear from the two panels of Figure 3 that history of exacerbation is associated with lower survival and increased cost over the lifetime of the patient.

Analysis of uncertainty

A probabilistic sensitivity analysis was employed to explore the uncertainty in lifetime costs and QALYs for two types of patient based on ECLIPSE equations: those with no history of exacerbation at study entry, and those with a history of exacerbation at study entry. These results are presented on the cost-effectiveness plane in Figure 4. Summary results of the uncertainty analysis reveal uncertainty in estimates for these two patient subgroups: the additional QALYs was 0.48 for the no-exacerbation history group (95% CI: – 1.15, 1.91) with the additional costs for the exacerbation group being £4961 (95% CI: –£491, £11,607) more expensive.

DISCUSSION

We have presented a new model of COPD that was constructed from an initial conceptualization of the disease, and validated using the data source that was used to estimate model parameters. To date, most other models have employed state transition models based on % predicted FEV₁ as a measure of disease progression. In the present analysis, we have broadened the definition of COPD progression to incorporate exacerbations, lung function, exercise capacity, and symptoms as central attributes of the condition. This approach is consistent with a more contemporary definition of disease severity based on the multifactorial understanding of COPD [7-9]. Although all previous models have incorporated exacerbations they have tended to do so based on the consideration that this is a state that is dependent only on % predicted FEV₁, and without estimating the relationship between exacerbations and disease progression. One exception is the Dutch population model of COPD, where each exacerbation causes the FEV₁% predicted to decline with 0.19% (95% CI: 0.092, 0.29) [26].

The implementation of the model is also novel. The use of a linked equations approach is not commonly used in HTA modeling, though it has clear links to the epidemiological literature of causal modeling. The approach was made possible through the existence of the ECLIPSE study, which provided a rich source of data from which to estimate the interconnected relationships that defined our conceptual model. Furthermore, we were able to show that the model was able to predict back the outcomes of the ECLIPSE study – although the less than perfect fit in some cases was due to the fact that the structure imposed by the conceptual model required all equations to be fit in a particular way, with particular interdependencies. For example, the conceptual model suggested that exacerbation history was expected to impact lung function [12], while lung function was expected to in turn impact the chance of exacerbation, and the empirical results confirmed this to be the case [13]. The resulting model estimated both jointly, adding structure to the analysis. An unrestricted prediction model of each outcome independently without representing those interdependencies would undoubtedly have provided a better fit to the data, but would have lost the richness of the interdependencies the current model is able to estimate. It is these interdependencies that allow the estimation of the impact of treatment that is shown to affect a surrogate endpoint (e.g., symptoms and/or FEV₁% predicted) on final outcomes.

ECLIPSE was an observational study, designed to gain a better understanding of COPD as a disease. This made it ideal in many respects for developing a new model of COPD disease progression. The purpose of developing the present model was to provide a method for estimating long-term treatment effects where new and existing treatments for COPD are observed to impact on a variety of prognostic markers. We anticipate that

the model is most likely to be used when treatment is shown to impact a combination of the disease progression attributes of exacerbations, lung function, exercise capacity, or symptoms.

One of the features of the Galaxy COPD model is the way in which it estimates patient-characteristic specific uncertainty in a manner that captures uncertainty in prognosis for individual patients with different characteristics. In this way, the model is able to represent uncertainty in the predicted costs and QALY outcomes based on the estimated parameters, which include parameters describing heterogeneity between individuals. The uncertainty analysis is therefore nested within the analysis of heterogeneity with the consequence that while uncertainty can be quantified for individual patient predictions (or equivalently for homogeneous cohorts) it is not clear how uncertainty can be represented in the mean outcomes of heterogeneous cohorts.

The strengths of our approach include explicit documenting of an underlying conceptual model, and validation of the model constructed according to best practice guidelines [10,11,27]. Furthermore, the model incorporates not only the effect of lung function, but also exacerbations, exercise capacity, and symptoms. When combined with baseline prognostic variables, this results in a highly flexible model that can generate predicted changes in QALYs and health service resource costs associated with a wide variety of potential treatments or disease management strategies for COPD, as well as explore potential subgroup analyses. Treatment effects can be incorporated into the model in two ways. Firstly, if there is evidence of the treatment effect on a given surrogate endpoint included in the model, the effect of changes to this endpoint on the final cost, survival, and HRQoL (QALY) outcomes can be estimated. Secondly, if direct evidence of the treatment effect on both surrogate and final outcomes is available, then the model can estimate the central association corrected treatment effect that acts independently of the central associations.

Nevertheless, there are limitations to the modeling approach adopted. Firstly, the model is based on a single, albeit large, cohort study of COPD, and therefore the generalizability of the model is dependent on the generalizability of the ECLIPSE study cohort. The linked equations approach to modeling is likely to be unfamiliar to many potential users of the model and this may limit its acceptance by decision makers. For this reason, an extensive validation of the model predictions is required. An internal validation against the ECLIPSE data was presented, and revealed that in seeking to predict a number of different outcomes simultaneously, the fit achieved was not as good as if a single model had been used to fit each of these outcomes independently. Nevertheless, the ability of a model to fit the data used to estimate its parameters is a necessary, but not

sufficient, condition for validation. In practice, external validation (i.e., the ability of the model to predict data not used in its construction) is much more important than internal validation. In the next paper of the series, we will report the ability of the model to predict outcomes in two large clinical trials that included COPD patients: the TORCH study [15] and the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study [28].

CONCLUSIONS

We have reported the conceptualization, implementation, and internal validation of a new form of model for COPD that is based on a series of linked equations estimated from a longitudinal cohort study of COPD patients. This Galaxy COPD model is capable of predicting COPD outcomes for a variety of potential treatment effects on intermediate risk factors in both the short and long term. Further external validation of short- and long-term predictions of the model is required.

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AUTHOR CONTRIBUTIONS

AB, MC, NL, DL, MT, and **HM** were involved in the conception and design of the study, data analysis, and data interpretation; **TB, NR, SG, AE,** and **CC** contributed to the conception and design of the

study/model and performed programming, data analysis, and reporting; **MRvM** was involved in developing the conceptual model, designing the study, and interpreting the data. She reviewed the article critically and approved the final version that was submitted; **ASI** contributed to the design, analysis, and data interpretation.

AUTHOR CONFLICTS OF INTEREST

MC, AI, MT, HM, NL are employees of and hold stock in GSK. **SGM** was an employee of GSK at the time of the research and analyses of this project, and is currently an employee of Amgen.

AB, TB, NR, AE, CC have received funding as a consultant and through Oxford Outcomes Ltd (now known as ICON Plc) from GSK related to the development of this model.

MRvM has published on other economic models of chronic obstructive pulmonary disease, either developed with public funding or pharmaceutical industry funding. She has received a fee for participating in the Steering Group. In recent years she has received unrestricted research grants from Astellas (Nycomed/Takeda), Boehringer Ingelheim, and GSK. She also received speaker's fees from these companies.

DAL has received grant support, honoraria and consultancy fees from GSK. He is the Chair of the GSK Respiratory Therapy Area Board.

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Table 1 Model Predictions Over the 3-Year Timeframe of ECLIPSE

	Baseline		Year 1		Year 2		Year 3	
Individual simulations	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>n</i> = 1957	(95% CI)		(95% CI)		(95% CI)		(95% CI)	
Predicted survival, %	100.0		96.9	2.8	92.2	6.5	86.9	10.3
			(96.1, 97.6)		(91, 93.4)		(85.4, 88.4)	
FEV₁ % predicted, %	48.1	15.6	47.0	15.5	46.1	15.3	45.2	15.2
	(47.4, 48.8)		(46.3, 47.7)		(45.4, 46.8)		(44.5, 45.8)	
FEV₁, mL	1343	513	1302	507	1265	499	1227	492
	(1320, 1365)		(1280, 1324)		(1243, 1287)		(1206, 1249)	
Total exacerbations in previous 12 months			1.236	0.711	1.215	0.713	1.205	0.720
			(1.204, 1.267)		(1.184, 1.247)		(1.173, 1.237)	
<i>Moderate, count</i>			1.032	0.570	0.968	0.537	0.908	0.503
			(1.007, 1.057)		(0.945, 0.992)		(0.885, 0.930)	
<i>Severe, count</i>			0.204	0.182	0.247	0.222	0.297	0.269
			(0.196, 0.212)		(0.237, 0.257)		(0.286, 0.309)	

Dyspnea symptoms

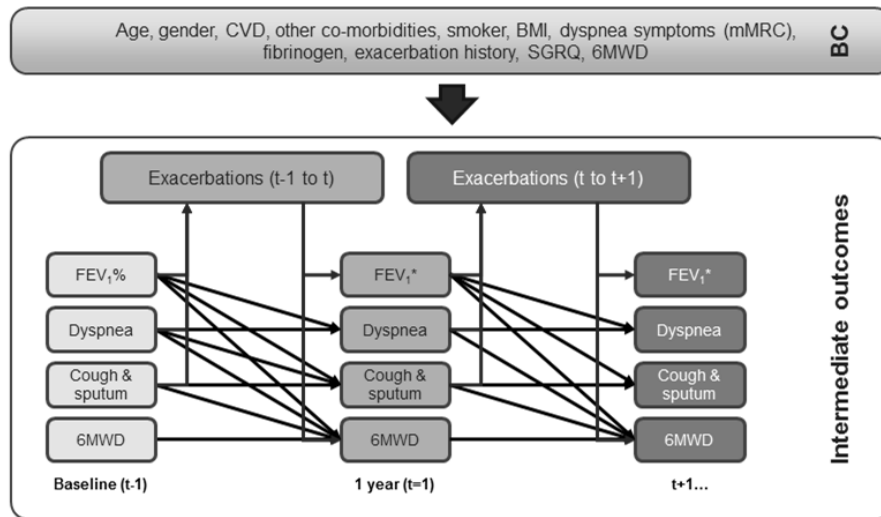
<i>Most days, %</i>	58.1 (55.9, 60.3)	29.4	58.8 (56.6, 60.9)	29.4	60.1 (57.9, 62.2)	29.3	61.3 (59.2, 63.5)	29.1
<i>Several days, %</i>	35.3 (33.2, 37.4)	22.3	34.7 (32.6, 36.8)	22.1	33.5 (31.4, 35.6)	22.0	32.4 (30.4, 34.5)	21.9
<i>None, %</i>	6.6		6.5		6.4		6.3	
Cough and sputum								
<i>With criteria,* %</i>	48.3 (46.1, 50.5)	24.5	47.5 (45.3, 49.7)	24.5	46.9 (44.6, 49.1)	24.6	46.2 (44, 48.4)	24.6
<i>Without criteria,† %</i>	51.7		52.5		53.1		53.8	
SGRQ-C score	50 (49.1, 50.9)	20.164	51.2 (50.3, 52.2)	20.686	52.2 (51.3, 53.2)	20.723	53.2 (52.3, 54.2)	20.755
6MWD, m	369.9 (364.5, 375.3)	121.346	362.6 (357.3, 368.0)	121.393	353 (347.7, 358.3)	119.699	343.4 (338.2, 348.6)	117.986

6MWD, six-minute walk distance; FEV₁, forced expiratory volume in one second; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire for COPD.

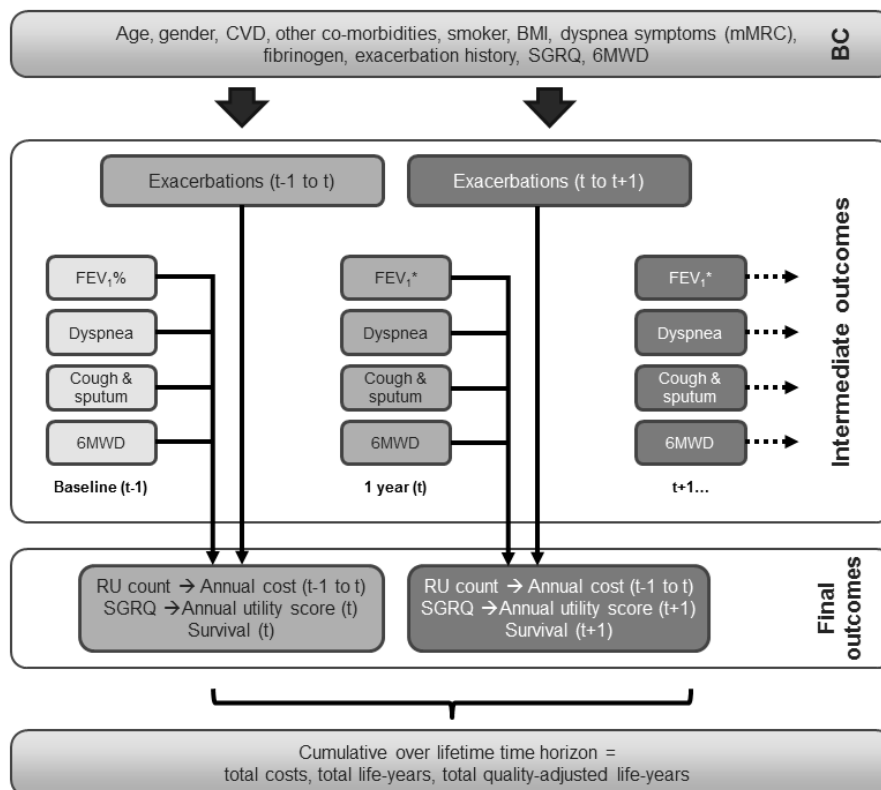
*With criteria: cough and/or sputum most days per week; †Without criteria: cough and/or sputum not at all or several days per week

Figure 1. Linking baseline prognostic variables, through disease progression attributes, to final COPD outcomes. Panel (a) shows the relationship between the central attributes in the different time periods. Panel (b) shows the relationship between the central attributes and the final health outcomes.

a)



b)



*The associations between disease progression attributes shown in Figure 1a are omitted to aid clarity of presentation. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; BMI, body mass index; mMRC, modified Medical Research Council questionnaire; SGRQ, St George's Respiratory Questionnaire score; 6MWD, six-minute walking distance; BC, baseline covariates; FEV₁, forced expiratory volume in one second; RU, resource utilization; t, time; QALY, quality-adjusted life years. *FEV₁ (mL) was calculated using the risk equation at year 't' and converted to FEV₁ % predicted based on the cohort profile.*

Figure 2. Joint distribution of predicted lifetime costs and QALYs for individual patients on the cost-effectiveness plane together with histograms of the cost and QALY histograms showing heterogeneity across the 1957 patients with complete data in ECLIPSE.

Lifetime costs (in £000s) on natural log scale. QALY, quality-adjusted life years.

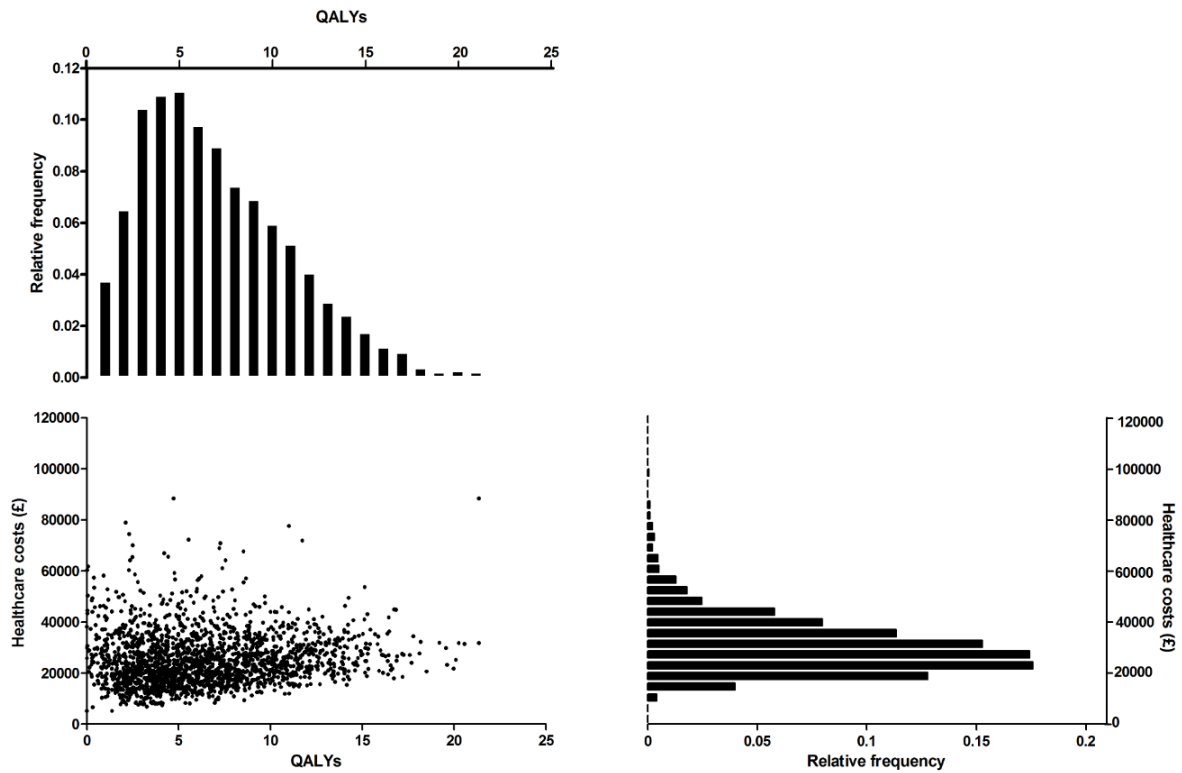
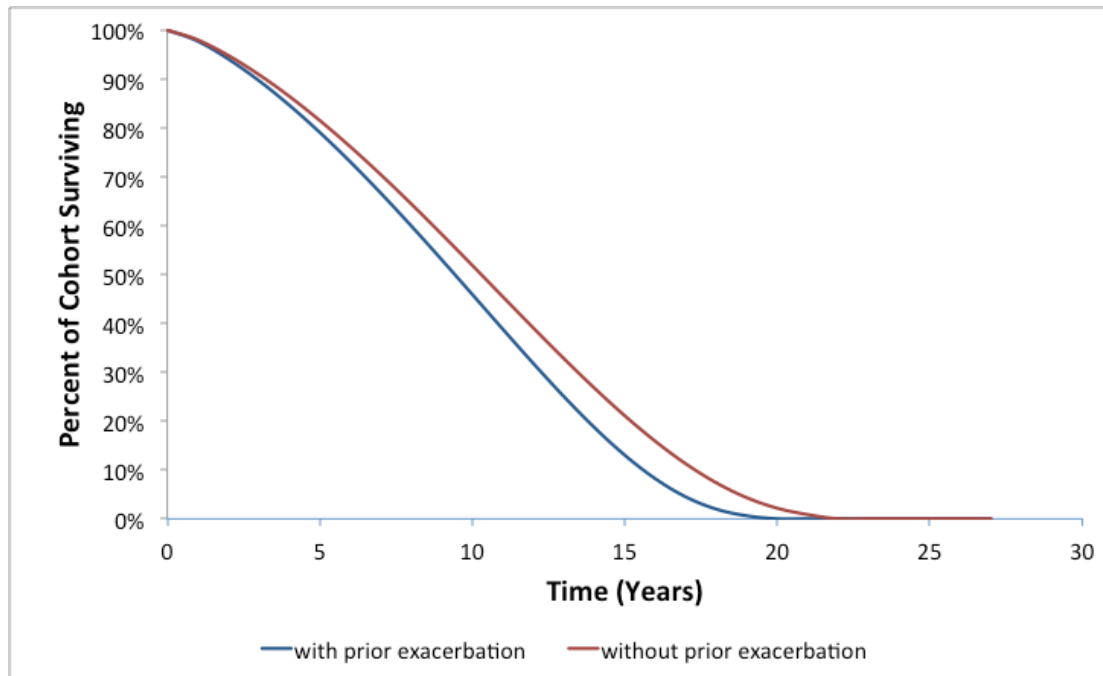


Figure 3. Lifetime projections for ECLIPSE cohort of (a) survival and (b) cumulative costs for patients with and without prior exacerbations.

(a)



(b)

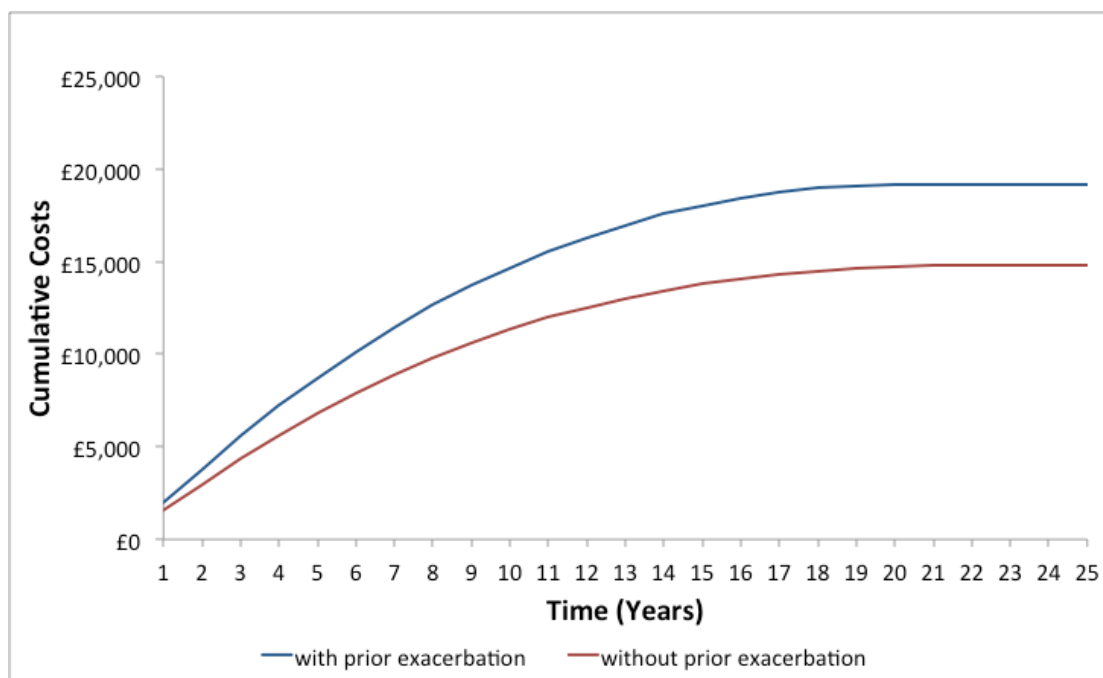
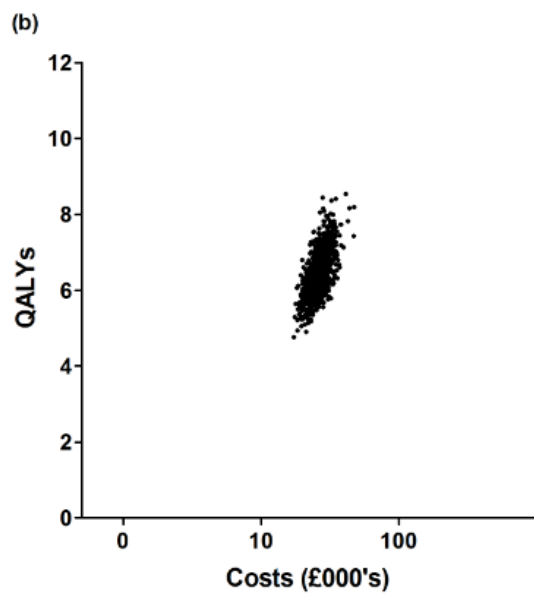
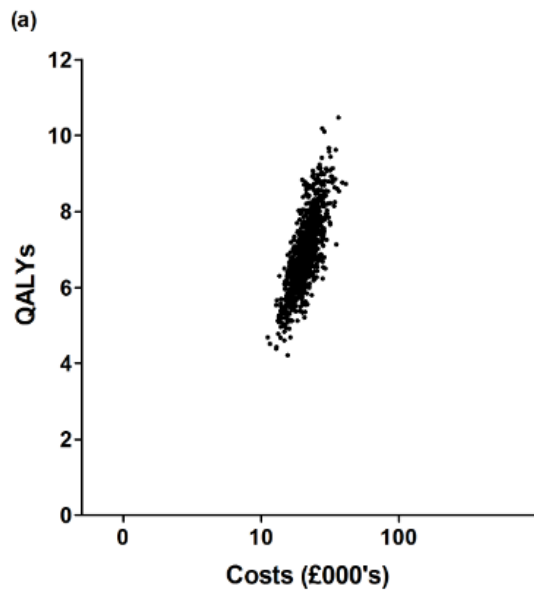
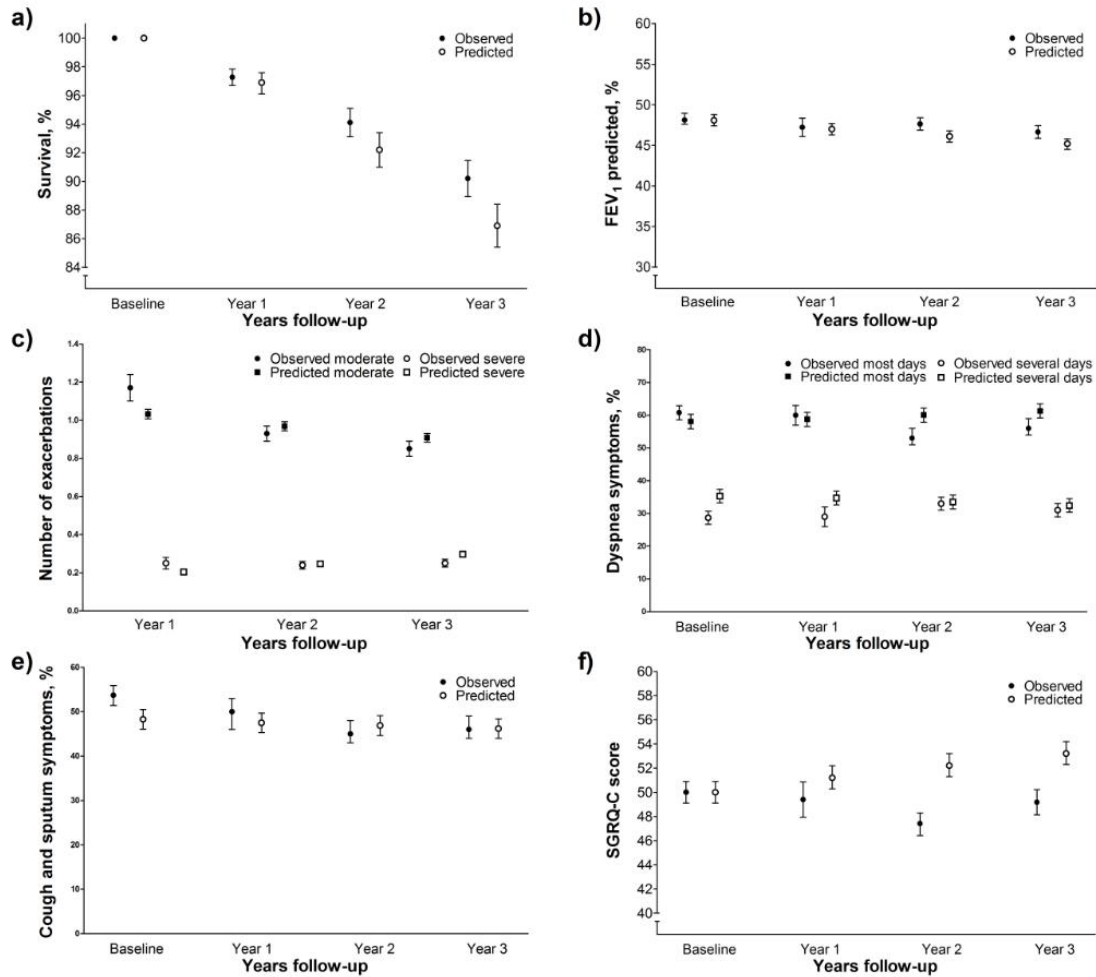


Figure 4. Illustration of probabilistic uncertainty for ECLIPSE subgroups on the cost-effectiveness plane for (a) patients with no history of exacerbation and (b) patients with a history of exacerbations.



QALY, quality-adjusted life years.

Figure 5. Observed versus predicted outcomes from ECLIPSE over three years for (a) survival (b) % predicted FEV₁ (c) moderate and severe exacerbations (d) dyspnea symptoms (e) cough and/or sputum symptoms and (f) SGRQ-C score.



FEV₁, forced expiratory volume in one second; SGRQ-C, St George's Respiratory Questionnaire for COPD.

**Development of the Galaxy Chronic Obstructive Pulmonary Disease
(COPD) Model Using Data from ECLIPSE: Internal Validation of a
Linked Equations Cohort Model**

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Sebastian Gonzalez-McQuire, MSc[†], Afisi S. Ismaila, PhD, Alex Exuzides, PhD, Chris Colby, PhD,
Maggie Tabberer, MSc, Hana Muellerova, PhD, Nicholas Locantore, PhD, Maureen Rutten van-
Mölken, PhD, David A. Lomas, PhD FRCP*

Online supplementary material

The TORCH study included three years' follow-up for every patient without censoring. The equations reported represent the estimated yearly resource use estimated from the three years of resource use data collected in TORCH

Table A1 Baseline Patient Characteristics for ECLIPSE and TORCH

	ECLIPSE	TORCH (Pooled All Arms)
	(n = 1957)	(n = 6108)
<i>Baseline characteristics</i>		
Mean age (SD), yrs	63.4 (7.1)	65.0 (8.3)
Gender (male), %	65.5	76.0
Mean height (SD), cm	169.4 (8.8)	168.7 (8.8)
Body mass index, %		
Low ≤ 20 kg/m ²	14.7	13.0
Med $>20 - \leq 30$ kg/m ²	63.1	70.0
High >30 kg/m ²	22.3	17.0
Current smokers, %	36.6	43.0

CVD comorbidity, %	32.9	22.0
'Other' comorbidity,* %	73.3	79.0
≥1 exacerbation in prior year, %	47.1	57.0
Mean exacerbations in prior year (SD)	0.78 (0.88)	0.89 (0.86)
Mean fibrinogen (SD), mcg/mL	460.5 (104.8)	–
mMRC score, %		
0	12.7	7.0
1	34.0	42.5
≥2	53.2	50.5

Longitudinal outcomes

FEV₁, mL

Mean (SD) 1342 (513) 1226 (444)

95% CI 1320, 1365 1215, 1237

FEV₁% predicted

Mean (SD) 48.1 (15.5) 44.0 (12.4)

95% CI 47.4, 48.8 43.7, 44.3

Dyspnea symptoms (most days per week), %

95% CI 60.8 48.0

58.6, 62.9 46.0, 49.0

Dyspnea symptoms (several days per week), %

Mean 28.7 45.0

95% CI	26.7, 30.7	44.0, 46.0
Dyspnea symptoms (none), %		
Mean	10.6	7.0
95% CI	9.22, 11.9	7.0, 8.0
Cough or sputum (most days per week), %		
Mean	53.7	49.0
95% CI	51.4, 55.9	48.0, 50.0
6MWD, m		
Mean (SD)	369 (121)	—
95% CI	365, 375	
SGRQ-C score		
Mean (SD)	48.1 (15.5)	49.3 (17.1)

95% CI	47.4, 48.8	48.8, 49.8
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SD, standard deviation; 6MWD, six-minute walking distance; CI, confidence interval; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council questionnaire; SD, standard deviation; SGRQ-C, St George's Respiratory Questionnaire for COPD. *'Other' comorbidity includes any reported non-CVD comorbidity.

APPENDIX A TORCH Resource Utilization Risk Equations

Table A2 Resource Utilization – Ward Days (excluding ICU wards)

Explanatory Variable	Effect	95% Confidence Intervals		P Value
		Lower	Upper	
Intercept	-1.0688	-1.7276	-0.4101	0.0015
Time, years	0.1103	0.0369	0.1836	0.0032
Recent moderate exacerbations	-0.0781	-0.0939	-0.0624	<0.0001
Recent severe exacerbations	0.4721	0.4518	0.4925	<0.0001
FEV ₁ % predicted (lagged 12 months)	-0.0149	-0.0190	-0.0108	<0.0001
Dyspnea symptom (lagged 12 months) - most days versus none	0.2125	-0.0232	0.4482	0.0773
Dyspnea symptom (lagged 12 months) - several days versus none	0.2679	0.0388	0.4969	0.0219
Cough and sputum (lagged 12 months)	0.1864	0.0660	0.3067	0.0024
Age, years	0.0105	0.0032	0.0178	0.0051
CVD comorbidity (yes versus no)	0.0269	-0.0996	0.1535	0.6768
Other comorbidity (yes versus no)*	-0.1690	-0.3047	-0.0334	0.0146
Smoking status (current versus former)	-0.1992	-0.3185	-0.0799	0.0011
Gender (female versus male)	-0.1495	-0.2951	-0.0039	0.0442

BMI (high versus normal)	-0.3781	-0.5557	-0.2005	<0.0001
BMI (low versus normal)	0.2960	0.1678	0.4241	<0.0001
Baseline mMRC (mMRC \geq 2)	-0.0046	-0.2553	0.2461	0.9715
Baseline SGRQ	0.0147	0.0109	0.0185	<0.0001
Prior exacerbations (\geq 1 versus 0)	0.4613	0.3383	0.5843	<0.0001

Number of patients=4669

Number of observations=11,463

AIC=63,631.99

AIC, Akaike information criterion; BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; ICU, intensive care unit; mMRC, modified Medical Research Council score; SGRQ, St George's respiratory questionnaire. *Other, any reported non-CVD comorbidity. Bold = $P < 0.05$.

Table A3 Resource Utilization – ICU Days

Explanatory Variable	Effect	95% Confidence Intervals		P Value
		Lower	Upper	
Intercept	-2.1133	-4.2101	-0.0166	0.0482
Time, years	0.5465	0.2952	0.7979	<0.0001
Recent moderate exacerbations	0.0245	-0.0161	0.0650	0.2371
Recent severe exacerbations	0.4223	0.3608	0.4838	<0.0001
FEV ₁ % predicted (lagged 12 months)	-0.0238	-0.0377	-0.0100	0.0007
Dyspnea symptoms (lagged 12 months) - most days versus none	-0.5286	-1.2178	0.1607	0.1328
Dyspnea symptoms (lagged 12 months) - several days versus none	-0.0624	-0.6960	0.5712	0.8470
Cough and sputum (lagged 12 months)	-0.0344	-0.4437	0.3750	0.8693
Age, years	-0.0029	-0.0275	0.0216	0.8153
CVD comorbidity (yes versus no)	0.6546	0.2688	1.0404	0.0009
Other comorbidity (yes versus no)*	0.3295	-0.1954	0.8544	0.2186
Smoking status (current versus former)	0.3026	-0.0922	0.6974	0.1330
Gender (female versus male)	-0.9816	-1.5658	-0.3974	0.0010
BMI (high versus normal)	0.0403	-0.4761	0.5567	0.8784

BMI (low versus normal)	0.2310	-0.2199	0.6819	0.3154
Baseline mMRC (mMRC ≥ 2)	-0.7611	-1.3680	-0.1543	0.0140
Baseline SGRQ	0.0142	0.0015	0.0268	0.0282
Prior exacerbations (≥ 1 versus 0)	-0.0076	-0.3889	0.3737	0.9688

Number of patients=4669

Number of observations=11,463

AIC=10,959.29

AIC, Akaike Information Criterion; BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; ICU, intensive care unit; mMRC, modified Medical Research Council score; SGRQ, St George's Respiratory Questionnaire. *Other, any reported non-CVD comorbidity. Bold = $P < 0.05$.

Table A4 Resource Utilization – Emergency Room Visits

Explanatory Variable	Effect	95% Confidence Intervals		P Value
		Lower	Upper	
Intercept	-2.3762	-4.2039	-0.5485	0.0108
Time, years	-0.087	-0.2969	0.1229	0.4168
Recent moderate exacerbations	0.076	0.0427	0.1093	<0.0001
Recent severe exacerbations	0.2387	0.1736	0.3038	<0.0001
FEV ₁ % predicted (lagged 12 months)	-0.0200	-0.0319	-0.0082	0.0002
Dyspnea symptoms (lagged 12 months) - most days versus none	0.1244	-0.5732	0.8219	0.7268
Dyspnea symptoms (lagged 12 months) - several days versus none	0.1653	-0.4980	0.8286	0.6252
Cough and sputum (lagged 12 months)	-0.0627	-0.4055	0.2801	0.7200
Age, years	0.0157	-0.0056	0.0370	0.1489
CVD comorbidity (yes versus no)	-0.1036	-0.4877	0.2806	0.5973
Other comorbidity (yes versus no)*	-0.2442	-0.6403	0.1520	0.2270
Smoking status (current versus former)	-0.1766	-0.5235	0.1703	0.3185
Gender (female versus male)	-0.4055	-0.8142	0.0032	0.0518
BMI (high versus normal)	-0.6200	-1.1691	-0.0709	0.0269

BMI (low versus normal)	0.3220	-0.0449	0.6889	0.0854
Baseline mMRC (mMRC ≥ 2)	-0.4203	-0.9795	0.1390	0.1408
Baseline SGRQ	0.0046	-0.0061	0.0152	0.4013
Prior exacerbations (≥ 1 versus 0)	0.2226	-0.1104	0.5557	0.1901

Number of patients=4669

Number of observations=11,463

AIC=8856.77

AIC, Akaike information criterion; BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council score; SGRQ, St George's respiratory questionnaire. *Other, any reported non-CVD comorbidity. Bold = $P < 0.05$.

Table A5 Resource Utilization – Day and Night Home Visits

Explanatory Variable	Effect	95% Confidence Intervals		P Value
		Lower	Upper	
Intercept	-7.1905	-10.5055	-3.8755	< 0.0001
Time, years	-0.3722	-0.7330	-0.0114	0.0432
Recent moderate exacerbations	0.0243	-0.0452	0.0938	0.4929
Recent severe exacerbations	0.1544	-0.0022	0.3110	0.0533
FEV ₁ % predicted (lagged 12 months)	-0.0106	-0.0291	0.0079	0.2603
Dyspnea symptoms (lagged 12 months) - most days versus none	-0.8936	-1.8308	0.0435	0.0616
Dyspnea symptoms (lagged 12 months) - several days versus none	-0.3437	-1.1905	0.5031	0.4263
Cough and sputum (lagged 12 months)	-0.0562	-0.6063	0.4940	0.8414
Age, years	0.0297	-0.0053	0.0648	0.0965
CVD comorbidity (yes versus no)	0.1027	-0.4805	0.6859	0.7300
Other comorbidity (yes versus no)*	0.3729	-0.3412	1.0869	0.3061
Smoking status (current versus former)	-0.1645	-0.7229	0.3938	0.5635
Gender (female versus male)	-0.1454	-0.7972	0.5063	0.6618
BMI (high versus normal)	-0.7955	-1.7509	0.1599	0.1027

BMI (low versus normal)	0.2669	-0.3350	0.8687	0.3848
Baseline mMRC (mMRC ≥ 2)	0.9875	-0.6672	2.6422	0.2421
Baseline SGRQ	0.0127	-0.0042	0.0296	0.1417
Prior Exacerbations (≥ 1 versus 0)	1.3104	0.6188	2.0019	0.0002

Number of patients=4669

Number of observations=11,463

AIC=3025.99

AIC, Akaike information criterion; BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council score; SGRQ, St George's respiratory questionnaire. *Other, any reported non-CVD comorbidity. Bold = $P < 0.05$. Note: includes day and night time home visits by a health care worker.

Table A6 Resource Utilization – Outpatient Physician Office Visits

Explanatory Variable	Effect	95% Confidence Intervals		P Value
		Lower	Upper	
Intercept	-0.3691	-1.1591	0.4209	0.3598
Time, years	0.0531	-0.0369	0.1430	0.2476
Recent moderate exacerbations	0.1105	0.0981	0.1230	<0.0001
Recent severe exacerbations	0.0391	-0.0129	0.0912	0.1405
FEV ₁ % predicted (lagged 12 months)	-0.0108	-0.0158	-0.0058	<0.0001
Dyspnea symptoms (lagged 12 months) - most days versus none	0.6740	0.3144	1.0335	0.0002
Dyspnea symptom (lagged 12 months) - several days versus none	0.4651	0.1161	0.8142	0.0090
Cough and sputum (lagged 12 months)	0.1559	0.0074	0.3044	0.0396
Age, years	-0.0114	-0.0201	-0.0027	0.0100
CVD comorbidity (yes versus no)	-0.0645	-0.2312	0.1022	0.4480
Other comorbidity (yes versus no)*	0.0262	-0.1691	0.2214	0.7928
Smoking status (current versus former)	-0.2163	-0.3653	-0.0673	0.0044
Gender (female versus male)	0.1847	0.0287	0.3407	0.0203
BMI (high versus normal)	-0.2485	-0.4379	-0.0591	0.0101

BMI (low versus normal)	-0.2544	-0.4428	-0.0661	0.0081
Baseline mMRC (mMRC \geq 2)	-0.1588	-0.4185	0.1009	0.2307
Baseline SGRQ	-0.0016	-0.0063	0.0030	0.4930
Prior Exacerbations (\geq 1 versus 0)	0.3351	0.1898	0.4805	<0.0001

Number of Patients=4669

Number of Observations=11,463

AIC=25,644.62

AIC, Akaike information criterion; BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council score; SGRQ, St George's respiratory questionnaire. *Other, any reported non-CVD comorbidity.

Table A7 Resource Utilization – Hospital Outpatient Visits

Explanatory Variable	Effect	95% Confidence Intervals		P Value
		Lower	Upper	
Intercept	-0.9087	-2.1694	0.3519	0.1577
Time, years	-0.1898	-0.3425	-0.0371	0.0148
Recent moderate exacerbations	0.0844	0.0589	0.1100	<0.0001
Recent severe exacerbations	0.0406	-0.0485	0.1298	0.3715
FEV ₁ % predicted (lagged 12 months)	-0.0123	-0.0202	-0.0044	0.0023
Dyspnea symptoms (lagged 12 months) - most days versus none	-0.576	-1.0130	-0.1390	0.0098
Dyspnea symptoms (lagged 12 months) - several days versus none	-0.1533	-0.5544	0.2479	0.4539
Cough and sputum (lagged 12 months)	0.1369	-0.1030	0.3768	0.2635
Age, years	-0.0011	-0.0156	0.0134	0.8816
CVD comorbidity (yes versus no)	0.0388	-0.2226	0.3003	0.7709
Other comorbidity (yes versus no)*	-0.2584	-0.5279	0.0110	0.0601
Smoking status (current versus former)	-0.4398	-0.6877	-0.1918	0.0005
Gender (female versus male)	-0.6256	-0.9357	-0.3155	<0.0001
BMI (high versus normal)	-0.6665	-1.0561	-0.2768	0.0008

BMI (low versus normal)	0.2183	-0.0504	0.4869	0.1113
Baseline mMRC (mMRC ≥ 2)	0.0975	-0.3818	0.5769	0.6900
Baseline SGRQ	0.0140	0.0065	0.0214	0.0002
Prior Exacerbations (≥ 1 versus 0)	0.4280	0.1844	0.6717	0.0006

Number of Patients=4669

Number of Observations=11463

AIC=22427.22

AIC, Akaike information criterion; BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council score; SGRQ, St George's respiratory questionnaire. *Other, any reported non-CVD comorbidity.

APPENDIX B Covariance matrices

Table A8 Covariance matrix (moderate exacerbations; fixed effects)

	Intercept	Study years	Time* prior exac.	Any FEV ₁ % predicted	Dyspnea (lagged 12 months), most days	Dyspnea (lagged 12 months), several days	Any symptom	Age	CVD comorbidity (yes)	Other comorbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	Baseline 6MWD	Fibrinogen	Baseline mMRC	Baseline SGRQ	Prior exac.
Intercept	0.0526700	-0.0040100	0.0038690	-0.0000520	-0.0027300	-0.0030180	0.0003053	-0.0003780	0.0004249	-0.0000790	-0.0012830	-0.0008700	-0.0005290	-0.0013160	-0.0000150	-0.0000084	-0.0003970	-0.0000780	-0.0088560
Study years	-0.0040100	0.0018570	-0.0018560	0.0000015	0.0000401	0.0000467	0.0000196	0.0000003	0.0000093	-0.0000032	-0.0000073	-0.0000140	-0.0000029	0.0000240	-0.0000001	0.0000000	0.0000069	0.0000001	0.0038940
Time* prior exac.	0.0038690	-0.0018560	0.0026590	-0.0000001	0.0000112	-0.0000470	-0.0000240	0.0000004	-0.0000220	0.0000044	0.0000136	0.0000090	-0.0000140	-0.0000370	0.0000000	0.0000000	-0.0000003	-0.0000001	-0.0055300
Any FEV₁ % predicted	-0.0000520	0.0000015	-0.0000001	0.0000014	0.0000121	0.0000059	-0.0000020	-0.0000004	-0.0000031	-0.0000043	-0.0000042	-0.0000091	-0.0000087	0.0000071	0.0000000	0.0000000	0.0000062	0.0000001	0.0000047
Dyspnea (lagged 12 months), most days	-0.0027300	0.0000401	0.0000112	0.0000121	0.0045110	0.0037940	-0.0002440	-0.0000093	-0.0000430	-0.0000560	-0.0000280	-0.0001220	-0.0000540	0.0000276	-0.0000005	0.0000002	-0.0001020	-0.0000160	-0.0000680
Dyspnea (lagged 12 months), several	-0.0030180	0.0000467	-0.0000470	0.0000059	0.0037940	0.0044850	-0.0000570	-0.0000044	-0.0000570	-0.0000720	-0.0000820	-0.0000740	0.0000341	-0.0000100	-0.0000006	0.0000002	-0.0000400	-0.0000080	0.0000150
Any symptom	0.0003053	0.0000196	-0.0000240	-0.0000020	-0.0002440	-0.0000570	0.0011110	-0.0000018	0.0000188	-0.0000630	-0.0002620	0.0001260	0.0000371	-0.0000330	-0.0000002	-0.0000002	0.0000221	-0.0000055	-0.0000200
Age	-0.0003780	0.0000003	0.0000004	-0.0000004	-0.0000093	-0.0000044	-0.0000018	0.0000060	-0.0000086	-0.0000063	0.0000220	0.0000123	0.0000099	0.0000044	0.0000001	-0.0000001	-0.0000046	0.0000005	0.0000010
CVD comorbidity (yes)	0.0004249	0.0000093	-0.0000220	-0.0000031	-0.0000430	-0.0000570	0.0000188	-0.0000086	0.0012310	-0.0001450	0.0000133	0.0001986	-0.0000840	-0.0000460	0.0000001	0.0000001	-0.0000190	-0.0000022	0.0000230
Other comorbidity (yes)	-0.0000790	-0.0000032	0.0000044	-0.0000043	-0.0000560	-0.0000720	-0.0000630	-0.0000063	-0.0001450	0.0014140	0.0000499	-0.0001830	-0.0001230	0.0001169	0.0000001	-0.0000001	-0.0000490	-0.0000025	-0.0000210
Current smoker	-0.0012830	-0.0000073	0.0000136	-0.0000042	-0.0000280	-0.0000820	-0.0002620	0.0000220	0.0000133	0.0000499	0.0012970	0.0000006	0.0001044	-0.0001800	-0.0000002	-0.0000004	0.0000651	-0.0000003	0.0000199
Female	-0.0008700	-0.0000140	0.0000090	-0.0000091	-0.0001220	-0.0000740	0.0001260	0.0000123	0.0001986	-0.0001830	0.0000006	0.0011330	0.0001050	-0.0001530	0.0000008	-0.0000003	-0.0000640	0.0000027	-0.0001030
High BMI	-0.0005290	-0.0000029	-0.0000140	-0.0000087	-0.0000540	0.0000341	0.0000371	0.0000099	-0.0000840	-0.0001230	0.0001044	0.0001050	0.0016080	0.0002966	0.0000010	-0.0000008	-0.0000350	-0.0000004	0.0000774
Low BMI	-0.0013160	0.0000240	-0.0000370	0.0000071	0.0000276	-0.0000100	-0.0000330	0.0000044	-0.0000460	0.0001169	-0.0001800	-0.0001530	0.0002966	0.0021680	0.0000002	0.0000007	0.0000760	-0.0000018	0.0000486
Baseline 6MWD	-0.0000150	-0.0000001	0.0000000	0.0000000	-0.0000005	-0.0000006	-0.0000002	0.0000001	0.0000001	0.0000001	-0.0000002	0.0000008	0.0000010	0.0000002	0.0000000	0.0000000	0.0000012	0.0000000	0.0000000
Fibrinogen	-0.0000084	0.0000000	0.0000000	0.0000000	0.0000002	0.0000002	-0.0000002	-0.0000001	0.0000001	-0.0000001	-0.0000004	-0.0000003	-0.0000008	0.0000007	0.0000000	0.0000000	0.0000000	0.0000000	-0.0000003
Baseline mMRC	-0.0003970	0.0000069	-0.0000003	0.0000062	-0.0001020	-0.0000400	0.0000221	-0.0000046	-0.0000190	-0.0000490	0.0000651	-0.0000640	-0.0000350	0.0000760	0.0000012	0.0000000	0.0014800	-0.0000140	-0.0000420
Baseline SGRQ	-0.0000780	0.0000001	-0.0000001	0.0000001	-0.0000160	-0.0000080	-0.0000055	0.0000005	-0.0000022	-0.0000025	-0.0000003	0.0000027	-0.0000004	-0.0000018	0.0000000	0.0000000	-0.0000140	0.0000012	-0.0000038
Prior exac.	-0.0088560	0.0038940	-0.0055300	0.0000047	-0.0000680	0.0000150	-0.0000200	0.0000010	0.0000230	-0.0000210	0.0000199	-0.0001030	0.0000774	0.0000486	0.0000000	-0.0000003	-0.0000420	-0.0000038	0.0127100

BMI, body-mass index; CVD, cardiovascular disease; exac., exacerbation; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A9 Covariance matrix for (severe exacerbations; fixed effects)

	Intercept	Study years	Time* prior exac.	Any FEV ₁ % predicted	Dyspnea (lagged 12 months), most days	Dyspnea (lagged 12 months), several days	Any symptom	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	6MWD	Fibrinogen	Baseline mMRC	Baseline SGRQ	Prior exac.
Intercept	0.2247400	-0.0175600	0.0168900	-0.0001880	-0.0150100	-0.0161400	0.0010630	-0.0015930	0.0015130	-0.0003440	-0.0053640	-0.0039950	-0.0016840	-0.0047160	-0.0000560	-0.0000310	-0.0020840	-0.0003280	-0.0411900
Study years	-0.0175600	0.0076740	-0.0076680	0.0000068	0.0001416	0.0002067	0.0001327	0.0000001	0.0000169	0.0000033	-0.0000470	-0.0000700	-0.0000620	0.0000609	-0.0000008	-0.0000001	0.0000135	-0.0000004	0.0173800
Time* prior exac.	0.0168900	-0.0076680	0.0107900	0.0000002	0.0001356	-0.0000910	-0.0002170	0.0000031	-0.0001180	0.0000089	0.0000976	0.0000258	0.0000252	-0.0001210	0.0000004	0.0000003	0.0000092	0.0000005	-0.0239800
Any FEV₁ % predicted	-0.0001880	0.0000068	0.0000002	0.0000067	0.0000526	0.0000280	-0.0000076	-0.0000020	-0.0000170	-0.0000130	-0.0000160	-0.0000450	-0.0000390	0.0000258	-0.0000002	0.0000001	0.0000257	0.0000002	0.0000173
Dyspnea (lagged 12 months), most days	-0.0150100	0.0001416	0.0001356	0.0000526	0.0200500	0.0176500	-0.0009830	-0.0000200	-0.0001420	-0.0002930	-0.0000850	-0.0003720	-0.0000150	-0.0001180	-0.0000010	0.0000004	-0.0002710	-0.0000510	-0.0003410
Dyspnea (lagged 12 months), several	-0.0161400	0.0002067	-0.0000910	0.0000280	0.0176500	0.0212800	-0.0001910	-0.0000059	-0.0001190	-0.0004130	-0.0002590	-0.0002110	0.0002245	-0.0003160	-0.0000016	0.0000005	-0.0000840	-0.0000240	0.0000596
Any symptom	0.0010630	0.0001327	-0.0002170	-0.0000076	-0.0009830	-0.0001910	0.0044290	-0.0000070	-0.0000004	-0.0002240	-0.0010430	0.0004606	0.0000862	-0.0001250	-0.0000007	-0.0000008	0.0000853	-0.0000210	0.0001418
Age	-0.0015930	0.0000001	0.0000031	-0.0000020	-0.0000200	-0.0000059	-0.0000070	0.0000247	-0.0000290	-0.0000250	0.0000844	0.0000578	0.0000327	0.0000207	0.0000002	-0.0000002	-0.0000210	0.0000017	0.0000041
CVD co-morbidity (yes)	0.0015130	0.0000169	-0.0001180	-0.0000170	-0.0001420	-0.0001190	-0.0000004	-0.0000290	0.0043170	-0.0005070	0.0001206	0.0007453	-0.0002300	-0.0001660	0.0000007	0.0000002	-0.0001610	-0.0000083	0.0001474
Other co-morbidity (yes)	-0.0003440	0.0000033	0.0000089	-0.0000130	-0.0002930	-0.0004130	-0.0002240	-0.0000250	-0.0005070	0.0052340	0.0000754	-0.0007720	-0.0005840	0.0003829	0.0000003	0.0000000	-0.0002360	-0.0000080	-0.0000710
Current smoker	-0.0053640	-0.0000470	0.0000976	-0.0000160	-0.0000850	-0.0002590	-0.0010430	0.0000844	0.0001206	0.0000754	0.0048930	0.0000833	0.0004544	-0.0005350	-0.0000004	-0.0000011	0.0003857	-0.0000025	0.0001153
Female	-0.0039950	-0.0000700	0.0000258	-0.0000450	-0.0003720	-0.0002110	0.0004606	0.0000578	0.0007453	-0.0007720	0.0000833	0.0049020	0.0003239	-0.0006610	0.0000032	-0.0000008	-0.0002630	0.0000108	-0.0003600
High BMI	-0.0016840	-0.0000620	0.0000252	-0.0000390	-0.0000150	0.0002245	0.0000862	0.0000327	-0.0002300	-0.0005840	0.0004544	0.0003239	0.0067820	0.0012630	0.0000032	-0.0000024	-0.0000180	-0.0000033	0.0000671
Low BMI	-0.0047160	0.0000609	-0.0001210	0.0000258	-0.0001180	-0.0003160	-0.0001250	0.0000207	-0.0001660	0.0003829	-0.0005350	-0.0006610	0.0012630	0.0065920	0.0000003	0.0000026	0.0003608	-0.0000050	0.0000159
6MWD	-0.0000560	-0.0000008	0.0000004	-0.0000002	-0.0000010	-0.0000016	-0.0000007	0.0000002	0.0000007	0.0000003	-0.0000004	0.0000032	0.0000032	0.0000003	0.0000001	0.0000000	0.0000050	0.0000002	-0.0000010
Fibrinogen	-0.0000310	-0.0000001	0.0000003	0.0000001	0.0000004	0.0000005	-0.0000008	-0.0000002	0.0000002	0.0000000	-0.0000011	-0.0000008	-0.0000024	0.0000026	0.0000000	0.0000001	-0.0000001	0.0000000	-0.0000011
Baseline mMRC	-0.0020840	0.0000135	0.0000092	0.0000257	-0.0002710	-0.0000840	0.0000853	-0.0000210	-0.0001610	-0.0002360	0.0003857	-0.0002630	-0.0000180	0.0003608	0.0000050	-0.0000001	0.0061180	-0.0000490	-0.0003410
Baseline SGRQ	-0.0003280	-0.0000004	0.0000005	0.0000002	-0.0000510	-0.0000240	-0.0000210	0.0000017	-0.0000083	-0.0000080	-0.0000025	0.0000108	-0.0000033	-0.0000050	0.0000002	0.0000000	-0.0000490	0.0000046	-0.0000190
Prior exac.	-0.0411900	0.0173800	-0.0239800	0.0000173	-0.0003410	0.0000596	0.0001418	0.0000041	0.0001474	-0.0000710	0.0001153	-0.0003600	0.0000671	0.0000159	-0.0000010	-0.0000011	-0.0003410	-0.0000190	0.0581200

BMI, body-mass index; CVD, cardiovascular disease; exac., exacerbation; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A10 Covariance matrix (FEV₁; fixed effects)

	Intercept	Study years	Time* smoker	Moderate exac.	Severe exac.	Height	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI	Low BMI	Baseline 6MWD	Fibrinogen	Baseline mMRC	Baseline SGRQ	Prior exac.
Intercept	82182.	-21.1117000	19.304400	-8.4971000	-3.1467000	364.5300000	195.1300000	-7.3696000	-233.19000	-612.36000	-4811.2100	-272.74000	-370.5400	-5.4084000	-3.6456000	-158.77000	-36.9438000	-302.14000
Study years	-21.11170	9.9497000	-9.9098000	0.0059500	-0.5218000	-0.0005000	0.0082350	0.0934100	-0.0206700	20.6269000	-0.1832000	-0.0461500	0.0117100	-0.0013900	0.0010710	0.0684000	0.0021770	0.1704000
Time*smoker	19.3044000	-9.9098000	28.663300	0.6580000	-0.6502000	0.0050310	0.0166200	-0.0766400	0.0107400	-59.3219000	0.2148000	0.1170000	0.3585000	-0.0011700	-0.0021300	-0.2924000	0.0110700	-0.5572000
Moderate exac.	-8.497100	0.0059500	0.6580000	5.3156000	1.1220000	0.0576000	0.0013130	0.7139000	-0.3620000	-0.5647000	-0.0679800	0.8369000	0.4332000	-0.0007600	-0.0058400	-0.3035000	-0.0404600	-4.2729000
Severe exac.	-3.146700	-0.5218000	-0.6502000	1.1220000	18.069300	0.0582900	-0.0354300	-0.3745000	0.3194000	1.8311000	0.8986000	1.4770000	-1.5820000	0.0037330	-0.0097800	-0.1642000	-0.0959100	-3.4465000
Height	-364.5300	-0.0005000	0.0050310	0.0576000	0.0582900	1.9854000	0.2632000	0.6210000	0.7577000	0.2111000	23.9684000	-0.3289000	0.7476000	-0.0067900	0.0029780	0.5416000	0.0531900	1.0033000
Age	-195.1300	0.0082350	0.0166200	0.0013130	-0.0354300	0.2632000	2.2090000	-3.3801000	-2.6328000	6.9994000	6.6143000	3.3859000	0.6074000	0.0232600	-0.0181000	-1.1492000	0.1564000	1.1859000
CVD co-morbidity (yes)	-7.369600	0.0934100	-0.0766400	0.7139000	-0.3745000	0.6210000	-3.3801000	451.48000	-71.3392000	-6.4798000	69.2478000	-34.9238000	-0.9924000	0.0606500	0.0219200	-1.0110000	-0.4525000	-2.4974000
Other co-morbidity (yes)	-233.1900	-0.0206700	0.0107400	-0.3620000	0.3194000	0.7577000	-2.6328000	-71.3392000	515.08000	4.9674000	-70.9318000	-68.9301000	56.6916000	-0.0112400	0.0092280	0.4984000	-1.0762000	-0.4765000
Current smoker	612.3600000	20.6269000	-59.321900	-0.5647000	1.8311000	0.2111000	6.9994000	-6.4798000	4.9674000	565.32000	2.6388000	38.6468000	-79.5795000	-0.0653600	-0.1023000	35.4339000	-0.4423000	19.9507000
Female	-4811.2100	-0.1832000	0.2148000	-0.0679800	0.8986000	23.9684000	6.6143000	69.2478000	-70.9318000	2.6388000	726.2800000	22.7179000	-40.2152000	0.1387000	-0.0626500	8.8505000	1.7299000	-9.9670000
High BMI	-272.7400	-0.0461500	0.1170000	0.8369000	1.4770000	-0.3289000	3.3859000	-34.9238000	-68.9301000	38.646800	22.7179000	590.97000	126.34000	0.3013000	-0.2722000	-8.1444000	0.0691300	28.2300000
Low BMI	-370.5400	0.0117100	0.3585000	0.4332000	-1.5820000	0.7476000	0.6074000	-0.9924000	56.6916000	-79.5795000	-40.2152000	126.340000	835.390000	0.0511600	0.2225000	18.8557000	-1.2035000	-25.0944000
Baseline 6MWD	-5.408400	-0.0013900	-0.0011700	-0.0007600	0.0037330	-0.0067900	0.0232600	0.0606500	-0.0112400	-0.0653600	0.1387000	0.3013000	0.0511600	0.0093660	0.0007610	0.4658000	0.0167300	0.0614200
Fibrinogen	-3.645600	0.0010710	-0.0021300	-0.0058400	-0.0097800	0.0029780	-0.0181000	0.0219200	0.0092280	-0.1023000	-0.0626500	-0.2722000	0.2225000	0.0007610	0.0096210	-0.0578000	-0.0049400	-0.1207000
Baseline mMRC	-158.7700	0.0684000	-0.2924000	-0.3035000	-0.1642000	0.5416000	-1.1492000	-1.0110000	0.4984000	35.4339000	8.8505000	-8.1444000	18.8557000	0.4658000	-0.0578000	558.8100000	-6.1569000	-23.2089000
Baseline SGRQ	-36.94380	0.0021770	0.0110700	-0.0404600	-0.0959100	0.0531900	0.1564000	-0.4525000	-1.0762000	-0.4423000	1.7299000	0.0691300	-1.2035000	0.0167300	-0.0049400	-6.1569000	0.3796000	-1.7660000
Prior exac.	-302.1400	0.1704000	-0.5572000	-4.2729000	-3.4465000	1.0033000	1.1859000	-2.4974000	-0.4765000	19.9507000	-9.9670000	28.2300000	-25.0944000	0.0614200	-0.1207000	-23.2089000	-1.7660000	403.290000

BMI, body-mass index; CVD, cardiovascular disease; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A11 Covariance matrix (dyspnea, most versus none or several days; fixed effects)

	Intercept	Study years	FEV ₁ % predicted	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	Baseline 6MWD	Fibrinogen	MMRC GOLD	Baseline SGRQ	Prior exac.
Intercept	0.7879000	-0.0114100	-0.0008700	-0.0068600	0.0074680	0.0003550	-0.0225400	-0.0149200	-0.0119300	-0.0169600	-0.0002800	-0.0001700	-0.0058500	-0.0015500	-0.0098300
Study years	-0.0114100	0.0043470	0.0000093	0.0000110	-0.0000600	0.0000100	0.0000037	0.0000074	0.0000180	0.0001120	-0.0000012	0.0000009	0.0000490	0.0000140	0.0001260
FEV₁ % predicted	-0.0008700	0.0000093	0.0000230	-0.0000034	-0.0000500	-0.0001000	-0.0000400	-0.0001200	-0.0001200	0.0001110	-0.0000003	0.0000004	0.0000700	-0.0000005	0.0000610
Age	-0.0068600	0.0000110	-0.0000034	0.0001040	-0.0001500	-0.0001200	0.0003240	0.0001930	0.0001840	0.0000030	0.0000012	-0.0000010	-0.0000700	0.0000081	0.0000500
CVD co-morbidity (yes)	0.0074680	-0.0000600	-0.0000500	-0.0001500	0.0214000	-0.0033300	-0.0002500	0.0033350	-0.0012900	-0.0001100	0.0000036	0.0000000	-0.0002100	-0.0000400	-0.0003500
Other co-morbidity (yes)	0.0003550	0.0000100	-0.0001000	-0.0001200	-0.0033300	0.0246400	0.0002980	-0.0034500	-0.0027800	0.0020490	-0.0000005	-0.0000015	-0.0000700	-0.0000400	-0.0002300
Current smoker	-0.0225400	0.0000037	-0.0000400	0.0003240	-0.0002500	0.0002980	0.0209000	0.0001470	0.0023790	-0.0040900	-0.0000014	-0.0000062	0.0013720	-0.0000300	0.0008190
Female	-0.0149200	0.0000074	-0.0001200	0.0001930	0.0033350	-0.0034500	0.0001470	0.0212500	0.0022060	-0.0029400	0.0000110	-0.0000076	-0.0003900	0.0000530	-0.0013100
High BMI	-0.0119300	0.0000180	-0.0001200	0.0001840	-0.0012900	-0.0027800	0.0023790	0.0022060	0.0282700	0.0052260	0.0000160	-0.0000100	-0.0007400	-0.0000005	0.0012650
Low BMI	-0.0169600	0.0001120	0.0001110	0.0000030	-0.0001100	0.0020490	-0.0040900	-0.0029400	0.0052260	0.0400600	0.0000003	0.0000150	0.0011020	-0.0000400	-0.0008000
Baseline 6MWD	-0.0002800	-0.0000012	-0.0000003	0.0000012	0.0000036	-0.0000005	-0.0000014	0.0000110	0.0000160	0.0000003	0.0000004	0.0000000	0.0000190	0.0000006	0.0000024
Fibrinogen	-0.0001700	0.0000009	0.0000004	-0.0000010	0.0000000	-0.0000015	-0.0000062	-0.0000076	-0.0000100	0.0000150	0.0000000	0.0000005	0.0000001	-0.0000001	-0.0000050
mMRC	-0.0058500	0.0000490	0.0000700	-0.0000700	-0.0002100	-0.0000700	0.0013720	-0.0003900	-0.0007400	0.0011020	0.0000190	0.0000001	0.0252500	-0.0002600	-0.0006300
Baseline SGRQ	-0.0015500	0.0000140	-0.0000005	0.0000081	-0.0000400	-0.0000400	-0.0000300	0.0000530	-0.0000005	-0.0000400	0.0000006	-0.0000001	-0.0002600	0.0000230	-0.0000700
Prior exac.	-0.0098300	0.0001260	0.0000610	0.0000500	-0.0003500	-0.0002300	0.0008190	-0.0013100	0.0012650	-0.0008000	0.0000024	-0.0000050	-0.0006300	-0.0000700	0.0189000

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A12 Covariance matrix (dyspnea,(none vs most or several days; fixed effects)

	Intercept	Study years	FEV ₁ % predicted	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI	Low BMI category	Baseline 6MWD	Fibrinogen	MMRC GOLD	Baseline SGRQ	Prior exac.
Intercept	1.5051000	-0.0223400	-0.0021300	-0.0128800	0.0180800	0.0093590	-0.0483000	-0.0240300	-0.0239300	-0.0315700	-0.0005600	-0.0003500	-0.0075100	-0.0027600	-0.0160400
Study years	-0.0223400	0.0089490	0.0000190	0.0000150	0.0000870	-0.0001700	-0.0000300	0.0001750	0.0001920	0.0003180	-0.0000014	0.0000017	0.0001300	0.0000150	0.0002620
FEV₁ % predicted	-0.0021300	0.0000190	0.0000400	-0.0000028	-0.0000700	-0.0001700	-0.0000500	-0.0001700	-0.0001700	0.0001690	-0.0000007	0.0000008	0.0001640	0.0000025	0.0001300
Age	-0.0128800	0.0000150	-0.0000028	0.0001940	-0.0003700	-0.0003000	0.0006460	0.0003000	0.0003570	0.0000170	0.0000026	-0.0000019	-0.0001800	0.0000180	0.0000430
CVD co-morbidity (yes)	0.0180800	0.0000870	-0.0000700	-0.0003700	0.0425400	-0.0074500	-0.0018700	0.0069940	-0.0020000	0.0005560	0.0000050	0.0000003	-0.0008300	-0.0000600	-0.0002900
Other co-morbidity (yes)	0.0093590	-0.0001700	-0.0001700	-0.0003000	-0.0074500	0.0447300	0.0003590	-0.0069100	-0.0062700	0.0049250	0.0000001	-0.0000029	0.0009360	-0.0001400	-0.0006500
Current smoker	-0.0483000	-0.0000300	-0.0000500	0.0006460	-0.0018700	0.0003590	0.0397800	-0.0004200	0.0039290	-0.0083700	-0.0000007	-0.0000089	0.0016810	0.0000110	0.0009710
Female	-0.0240300	0.0001750	-0.0001700	0.0003000	0.0069940	-0.0069100	-0.0004200	0.0398900	0.0043140	-0.0056600	0.0000220	-0.0000200	-0.0004300	0.0000580	-0.0028600
High BMI	-0.0239300	0.0001920	-0.0001700	0.0003570	-0.0020000	-0.0062700	0.0039290	0.0043140	0.0550300	0.0090430	0.0000350	-0.0000300	-0.0012700	-0.0000200	0.0023230
Low BMI	-0.0315700	0.0003180	0.0001690	0.0000170	0.0005560	0.0049250	-0.0083700	-0.0056600	0.0090430	0.0906800	-0.0000032	0.0000290	-0.0003200	-0.0000300	-0.0008300
Baseline 6MWD	-0.0005600	-0.0000014	-0.0000007	0.0000026	0.0000050	0.0000001	-0.0000007	0.0000220	0.0000350	-0.0000032	0.0000009	0.0000000	0.0000390	0.0000012	0.0000065
Fibrinogen	-0.0003500	0.0000017	0.0000008	-0.0000019	0.0000003	-0.0000029	-0.0000089	-0.0000200	-0.0000300	0.0000290	0.0000000	0.0000010	-0.0000035	-0.0000001	-0.0000100
mMRC	-0.0075100	0.0001300	0.0001640	-0.0001800	-0.0008300	0.0009360	0.0016810	-0.0004300	-0.0012700	-0.0003200	0.0000390	-0.0000035	0.0525700	-0.0006000	-0.0006600
Baseline SGRQ	-0.0027600	0.0000150	0.0000025	0.0000180	-0.0000600	-0.0001400	0.0000110	0.0000580	-0.0000200	-0.0000300	0.0000012	-0.0000001	-0.0006000	0.0000430	-0.0001400
Prior exac.	-0.0160400	0.0002620	0.0001300	0.0000430	-0.0002900	-0.0006500	0.0009710	-0.0028600	0.0023230	-0.0008300	0.0000065	-0.0000100	-0.0006600	-0.0001400	0.0371300

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A13 Covariance matrix (cough and sputum; fixed effects)

	Intercept	Study years	FEV ₁ % predicted	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI	Low BMI	Baseline 6MWD	Fibrinogen	MMRC GOLD	Baseline SGRQ	Prior exac.
Intercept	0.8995000	-0.0106800	-0.0010000	-0.0078700	0.0120800	-0.0027000	-0.0344400	-0.0125300	-0.0115500	-0.0198100	-0.0003200	-0.0001900	-0.0074200	-0.0017500	-0.0113300
Study years	-0.0106800	0.0042290	0.0000180	0.0000051	-0.0000300	-0.0000500	-0.0000600	-0.0000300	-0.0000200	0.0001050	-0.0000013	0.0000009	0.0000310	0.0000038	0.0000800
FEV₁ % predicted	-0.0010000	0.0000180	0.0000230	-0.0000035	-0.0000400	-0.0000900	-0.0000800	-0.0001100	-0.0001200	0.0001210	-0.0000005	0.0000005	0.0000900	0.0000027	0.0000660
Age	-0.0078700	0.0000051	-0.0000035	0.0001190	-0.0002000	-0.0001300	0.0004230	0.0001840	0.0002120	0.0000230	0.0000013	-0.0000011	-0.0000800	0.0000083	0.0000480
CVD co-morbidity (yes)	0.0120800	-0.0000300	-0.0000400	-0.0002000	0.0250500	-0.0042300	-0.0022400	0.0044650	-0.0012700	-0.0005600	0.0000046	-0.0000006	-0.0002800	-0.0000700	-0.0009500
Other co-morbidity (yes)	-0.0027000	-0.0000500	-0.0000900	-0.0001300	-0.0042300	0.0285300	0.0020180	-0.0047100	-0.0039100	0.0027170	-0.0000006	-0.0000001	-0.0003400	-0.0000500	0.0001740
Current smoker	-0.0344400	-0.0000600	-0.0000800	0.0004230	-0.0022400	0.0020180	0.0284200	-0.0020500	0.0012160	-0.0039000	-0.0000045	-0.0000052	0.0019890	0.0000660	0.0021570
Female	-0.0125300	-0.0000300	-0.0001100	0.0001840	0.0044650	-0.0047100	-0.0020500	0.0248200	0.0028160	-0.0035300	0.0000150	-0.0000088	-0.0007000	0.0000072	-0.0021400
High BMI	-0.0115500	-0.0000200	-0.0001200	0.0002120	-0.0012700	-0.0039100	0.0012160	0.0028160	0.0328700	0.0059290	0.0000200	-0.0000200	-0.0009800	-0.0000300	0.0007520
Low BMI	-0.0198100	0.0001050	0.0001210	0.0000230	-0.0005600	0.0027170	-0.0039000	-0.0035300	0.0059290	0.0453900	-0.0000011	0.0000160	0.0010590	-0.0000400	-0.0007000
Baseline 6MWD	-0.0003200	-0.0000013	-0.0000005	0.0000013	0.0000046	-0.0000006	-0.0000045	0.0000150	0.0000200	-0.0000011	0.0000005	0.0000000	0.0000230	0.0000008	0.0000014
Fibrinogen	-0.0001900	0.0000009	0.0000005	-0.0000011	-0.0000006	-0.0000001	-0.0000052	-0.0000088	-0.0000200	0.0000160	0.0000000	0.0000005	-0.0000014	-0.0000002	-0.0000045
mMRC	-0.0074200	0.0000310	0.0000900	-0.0000800	-0.0002800	-0.0003400	0.0019890	-0.0007000	-0.0009800	0.0010590	0.0000230	-0.0000014	0.0299100	-0.0003100	-0.0006000
Baseline SGRQ	-0.0017500	0.0000038	0.0000027	0.0000083	-0.0000700	-0.0000500	0.0000660	0.0000072	-0.0000300	-0.0000400	0.0000008	-0.0000002	-0.0003100	0.0000220	-0.0000700
Prior exac.	-0.0113300	0.0000800	0.0000660	0.0000480	-0.0009500	0.0001740	0.0021570	-0.0021400	0.0007520	-0.0007000	0.0000014	-0.0000045	-0.0006000	-0.0000700	0.0217700

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A14 Covariance matrix (6MWD; fixed effects)

	Intercept	Study years	Moderate exac.	Severe exac.	FEV ₁ % predicted	Dyspnea (lagged 12 months), most days	Dyspnea (lagged 12 months), several days	Any symptom	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	Fibrinogen	Baseline mMRC	Baseline SGRQ	Prior exac.
Intercept	775.57000	-8.1279000	-0.8200000	0.3437000	-1.4927000	-14.07190	-15.073700	1.6746000	-8.0683000	13.1251000	1.8159000	-32.627900	10.1131000	-0.8853000	-24.723600	-0.1920000	8.7820000	-1.2086000	-7.5818000
Study years	-8.1279000	2.5871000	0.1544000	-0.1592000	0.0211600	0.3901000	0.2552000	0.2683000	0.0050860	0.0218600	-0.1065000	-0.0052400	-0.0765400	0.0233600	0.1484000	0.0007810	0.1915000	0.0035600	0.0071740
Moderate exac.	-0.8200000	0.1544000	1.7882000	0.2656000	0.0142200	-0.1438000	-0.0326500	-0.1156000	-0.0023300	0.1664000	-0.1218000	0.2943000	-0.4142000	0.2204000	0.1569000	-0.0014000	-0.0301800	-0.0071600	-1.3698000
Severe exac.	0.3437000	-0.1592000	0.2656000	7.1219000	0.0450000	0.2924000	0.1839000	-0.1609000	-0.0242500	-0.1106000	-0.0251800	0.0031960	-0.1446000	0.2738000	-0.3601000	-0.0016500	0.1315000	-0.0270900	-1.0229000
FEV₁ % predicted	-1.4927000	0.0211600	0.0142200	0.0450000	0.0237500	0.1165000	0.0609200	-0.0047300	-0.0021000	-0.0533500	-0.0918200	-0.0432500	-0.1223000	-0.1121000	0.1122000	0.0005130	0.1192000	0.0032210	0.0581000
Dyspnea (lagged 12 months), most days	-14.071900	0.3901000	-0.1438000	0.2924000	0.1165000	30.709500	21.9915000	-2.1325000	-0.1107000	-0.0093100	-0.3952000	-0.1609000	-0.9340000	-0.7825000	0.0805900	0.0023850	-0.6171000	-0.1662000	-0.5665000
Dyspnea (lagged 12 months), several	-15.073700	0.2552000	-0.0326500	0.1839000	0.0609200	21.99150	26.5686000	-0.5228000	-0.0741700	-0.2457000	-0.1420000	-0.8161000	-0.7779000	-0.1035000	-0.1144000	0.0026770	-0.0218100	-0.0895000	-0.5971000
Any symptom	1.6746000	0.2683000	-0.1156000	-0.1609000	-0.0047300	-2.1325000	-0.5228000	12.0476000	-0.0356200	0.1295000	-0.3038000	-3.0651000	1.0620000	0.4315000	-0.0724200	-0.0013800	0.4068000	-0.0535000	-0.4823000
Age	-8.0683000	0.0050860	-0.0023300	-0.0242500	-0.0021000	-0.1107000	-0.0741700	-0.0356200	0.1347000	-0.2215000	-0.2008000	0.4602000	0.2160000	0.1751000	0.0747600	-0.0013800	-0.1400000	0.0079430	0.0537600
CVD co-morbidity (yes)	13.125100	0.0218600	0.1664000	-0.1106000	-0.0533500	-0.0093100	-0.2457000	0.1295000	-0.2215000	29.0187000	-4.4768000	-0.3791000	4.3891000	-1.7880000	-0.5230000	-0.0010500	-0.3387000	-0.0506000	-0.8083000
Other co-morbidity (yes)	1.8159000	-0.1065000	-0.1218000	-0.0251800	-0.0918200	-0.3952000	-0.1420000	-0.3038000	-0.2008000	-4.4768000	32.751400	0.5922000	-4.6456000	-3.9144000	3.1410000	-0.0004900	-0.5080000	-0.0826500	-0.2466000
Current smoker	-32.627900	-0.0052400	0.2943000	0.0031960	-0.0432500	-0.1609000	-0.8161000	-3.0651000	0.4602000	-0.3791000	0.5922000	28.8038000	-0.2382000	2.8981000	-5.0347000	-0.0086900	2.0561000	-0.0119600	0.8870000
Female	-10.113100	-0.0765400	-0.4142000	-0.1446000	-0.1223000	-0.9340000	-0.7779000	1.0620000	0.2160000	4.3891000	-4.6456000	-0.2382000	28.0869000	1.9795000	-3.3595000	-0.0098600	-1.2498000	0.0303500	-1.5562000
High BMI	-0.8853000	0.0233600	0.2204000	0.2738000	-0.1121000	-0.7825000	-0.1035000	0.4315000	0.1751000	-1.7880000	-3.9144000	2.8981000	1.9795000	36.850400	7.1900000	-0.0215600	-1.9559000	-0.0433500	0.9466000
Low BMI	-24.72360	0.1484000	0.1569000	-0.3601000	0.1122000	0.0805900	-0.1144000	-0.0724200	0.0747600	-0.5230000	3.1410000	-5.0347000	-3.3595000	7.1900000	54.9424000	0.0185300	1.1167000	-0.0506500	-1.2836000
Fibrinogen	-0.1920000	0.0007810	-0.0014000	-0.0016500	0.0005130	0.0023850	0.0026770	-0.0013800	-0.0013800	-0.0010500	-0.0004900	-0.0086900	-0.0098600	-0.0215600	0.0185300	0.0006140	-0.0041800	-0.0002900	-0.0052300
Baseline mMRC	8.7820000	0.1915000	-0.0301800	0.1315000	0.1192000	-0.6171000	-0.0218100	0.4068000	-0.1400000	-0.3387000	-0.5080000	2.0561000	-1.2498000	-1.9559000	1.1167000	-0.0041800	34.123300	-0.4139000	-1.0117000
Baseline SGRQ	-1.2086000	0.0035600	-0.0071600	-0.0270900	0.0032210	-0.1662000	-0.0895000	-0.0535000	0.0079430	-0.0506000	-0.0826500	-0.0119600	0.0303500	-0.0433500	-0.0506500	-0.0002900	-0.4139000	0.0242600	-0.1063000
Prior exac.	-7.5818000	0.0071740	-1.3698000	-1.0229000	0.0581000	-0.5665000	-0.5971000	-0.4823000	0.0537600	-0.8083000	-0.2466000	0.8870000	-1.5562000	0.9466000	-1.2836000	-0.0052300	-1.0117000	-0.1063000	26.6820000

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A15 Covariance matrix (SGRQ; fixed effects)

	Intercept	Study years	Moderate exac.	Severe exac.	6MWD	FEV ₁ % predicted	Dyspnea (lagged 12 months), most days	Dyspnea (lagged 12 months), several days	Any symptom	Age	CVD comorbidity (yes)	Other comorbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	Baseline 6MWD	Fibrinogen	Baseline mMRC	Prior exac.
Intercept	15.3825000	-0.1509000	-0.0308200	-0.0523300	-0.0018500	-0.0008800	-0.5054000	-0.3500000	0.0164300	-0.1392000	0.1036000	-0.0577600	-0.5141000	-0.5780000	-0.1809000	-0.4960000	-0.0030800	-0.0038600	-0.6183000	-0.3254000
Study years	-0.1509000	0.0470200	0.0030410	-0.0023300	0.0000580	0.0000100	-0.0016200	-0.0010000	0.0003620	0.0003100	0.0003530	-0.0007200	0.0017910	0.0030710	0.0000340	0.0038210	-0.0000600	0.0000190	0.0047310	0.0015730
Moderate exac.	-0.0308200	0.0030410	0.0295400	0.0038390	0.0000076	0.0000095	-0.0059200	-0.0034000	-0.0036900	0.0001800	0.0023250	-0.0030100	0.0053290	-0.0023200	0.0034100	0.0032640	-0.0000100	-0.0000200	-0.0017700	-0.0228200
Severe exac.	-0.0523300	-0.0023300	0.0038390	0.1036000	0.0000930	0.0000160	-0.0041100	0.0015590	0.0034550	0.0002100	-0.0023900	-0.0022900	-0.0007200	0.0089510	0.0074520	-0.0073100	-0.0000300	-0.0000400	-0.0011700	-0.0165800
6MWD	-0.0018500	0.0000580	0.0000076	0.0000930	0.0000071	-0.0000003	0.0001360	0.0000320	0.0000033	0.0000100	0.0000690	0.0000090	0.0001010	-0.0000500	0.0001470	0.0000840	-0.0000044	0.0000003	0.0001740	0.0000680
FEV₁ % predicted	-0.0008800	0.0000100	0.0000095	0.0000160	-0.0000003	0.0000004	0.0000730	0.0000300	-0.0000111	0.0000039	-0.0000200	-0.0000300	-0.0000200	0.0001240	-0.0000700	0.0000670	-0.0000002	0.0000003	0.0000560	0.0000360
Dyspnea (lagged 12 months), most days	-0.5054000	-0.0016200	-0.0059200	-0.0041100	0.0001360	0.0000730	0.5222000	0.3738000	-0.0444500	0.0008210	0.0021880	-0.0236700	0.0013510	0.0255100	-0.0169700	-0.0134600	-0.0000500	-0.0000300	-0.0476200	-0.0074400
Dyspnea (lagged 12 months), several	-0.3500000	-0.0010000	-0.0034000	0.0015590	0.0000320	0.0000300	0.3738000	0.4590000	-0.0110000	0.0000640	-0.0003300	-0.0142700	-0.0086700	0.0102300	-0.0084200	-0.0173700	-0.0000300	-0.0000098	-0.0270000	-0.0082000
Any symptom	0.0164300	0.0003620	-0.0036900	0.0034550	0.0000033	-0.0000011	-0.0444500	-0.0110000	0.1988000	-0.0005800	0.0074560	-0.0083700	-0.0476100	0.0184900	0.0096160	-0.0059300	0.0000073	-0.0000500	-0.0089200	-0.0108000
Age	-0.1392000	0.0003100	0.0001800	0.0002100	0.0000100	0.0000039	0.0008210	0.0000640	-0.0005800	0.0020440	-0.0033600	-0.0026600	0.0068350	0.0040260	0.0025420	0.0021350	0.0000055	-0.0000100	0.0020590	0.0021180
CVD comorbidity (yes)	0.1036000	0.0003530	0.0023250	-0.0023900	0.0000690	-0.0000200	0.0021880	-0.0003300	0.0074560	-0.0033600	0.4237000	-0.0671500	-0.0078800	0.0578000	-0.0259500	-0.0075600	0.0000360	-0.0000047	-0.0098200	-0.0094000
Other comorbidity (yes)	-0.0577600	-0.0007200	-0.0030100	-0.0022900	0.0000090	-0.0000300	-0.0236700	-0.0142700	-0.0083700	-0.0026600	-0.0671500	0.4802000	0.0074010	-0.0846500	-0.0603000	0.0414000	0.0000470	-0.0000100	-0.0198200	-0.0053300
Current smoker	-0.5141000	0.0017910	0.0053290	-0.0007200	0.0001010	-0.0000200	0.0013510	-0.0086700	-0.0476100	0.0068350	-0.0078800	0.0074010	0.4268000	-0.0098900	0.0412400	-0.0731900	-0.0000900	-0.0001100	0.0287200	0.0142000
Female	-0.5780000	0.0030710	-0.0023200	0.0089510	-0.0000500	0.0001240	0.0255100	0.0102300	0.0184900	0.0040260	0.0578000	-0.0846500	-0.0098900	0.4454000	0.0031690	-0.0268300	0.0000790	-0.0000089	0.0309700	-0.0018100
High BMI	-0.1809000	0.0000340	0.0034100	0.0074520	0.0001470	-0.0000700	-0.0169700	-0.0084200	0.0096160	0.0025420	-0.0259500	-0.0603000	0.0412400	0.0031690	0.5633000	0.1077000	0.0002430	-0.0003000	-0.0127800	0.0171200
Low BMI	-0.4960000	0.0038210	0.0032640	-0.0073100	0.0000840	0.0000670	-0.0134600	-0.0173700	-0.0059300	0.0021350	-0.0075600	0.0414000	-0.0731900	-0.0268300	0.1077000	0.7943000	-0.0000200	0.0002810	0.0139900	-0.0196400
Baseline 6MWD	-0.0030800	-0.0000600	-0.0000100	-0.0000300	-0.0000044	-0.0000002	-0.0000500	-0.0000300	0.0000073	0.0000055	0.0000360	0.0000470	-0.0000900	0.0000790	0.0002430	-0.0000200	0.0000110	0.0000004	0.0005000	0.0000630
Fibrinogen	-0.0038600	0.0000190	-0.0000200	-0.0000400	0.0000003	0.0000003	-0.0000300	-0.0000098	-0.0000500	-0.0000100	-0.0000047	-0.0000100	-0.0001100	-0.0000089	-0.0003000	0.0002810	0.0000004	0.0000092	-0.0000500	-0.0000700
Baseline mMRC	-0.6183000	0.0047310	-0.0017700	-0.0011700	0.0001740	0.0000560	-0.0476200	-0.0270000	-0.0089200	0.0020590	-0.0098200	-0.0198200	0.0287200	0.0309700	-0.0127800	0.0139900	0.0005000	-0.0000500	0.4499000	-0.0329000
Prior exac.	-0.3254000	0.0015730	-0.0228200	-0.0165800	0.0000680	0.0000360	-0.0074400	-0.0082000	-0.0108000	0.0021180	-0.0094000	-0.0053300	0.0142000	-0.0018100	0.0171200	-0.0196400	0.0000630	-0.0000700	-0.0329000	0.3934000

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A16 Covariance matrix (mortality; fixed effects)

	Moderate exac.	Severe exac.	6MWD augmented	FEV ₁ % predicted	Dyspnea (lagged 12 months), most days	Dyspnea (lagged 12 months), several days	Symptom most days	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	Fibrinogen	Baseline mMRC	Baseline SGRQ
Moderate exac.	0.0037852	-0.0009536	-0.0000004	0.0000214	-0.0004498	-0.0005837	-0.0003527	0.0000310	0.0002794	-0.0003335	0.0005495	-0.0006595	0.0004177	0.0001522	-0.0000025	-0.0004116	-0.0000333
Severe exac.	-0.0009536	0.0092594	0.0000064	0.0000494	0.0000921	0.0005358	0.0001759	-0.0000507	0.0008694	-0.0006272	0.0002450	0.0001818	0.0011632	-0.0001085	-0.0000010	0.0017171	-0.0000537
6MWD augmented	-0.0000004	0.0000064	0.0000006	-0.0000013	-0.0000227	-0.0000196	0.0000040	0.0000016	0.0000096	0.0000044	-0.0000004	0.0000186	0.0000240	-0.0000014	0.0000000	0.0000267	0.0000011
FEV₁ % predicted	0.0000214	0.0000494	-0.0000013	0.0000364	0.0002654	0.0001542	-0.0000687	-0.0000113	-0.0000885	-0.0000744	-0.0000956	-0.0002339	-0.0002044	0.0001396	0.0000005	0.0001059	0.0000023
Dyspnea (lagged 12 months), most days	-0.0004498	0.0000921	-0.0000227	0.0002654	0.0993131	0.0825069	-0.0052756	-0.0000633	-0.0004006	-0.0005589	0.0001624	-0.0019112	-0.0024726	-0.0023400	-0.0000013	-0.0029721	-0.0004801
Dyspnea (lagged 12 months), several	-0.0005837	0.0005358	-0.0000196	0.0001542	0.0825069	0.1007333	-0.0028780	-0.0001023	-0.0003788	-0.0013102	-0.0004381	-0.0004569	-0.0022597	-0.0045485	-0.0000013	-0.0020880	-0.0002572
Symptom most days	-0.0003527	0.0001759	0.0000040	-0.0000687	-0.0052756	-0.0028780	0.0254577	-0.0000664	0.0013234	-0.0013912	-0.0052671	0.0022173	0.0025811	-0.0001866	-0.0000048	0.0009641	-0.0001546
Age	0.0000310	-0.0000507	0.0000016	-0.0000113	-0.0000633	-0.0001023	-0.0000664	0.0001572	-0.0001580	-0.0001465	0.0004001	0.0002588	0.0002198	0.0000321	-0.0000006	-0.0001185	0.0000093
CVD co-morbidity (yes)	0.0002794	0.0008694	0.0000096	-0.0000885	-0.0004006	-0.0003788	0.0013234	-0.0001580	0.0232562	-0.0029193	-0.0000084	0.0036315	-0.0009330	0.0000515	-0.0000017	-0.0001970	-0.0000555
Other co-morbidity (yes)	-0.0003335	-0.0006272	0.0000044	-0.0000744	-0.0005589	-0.0013102	-0.0013912	-0.0001465	-0.0029193	0.0333684	0.0009624	-0.0043212	-0.0036254	0.0018382	-0.0000008	-0.0003483	-0.0000359
Current smoker	0.0005495	0.0002450	-0.0000004	-0.0000956	0.0001624	-0.0004381	-0.0052671	0.0004001	-0.0000084	0.0009624	0.0270082	0.0009413	0.0022005	-0.0034808	-0.0000024	0.0024520	-0.0000037
Female	-0.0006595	0.0001818	0.0000186	-0.0002339	-0.0019112	-0.0004569	0.0022173	0.0002588	0.0036315	-0.0043212	0.0009413	0.0294044	0.0015925	-0.0043518	-0.0000067	0.0000986	0.0000113
High BMI category	0.0004177	0.0011632	0.0000240	-0.0002044	-0.0024726	-0.0022597	0.0025811	0.0002198	-0.0009330	-0.0036254	0.0022005	0.0015925	0.0348637	0.0080983	-0.0000099	0.0000580	-0.0000084
Low BMI category	0.0001522	-0.0001085	-0.0000014	0.0001396	-0.0023400	-0.0045485	-0.0001866	0.0000321	0.0000515	0.0018382	-0.0034808	-0.0043518	0.0080983	0.0397087	0.0000151	0.0017781	-0.0000455
Fibrinogen	-0.0000025	-0.0000010	0.0000000	0.0000005	-0.0000013	-0.0000013	-0.0000048	-0.0000006	-0.0000017	-0.0000008	-0.0000024	-0.0000067	-0.0000099	0.0000151	0.0000004	-0.0000027	-0.0000002
Baseline mMRC	-0.0004116	0.0017171	0.0000267	0.0001059	-0.0029721	-0.0020880	0.0009641	-0.0001185	-0.0001970	-0.0003483	0.0024520	0.0000986	0.0000580	0.0017781	-0.0000027	0.0360665	-0.0003247
Baseline SGRQ	-0.0000333	-0.0000537	0.0000011	0.0000023	-0.0004801	-0.0002572	-0.0001546	0.0000093	-0.0000555	-0.0000359	-0.0000037	0.0000113	-0.0000084	-0.0000455	-0.0000002	-0.0003247	0.0000286

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A17 Covariance matrix for survival (fixed effects)

	Intercept	Moderate exac.	Severe exac.	6MWD augmented	FEV ₁ % predicted	Dyspnea most days	Dyspnea (lagged 12 months), several days	Symptoms most days	Age	CVD co-morbidity (yes)	Other co-morbidity (yes)	Current smoker	Female	High BMI category	Low BMI category	Fibrinogen	Baseline mMRC	Baseline SGRQ	Scale
Intercept	0.7445900	-0.0014810	-0.0008500	-0.0001700	-0.0003460	-0.0330840	-0.0302390	0.0066220	-0.0070450	-0.0008520	-0.0075890	-0.0209270	-0.0064020	-0.0105250	-0.0171820	-0.0001370	-0.0048730	-0.0010570	0.0148100
Moderate exac.	-0.0014810	0.0022350	-0.0011570	-0.0000003	0.0000127	-0.0002340	-0.0003090	-0.0002830	0.0000188	0.0001320	-0.0002220	0.0003450	-0.0003680	0.0002110	0.0001830	-0.0000012	-0.0002190	-0.0000185	-0.0000354
Severe exac.	-0.0008500	-0.0011570	0.0112520	0.0000042	0.0000289	0.0001590	0.0003350	0.0006050	-0.0000193	0.0004530	-0.0003470	0.0000299	0.0001660	0.0006880	-0.0005650	-0.0000017	0.0003520	-0.0000380	0.0000219
6MWD augmented	-0.0001700	-0.0000003	0.0000042	0.0000004	-0.0000006	-0.0000131	-0.0000102	0.0000026	0.0000005	0.0000025	0.0000027	-0.0000025	0.0000134	0.0000131	-0.0000033	0.0000000	0.0000151	0.0000007	0.0000088
FEV₁ % predicted	-0.0003460	0.0000127	0.0000289	-0.0000006	0.0000218	0.0001680	0.0001090	-0.0000321	-0.0000082	-0.0000563	-0.0000459	-0.0000618	-0.0001240	-0.0001160	0.0000624	0.0000002	0.0000622	0.0000013	0.0000333
Dyspnea (lagged 12 months), most days	-0.0330840	-0.0002340	0.0001590	-0.0000131	0.0001680	0.0582200	0.0482970	-0.0031610	-0.0000166	0.0000073	-0.0002790	-0.0000737	-0.0011880	-0.0016420	-0.0015430	-0.0000007	-0.0016600	-0.0002810	-0.0000582
Dyspnea (lagged 12 months), several days	-0.0302390	-0.0003090	0.0003350	-0.0000102	0.0001090	0.0482970	0.0588700	-0.0018030	-0.0000691	-0.0002550	-0.0008880	-0.0003900	-0.0003880	-0.0015950	-0.0030520	-0.0000017	-0.0012800	-0.0001460	0.0003330
Symptom most days	0.0066220	-0.0002830	0.0006050	0.0000026	-0.0000321	-0.0031610	-0.0018030	0.0149720	-0.0000611	0.0008050	-0.0010320	-0.0029990	0.0013300	0.0015030	-0.0002630	-0.0000031	0.0007990	-0.0000946	0.0002410
Age	-0.0070450	0.0000188	-0.0000193	0.0000005	-0.0000082	-0.0000166	-0.0000691	-0.0000611	0.0001000	-0.0000582	-0.0000547	0.0002680	0.0001090	0.0001400	0.0000684	0.0000000	-0.0000763	0.0000056	-0.0001460
CVD co-morbidity (yes)	-0.0008520	0.0001320	0.0004530	0.0000025	-0.0000563	0.0000073	-0.0002550	0.0008050	-0.0000582	0.0140810	-0.0018170	-0.0000540	0.0018910	-0.0004820	0.0006670	0.0000006	0.0000501	-0.0000384	-0.0009500
Other co-morbidity (yes)	-0.0075890	-0.0002220	-0.0003470	0.0000027	-0.0000459	-0.0002790	-0.0008880	-0.0010320	-0.0000547	-0.0018170	0.0199030	0.0007110	-0.0026670	-0.0020980	0.0011480	0.0000004	-0.0001750	-0.0000154	-0.0002970
Current smoker	-0.0209270	0.0003450	0.0000299	-0.0000025	-0.0000618	-0.0000737	-0.0003900	-0.0029990	0.0002680	-0.0000540	0.0007110	0.0158000	0.0006350	0.0011010	-0.0017360	-0.0000008	0.0011000	0.0000050	-0.0005780
Female	-0.0064020	-0.0003680	0.0001660	0.0000134	-0.0001240	-0.0011880	-0.0003880	0.0013300	0.0001090	0.0018910	-0.0026670	0.0006350	0.0172750	0.0008540	-0.0027290	-0.0000037	0.0002310	0.0000013	0.0006020
High BMI category	-0.0105250	0.0002110	0.0006880	0.0000131	-0.0001160	-0.0016420	-0.0015950	0.0015030	0.0001400	-0.0004820	-0.0020980	0.0011010	0.0008540	0.0202720	0.0050270	-0.0000049	-0.0002190	0.0000018	-0.0001300
Low BMI category	-0.0171820	0.0001830	-0.0005650	-0.0000033	0.0000624	-0.0015430	-0.0030520	-0.0002630	0.0000684	0.0006670	0.0011480	-0.0017360	-0.0027290	0.0050270	0.0237090	0.0000106	0.0009540	-0.0000204	-0.0012160
Fibrinogen	-0.0001370	-0.0000012	-0.0000017	0.0000000	0.0000002	-0.0000007	-0.0000017	-0.0000031	0.0000000	0.0000006	0.0000004	-0.0000008	-0.0000037	-0.0000049	0.0000106	0.0000002	-0.0000014	-0.0000001	-0.0000049
Baseline mMRC	-0.0048730	-0.0002190	0.0003520	0.0000151	0.0000622	-0.0016600	-0.0012800	0.0007990	-0.0000763	0.0000501	-0.0001750	0.0011000	0.0002310	-0.0002190	0.0009540	-0.0000014	0.0214270	-0.0001930	-0.0001810
Baseline SGRQ	-0.0010570	-0.0000185	-0.0000380	0.0000007	0.0000013	-0.0002810	-0.0001460	-0.0000946	0.0000056	-0.0000384	-0.0000154	0.0000050	0.0000013	0.0000018	-0.0000204	-0.0000001	-0.0001930	0.0000169	-0.0000011
Scale	0.0148100	-0.0000354	0.0000219	0.0000088	0.0000333	-0.0000582	0.0003330	0.0002410	-0.0001460	-0.0009500	-0.0002970	-0.0005780	0.0006020	-0.0001300	-0.0012160	-0.0000049	-0.0001810	-0.0000011	0.0028390

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A18 Covariance matrix (probability of hospitalization)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	0.2039000	0.0002030	-0.0005300	0.0023080	-0.0004400	-0.0159600	-0.0186700	0.0009240	-0.0017600	0.0033040	-0.0025900	-0.0109800	-0.0075100	-0.0015200	-0.0029600	-0.0245100	-0.0003600	-0.0036800
Time (log years)	0.0002030	0.0002990	0.0000290	-0.0000600	-0.0000028	0.0004000	0.0002300	0.0000300	0.0000046	0.0000028	-0.0000400	-0.0000100	-0.0000600	0.0000200	-0.0000200	-0.0000800	-0.0000010	-0.0000500
Moderate exac. count	-0.0005300	0.0000290	0.0002550	-0.0001100	0.0000041	-0.0002700	-0.0000900	-0.0001000	0.0000001	0.0000400	-0.0002500	0.0000940	-0.0002100	-0.0000300	-0.0001200	0.0001930	0.0000026	-0.0000800
Severe exac. count	0.0023080	-0.0000600	-0.0001100	0.0060100	-0.0000082	0.0001470	-0.0000400	0.0000360	-0.0000500	-0.0009400	-0.0002800	-0.0001900	-0.0002100	-0.0010800	-0.0001100	-0.0002200	-0.0000100	-0.0000500
FEV₁ % predicted	-0.0004400	-0.0000028	0.0000041	-0.0000082	0.0000093	0.0000730	0.0000290	-0.0000200	-0.0000014	-0.0000300	-0.0000200	-0.0000100	0.0000750	-0.0000200	0.0000590	0.0000280	0.0000010	0.0000044
Dyspnea (most days vs none)	-0.0159600	0.0004000	-0.0002700	0.0001470	0.0000730	0.0263900	0.0199600	-0.0020000	0.0000019	-0.0002800	-0.0009300	-0.0000900	-0.0002400	0.0004440	0.0004650	-0.0009300	-0.0000900	0.0000150
Dyspnea (several days vs none)	-0.0186700	0.0002300	-0.0000900	-0.0000400	0.0000290	0.0199600	0.0227900	0.0001990	0.0000170	0.0000960	-0.0002500	-0.0007000	-0.0001100	0.0001270	0.0001760	-0.0008100	-0.0000300	-0.0002000
Cough and sputum	0.0009240	0.0000300	-0.0001000	0.0000360	-0.0000200	-0.0020000	0.0001990	0.0080500	0.0000040	0.0005250	-0.0005300	-0.0015800	0.0004540	0.0004970	-0.0001600	0.0000380	-0.0000400	-0.0001800
Age	-0.0017600	0.0000046	0.0000001	-0.0000500	-0.0000014	0.0000019	0.0000170	0.0000040	0.0000280	-0.0000500	-0.0000400	0.0001310	0.0000430	0.0000300	-0.0000100	-0.0000700	0.0000015	-0.0000029
CVD co-morbidity	0.0033040	0.0000028	0.0000400	-0.0009400	-0.0000300	-0.0002800	0.0000960	0.0005250	-0.0000500	0.0106800	0.0003050	-0.0004100	0.0003910	-0.0001000	-0.0004300	0.0002370	-0.0000200	0.0000180
Other co-morbidity	-0.0025900	-0.0000400	-0.0002500	-0.0002800	-0.0000200	-0.0009300	-0.0002500	-0.0005300	-0.0000400	0.0003050	0.0092630	0.0004850	-0.0011000	-0.0006600	0.0010010	0.0000300	0.0000076	0.0002170
Current smoker	-0.0109800	-0.0000100	0.0000940	-0.0001900	-0.0000100	-0.0000900	-0.0007000	-0.0015800	0.0001310	-0.0004100	0.0004850	0.0078500	-0.0004000	0.0002180	-0.0010600	-0.0000700	0.0000130	-0.0001500
Sex	-0.0075100	-0.0000600	-0.0002100	-0.0002100	0.0000750	-0.0002400	-0.0001100	0.0004540	0.0000430	0.0003910	-0.0011000	-0.0004000	0.0106100	-0.0010200	0.0000130	-0.0000700	0.0000076	0.0004060
BMI (high vs normal)	-0.0015200	0.0000200	-0.0000300	-0.0010800	-0.0000200	0.0004440	0.0001270	0.0004970	0.0000300	-0.0001000	-0.0006600	0.0002180	-0.0010200	0.0175900	0.0024620	-0.0007200	-0.0000200	0.0002700
BMI (low vs normal)	-0.0029600	-0.0000200	-0.0001200	-0.0001100	0.0000590	0.0004650	0.0001760	-0.0001600	-0.0000100	-0.0004300	0.0010010	-0.0010600	0.0000130	0.0024620	0.0098460	-0.0004100	-0.0000200	-0.0006300
mMRC	-0.0245100	-0.0000800	0.0001930	-0.0002200	0.0000280	-0.0009300	-0.0008100	0.0000380	-0.0000700	0.0002370	0.0000300	-0.0000700	-0.0000700	-0.0007200	-0.0004100	0.0351500	-0.0001000	0.0004680
SGRQ	-0.0003600	-0.0000010	0.0000026	-0.0000100	0.0000010	-0.0000900	-0.0000300	-0.0000400	0.0000015	-0.0000200	0.0000076	0.0000130	0.0000076	-0.0000200	-0.0000200	-0.0001000	0.0000076	-0.0000400
Prior exac.	-0.0036800	-0.0000500	-0.0000800	-0.0000500	0.0000044	0.0000150	-0.0002000	-0.0001800	-0.0000029	0.0000180	0.0002170	-0.0001500	0.0004060	0.0002700	-0.0006300	0.0004680	-0.0000400	0.0080900

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; 6MWD, six-minute walk test distance.

Table A19 Covariance matrix (ward days)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	0.1091600	-0.0000820	0.0000461	0.0002187	-0.0002020	-0.0130400	-0.0145400	-0.0001030	-0.0009190	0.0012200	-0.0025030	-0.0041960	-0.0035270	-0.0013090	-0.0024520	-0.0109700	-0.0001730	-0.0022330
Time (log years)	-0.0000820	0.0001450	0.0000150	0.0000032	0.0000011	0.0001536	0.0001225	0.0000205	0.0000010	-0.0000360	-0.0000120	-0.0000310	0.0000206	-0.0000110	0.0000445	0.0000436	-0.0000001	-0.0000110
Moderate exac. count	0.0000461	0.0000150	0.0000646	-0.0000500	-0.0000007	-0.0001290	-0.0001240	0.0000168	0.0000005	0.0000798	-0.0000420	0.0000386	-0.0000640	-0.0000810	-0.0000140	-0.0000220	0.0000006	0.0000250
Severe exac. count	0.0002187	0.0000032	-0.0000500	0.0001072	0.0000045	0.0001159	0.0001277	0.0000593	-0.0000079	-0.0000610	-0.0000430	-0.0000260	0.0001778	-0.0001140	-0.0000590	0.0000752	-0.0000023	-0.0000036
FEV₁ % predicted	-0.0002020	0.0000011	-0.0000007	0.0000045	0.0000044	0.0000304	0.0000093	-0.0000093	-0.0000007	-0.0000055	-0.0000061	-0.0000100	0.0000374	-0.0000170	0.0000283	0.0000088	0.0000005	0.0000068
Dyspnea (most days vs none)	-0.0130400	0.0001536	-0.0001290	0.0001159	0.0000304	0.0145100	0.0120700	-0.0013250	0.0000259	0.0003144	0.0000296	-0.0003540	-0.0000720	-0.0001480	0.0010140	-0.0001980	-0.0000280	0.0001809
Dyspnea (several days vs none)	-0.0145400	0.0001225	-0.0001240	0.0001277	0.0000093	0.0120700	0.0136900	-0.0002080	0.0000368	0.0003118	0.0001811	-0.0003560	0.0000320	0.0003139	0.0007298	-0.0000550	-0.0000019	-0.0001140
Cough and sputum	-0.0001030	0.0000205	0.0000168	0.0000593	-0.0000093	-0.0013250	-0.0002080	0.0037650	0.0000025	-0.0000470	-0.0001200	-0.0005950	0.0001126	0.0005259	-0.0001040	0.0004401	-0.0000180	-0.0001050
Age	-0.0009190	0.0000010	0.0000005	-0.0000079	-0.0000007	0.0000259	0.0000368	0.0000025	0.0000140	-0.0000300	-0.0000130	0.0000539	0.0000165	0.0000246	-0.0000005	-0.0000340	0.0000005	0.0000018
CVD co-morbidity	0.0012200	-0.0000360	0.0000798	-0.0000610	-0.0000055	0.0003144	0.0003118	-0.0000470	-0.0000300	0.0041730	0.0002184	-0.0000410	-0.0000030	0.0000479	0.0000171	-0.0001600	-0.0000099	0.0000765
Other co-morbidity	-0.0025030	-0.0000120	-0.0000420	-0.0000430	-0.0000061	0.0000296	0.0001811	-0.0001200	-0.0000130	0.0002184	0.0047760	0.0004087	-0.0006140	-0.0001980	0.0002566	0.0001125	-0.0000048	0.0000929
Current smoker	-0.0041960	-0.0000310	0.0000386	-0.0000260	-0.0000100	-0.0003540	-0.0003560	-0.0005950	0.0000539	-0.0000410	0.0004087	0.0036990	-0.0004520	0.0000613	-0.0003120	-0.0000590	-0.0000009	0.0000977
Sex	-0.0035270	0.0000206	-0.0000640	0.0001778	0.0000374	-0.0000720	0.0000320	0.0001126	0.0000165	-0.0000030	-0.0006140	-0.0004520	0.0055080	-0.0003620	-0.0000440	0.0000696	0.0000041	-0.0000350
BMI (high vs normal)	-0.0013090	-0.0000110	-0.0000810	-0.0001140	-0.0000170	-0.0001480	0.0003139	0.0005259	0.0000246	0.0000479	-0.0001980	0.0000613	-0.0003620	0.0081920	0.0014770	-0.0006580	-0.0000120	0.0007783
BMI (low vs normal)	-0.0024520	0.0000445	-0.0000140	-0.0000590	0.0000283	0.0010140	0.0007298	-0.0001040	-0.0000005	0.0000171	0.0002566	-0.0003120	-0.0000440	0.0014770	0.0042600	-0.0003420	-0.0000051	-0.0002560
mMRC	-0.0109700	0.0000436	-0.0000220	0.0000752	0.0000088	-0.0001980	-0.0000550	0.0004401	-0.0000340	-0.0001600	0.0001125	-0.0000590	0.0000696	-0.0006580	-0.0003420	0.0163000	-0.0000440	-0.0001750
SGRQ	-0.0001730	-0.0000001	0.0000006	-0.0000023	0.0000005	-0.0000280	-0.0000019	-0.0000180	0.0000005	-0.0000099	-0.0000048	-0.0000009	0.0000041	-0.0000120	-0.0000051	-0.0000440	0.0000037	-0.0000180
Prior exac.	-0.0022330	-0.0000110	0.0000250	-0.0000036	0.0000068	0.0001809	-0.0001140	-0.0001050	0.0000018	0.0000765	0.0000929	0.0000977	-0.0000350	0.0007783	-0.0002560	-0.0001750	-0.0000180	0.0039300

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire

Table A20 Covariance matrix (intensive care unit)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	1.1393100	-0.0016900	0.0012370	0.0034540	-0.0023400	-0.1097300	-0.1224800	-0.0000670	-0.0106000	0.0081730	-0.0461400	-0.0618700	-0.0387200	-0.0248300	-0.0275800	-0.0460100	-0.0020340	-0.0157500
Time (log years)	-0.0016900	0.0020300	0.0001408	0.0001762	0.0000177	0.0015040	0.0013500	0.0001955	0.0000196	-0.0005020	-0.0003470	-0.0004870	0.0000077	0.0001811	0.0004686	0.0001856	0.0000001	-0.0001770
Moderate exac. count	0.0012370	0.0001408	0.0004546	-0.0004010	-0.0000120	-0.0011830	-0.0008580	-0.0001970	-0.0000110	0.0008472	-0.0004340	0.0004293	-0.0010230	-0.0003530	-0.0001970	-0.0001440	0.0000075	0.0000856
Severe exac. count	0.0034540	0.0001762	-0.0004010	0.0010000	0.0000509	0.0002784	0.0008151	0.0012930	-0.0000870	-0.0002570	-0.0002940	-0.0001340	0.0020560	-0.0017940	-0.0005790	0.0003371	-0.0000290	0.0002909
FEV₁ % predicted	-0.0023400	0.0000177	-0.0000120	0.0000509	0.0000514	0.0004166	0.0001538	-0.0001040	-0.0000087	-0.0000410	-0.0000660	-0.0000880	0.0003959	-0.0001080	0.0003339	0.0001027	0.0000061	0.0000707
Dyspnea (most days vs none)	-0.1097300	0.0015040	-0.0011830	0.0002784	0.0004166	0.1292900	0.0936600	-0.0145100	0.0003501	0.0008511	-0.0007060	-0.0034860	-0.0000880	-0.0005230	0.0133400	-0.0030620	-0.0003430	0.0040200
Dyspnea (several days vs none)	-0.1224800	0.0013500	-0.0008580	0.0008151	0.0001538	0.0936600	0.1092300	-0.0009320	0.0003995	0.0017940	0.0014470	-0.0028600	0.0000523	0.0052300	0.0076350	-0.0009980	-0.0000260	-0.0005070
Cough and sputum	-0.0000670	0.0001955	-0.0001970	0.0012930	-0.0001040	-0.0145100	-0.0009320	0.0453800	0.0000243	-0.0004220	-0.0020870	-0.0067460	0.0010150	0.0076630	-0.0007750	0.0045430	-0.0002170	-0.0013030
Age	-0.0106000	0.0000196	-0.0000110	-0.0000870	-0.0000087	0.0003501	0.0003995	0.0000243	0.0001619	-0.0002940	-0.0001880	0.0007178	0.0002506	0.0003265	-0.0000086	-0.0002500	0.0000058	-0.0000270
CVD co-morbidity	0.0081730	-0.0005020	0.0008472	-0.0002570	-0.0000410	0.0008511	0.0017940	-0.0004220	-0.0002940	0.0404600	-0.0007180	-0.0009620	-0.0004050	-0.0005300	-0.0009670	-0.0008500	-0.0000850	0.0014820
Other co-morbidity	-0.0461400	-0.0003470	-0.0004340	-0.0002940	-0.0000660	-0.0007060	0.0014470	-0.0020870	-0.0001880	-0.0007180	0.0743400	0.0033810	-0.0063760	-0.0034010	0.0018260	0.0012870	-0.0000220	0.0007403
Current smoker	-0.0618700	-0.0004870	0.0004293	-0.0001340	-0.0000880	-0.0034860	-0.0028600	-0.0067460	0.0007178	-0.0009620	0.0033810	0.0421300	-0.0038860	-0.0015410	-0.0038170	-0.0004660	0.0000250	0.0005934
Sex	-0.0387200	0.0000077	-0.0010230	0.0020560	0.0003959	-0.0000880	0.0000523	0.0010150	0.0002506	-0.0004050	-0.0063760	-0.0038860	0.0922400	-0.0024060	-0.0008090	-0.0006120	0.0000463	-0.0014900
BMI (high vs normal)	-0.0248300	0.0001811	-0.0003530	-0.0017940	-0.0001080	-0.0005230	0.0052300	0.0076630	0.0003265	-0.0005300	-0.0034010	-0.0015410	-0.0024060	0.0726300	0.0202100	-0.0055540	-0.0001460	0.0092990
BMI (low vs normal)	-0.0275800	0.0004686	-0.0001970	-0.0005790	0.0003339	0.0133400	0.0076350	-0.0007750	-0.0000086	-0.0009670	0.0018260	-0.0038170	-0.0008090	0.0202100	0.0549000	-0.0022130	-0.0001060	-0.0040450
mMRC	-0.0460100	0.0001856	-0.0001440	0.0003371	0.0001027	-0.0030620	-0.0009980	0.0045430	-0.0002500	-0.0008500	0.0012870	-0.0004660	-0.0006120	-0.0055540	-0.0022130	0.0994600	-0.0005240	-0.0015840
SGRQ	-0.0020340	0.0000001	0.0000075	-0.0000290	0.0000061	-0.0003430	-0.0000260	-0.0002170	0.0000058	-0.0000850	-0.0000220	0.0000250	0.0000463	-0.0001460	-0.0001060	-0.0005240	0.0000434	-0.0002010
Prior exac.	-0.0157500	-0.0001770	0.0000856	0.0002909	0.0000707	0.0040200	-0.0005070	-0.0013030	-0.0000270	0.0014820	0.0007403	0.0005934	-0.0014900	0.0092990	-0.0040450	-0.0015840	-0.0002010	0.0394000

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire

Table A21 Covariance matrix (emergency room visits)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	0.8437400	0.0005724	0.0000682	0.0032500	-0.0017690	-0.0885400	-0.1026900	0.0031460	-0.0077180	0.0086530	-0.0149000	-0.0375100	-0.0301700	-0.0083870	-0.0188900	-0.0500700	-0.0013680	-0.0165400
Time (log years)	0.0005724	0.0010800	0.0000125	0.0000641	0.0000018	0.0010690	0.0006949	0.0000284	0.0000087	-0.0000710	-0.0000640	-0.0001980	-0.0000140	0.0000760	0.0001486	-0.0000460	0.0000024	-0.0000390
Moderate exac. count	0.0000682	0.0000125	0.0002859	-0.0003060	-0.0000032	-0.0005830	-0.0003290	-0.0001410	-0.0000003	0.0001140	-0.0005290	0.0001047	-0.0006240	-0.0002270	-0.0000920	0.0001730	0.0000022	-0.0000590
Severe exac. count	0.0032500	0.0000641	-0.0003060	0.0010920	0.0000253	0.0002766	0.0000574	0.0006597	-0.0000570	0.0002649	-0.0000190	0.0000576	0.0013730	-0.0015890	-0.0005120	-0.0002840	-0.0000150	0.0001079
FEV₁ % predicted	-0.0017690	0.0000018	-0.0000032	0.0000253	0.0000364	0.0002578	0.0001145	-0.0000740	-0.0000053	-0.0000530	-0.0000320	-0.0000870	0.0002893	-0.0001200	0.0002316	0.0000600	0.0000052	0.0000507
Dyspnea (most days vs none)	-0.0885400	0.0010690	-0.0005830	0.0002766	0.0002578	0.1255400	0.1028400	-0.0090920	0.0000150	-0.0004160	-0.0024440	-0.0008110	-0.0013060	-0.0000480	0.0047950	-0.0025640	-0.0003520	-0.0003250
Dyspnea (several days vs none)	-0.1026900	0.0006949	-0.0003290	0.0000574	0.0001145	0.1028400	0.1134000	-0.0010350	0.0001238	-0.0005190	-0.0005920	-0.0018950	-0.0006020	0.0020650	0.0029690	-0.0009330	-0.0001120	-0.0019200
Cough and sputum	0.0031460	0.0000284	-0.0001410	0.0006597	-0.0000740	-0.0090920	-0.0010350	0.0302700	-0.0000046	-0.0003810	-0.0012290	-0.0055440	0.0010100	0.0022750	-0.0010140	0.0017620	-0.0001320	-0.0004810
Age	-0.0077180	0.0000087	-0.0000003	-0.0000570	-0.0000053	0.0000150	0.0001238	-0.0000046	0.0001171	-0.0002100	-0.0001830	0.0004841	0.0001939	0.0001421	-0.0000130	-0.0001410	0.0000047	0.0000409
CVD co-morbidity	0.0086530	-0.0000710	0.0001140	0.0002649	-0.0000530	-0.0004160	-0.0005190	-0.0003810	-0.0002100	0.0380100	0.0012460	0.0008099	-0.0004420	0.0011930	-0.0000640	-0.0000470	-0.0000510	0.0006794
Other co-morbidity	-0.0149000	-0.0000640	-0.0005290	-0.0000190	-0.0000320	-0.0024440	-0.0005920	-0.0012290	-0.0001830	0.0012460	0.0404100	0.0022980	-0.0043620	-0.0014670	0.0027620	0.0008016	-0.0000230	0.0010860
Current smoker	-0.0375100	-0.0001980	0.0001047	0.0000576	-0.0000870	-0.0008110	-0.0018950	-0.0055440	0.0004841	0.0008099	0.0022980	0.0310200	-0.0024680	0.0014060	-0.0034280	0.0000900	-0.0000160	0.0001707
Sex	-0.0301700	-0.0000140	-0.0006240	0.0013730	0.0002893	-0.0013060	-0.0006020	0.0010100	0.0001939	-0.0004420	-0.0043620	-0.0024680	0.0430100	-0.0025490	-0.0005650	-0.0009060	0.0000561	0.0000519
BMI (high vs normal)	-0.0083870	0.0000760	-0.0002270	-0.0015890	-0.0001200	-0.0000480	0.0020650	0.0022750	0.0001421	0.0011930	-0.0014670	0.0014060	-0.0025490	0.0776600	0.0111700	-0.0032020	-0.0000940	0.0045200
BMI (low vs normal)	-0.0188900	0.0001486	-0.0000920	-0.0005120	0.0002316	0.0047950	0.0029690	-0.0010140	-0.0000130	-0.0000640	0.0027620	-0.0034280	-0.0005650	0.0111700	0.0346400	-0.0004850	-0.0000450	-0.0019800
mMRC	-0.0500700	-0.0000460	0.0001730	-0.0002840	0.0000600	-0.0025640	-0.0009330	0.0017620	-0.0001410	-0.0000470	0.0008016	0.0000900	-0.0009060	-0.0032020	-0.0004850	0.0805600	-0.0003020	-0.0004560
SGRQ	-0.0013680	0.0000024	0.0000022	-0.0000150	0.0000052	-0.0003520	-0.0001120	-0.0001320	0.0000047	-0.0000510	-0.0000230	-0.0000160	0.0000561	-0.0000940	-0.0000450	-0.0003020	0.0000294	-0.0001150
Prior exac.	-0.0165400	-0.0000390	-0.0000590	0.0001079	0.0000507	-0.0003250	-0.0019200	-0.0004810	0.0000409	0.0006794	0.0010860	0.0001707	0.0000519	0.0045200	-0.0019800	-0.0004560	-0.0001150	0.0285600

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire

Table A22 Covariance matrix (days and nights at home)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	2.8069600	0.0042910	-0.0028370	0.0104500	-0.0045420	-0.1197100	-0.1612000	0.0111200	-0.0213600	0.0202900	-0.0708200	-0.1012200	-0.0938700	-0.0231900	-0.0413300	-0.6375400	-0.0034670	-0.0985200
Time (log years)	0.0042910	0.0029070	0.0001068	-0.0000880	-0.0000040	0.0034790	0.0021130	0.0006597	0.0000178	-0.0000870	-0.0001640	-0.0005230	-0.0000770	-0.0004100	0.0001206	0.0000132	-0.0000160	0.0001079
Moderate exac. count	-0.0028370	0.0001068	0.0012540	-0.0009310	-0.0000020	-0.0018440	-0.0009680	-0.0004530	0.0000265	0.0003873	-0.0014790	0.0004079	-0.0018130	-0.0007520	-0.0005650	0.0009193	0.0000093	-0.0001980
Severe exac. count	0.0104500	-0.0000880	-0.0009310	0.0062780	0.0000874	0.0021000	0.0009182	0.0010620	-0.0001910	-0.0005110	-0.0006910	0.0001064	0.0031080	-0.0006130	-0.0019520	-0.0006310	-0.0000700	-0.0006130
FEV₁ % predicted	-0.0045420	-0.0000040	-0.0000020	0.0000874	0.0000883	0.0005654	0.0002347	-0.0001470	-0.0000120	-0.0001240	-0.0000810	-0.0002000	0.0008312	-0.0003740	0.0005766	0.0002149	0.0000112	0.0001635
Dyspnea (most days vs none)	-0.1197100	0.0034790	-0.0018440	0.0021000	0.0005654	0.2275900	0.1607700	-0.0198800	0.0000956	-0.0033810	-0.0050760	-0.0042420	-0.0041450	0.0004823	0.0101700	-0.0061720	-0.0008820	-0.0002390
Dyspnea (several days vs none)	-0.1612000	0.0021130	-0.0009680	0.0009182	0.0002347	0.1607700	0.1853400	-0.0019470	0.0003588	-0.0023290	-0.0008440	-0.0051190	-0.0017550	0.0040100	0.0081660	-0.0022910	-0.0002770	-0.0034500
Cough and sputum	0.0111200	0.0006597	-0.0004530	0.0010620	-0.0001470	-0.0198800	-0.0019470	0.0780700	-0.0000500	-0.0001810	-0.0022340	-0.0141300	0.0016400	0.0029740	-0.0012240	0.0031790	-0.0003850	-0.0001800
Age	-0.0213600	0.0000178	0.0000265	-0.0001910	-0.0000120	0.0000956	0.0003588	-0.0000500	0.0003168	-0.0005410	-0.0004640	0.0012480	0.0006211	0.0004760	-0.0001470	-0.0003010	0.0000127	0.0000845
CVD co-morbidity	0.0202900	-0.0000870	0.0003873	-0.0005110	-0.0001240	-0.0033810	-0.0023290	-0.0001810	-0.0005410	0.0876800	0.0044070	0.0009843	-0.0009580	0.0017830	0.0000637	0.0021200	-0.0001340	0.0019790
Other co-morbidity	-0.0708200	-0.0001640	-0.0014790	-0.0006910	-0.0000810	-0.0050760	-0.0008440	-0.0022340	-0.0004640	0.0044070	0.1315000	0.0049580	-0.0108300	-0.0052270	0.0097800	0.0030250	-0.0001040	0.0029260
Current smoker	-0.1012200	-0.0005230	0.0004079	0.0001064	-0.0002000	-0.0042420	-0.0051190	-0.0141300	0.0012480	0.0009843	0.0049580	0.0805600	-0.0070460	0.0044830	-0.0106000	0.0028260	0.0000111	0.0002523
Sex	-0.0938700	-0.0000770	-0.0018130	0.0031080	0.0008312	-0.0041450	-0.0017550	0.0016400	0.0006211	-0.0009580	-0.0108300	-0.0070460	0.1096000	-0.0084730	-0.0001850	-0.0012200	0.0001424	0.0014420
BMI (high vs normal)	-0.0231900	-0.0004100	-0.0007520	-0.0006130	-0.0003740	0.0004823	0.0040100	0.0029740	0.0004760	0.0017830	-0.0052270	0.0044830	-0.0084730	0.2353300	0.0237900	-0.0106200	-0.0001640	0.0049220
BMI (low vs normal)	-0.0413300	0.0001206	-0.0005650	-0.0019520	0.0005766	0.0101700	0.0081660	-0.0012240	-0.0001470	0.0000637	0.0097800	-0.0106000	-0.0001850	0.0237900	0.0933600	-0.0013580	-0.0001330	-0.0025490
mMRC	-0.6375400	0.0000132	0.0009193	-0.0006310	0.0002149	-0.0061720	-0.0022910	0.0031790	-0.0003010	0.0021200	0.0030250	0.0028260	-0.0012200	-0.0106200	-0.0013580	0.7060700	-0.0008210	0.0001734
SGRQ	-0.0034670	-0.0000160	0.0000093	-0.0000700	0.0000112	-0.0008820	-0.0002770	-0.0003850	0.0000127	-0.0001340	-0.0001040	0.0000111	0.0001424	-0.0001640	-0.0001330	-0.0008210	0.0000739	-0.0003290
Prior exac.	-0.0985200	0.0001079	-0.0001980	-0.0006130	0.0001635	-0.0002390	-0.0034500	-0.0001800	0.0000845	0.0019790	0.0029260	0.0002523	0.0014420	0.0049220	-0.0025490	0.0001734	-0.0003290	0.1233000

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire

Table A23 Covariance matrix (office visits)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	0.1587500	0.0001214	0.0000996	0.0006582	-0.0003490	-0.0258700	-0.0284300	0.0008488	-0.0012750	0.0008523	-0.0049280	-0.0068270	-0.0058710	-0.0008890	-0.0035210	-0.0122200	-0.0002420	-0.0031080
Time (log years)	0.0001214	0.0002103	0.0000052	-0.0000360	0.0000000	0.0002090	0.0001219	0.0000162	0.0000011	0.0000050	-0.0000030	-0.0000240	-0.0000110	-0.0000200	0.0000070	0.0000035	0.0000002	0.0000018
Moderate exac. count	0.0000996	0.0000052	0.0000403	-0.0000590	-0.0000003	-0.0000600	-0.0000330	-0.0000140	-0.0000010	0.0000020	-0.0000960	0.0000161	-0.0001100	-0.0000480	-0.0000110	0.0000269	-0.0000004	-0.0000220
Severe exac. count	0.0006582	-0.0000360	-0.0000590	0.0007045	0.0000043	-0.0000680	-0.0000300	-0.0000140	-0.0000130	0.0000004	-0.0000210	-0.0000250	0.0002469	-0.0000260	-0.0001040	-0.0000450	-0.0000024	-0.0000410
FEV₁ % predicted	-0.0003490	0.0000000	-0.0000003	0.0000043	0.0000065	0.0000535	0.0000272	-0.0000120	-0.0000006	-0.0000070	-0.0000048	-0.0000160	0.0000608	-0.0000250	0.0000395	0.0000130	0.0000006	0.0000079
Dyspnea (most days vs none)	-0.0258700	0.0002090	-0.0000600	-0.0000680	0.0000535	0.0334900	0.0293000	-0.0018130	-0.0000079	-0.0001500	-0.0006360	-0.0000410	-0.0002130	0.0002069	0.0005667	-0.0006370	-0.0000690	-0.0000410
Dyspnea (several days vs none)	-0.0284300	0.0001219	-0.0000330	-0.0000300	0.0000272	0.0293000	0.0315300	-0.0002450	0.0000066	-0.0001020	-0.0002450	-0.0004120	-0.0001360	0.0002080	0.0004469	-0.0002120	-0.0000190	-0.0002860
Cough and sputum	0.0008488	0.0000162	-0.0000140	-0.0000140	-0.0000120	-0.0018130	-0.0002450	0.0057060	-0.0000078	0.0000029	-0.0002490	-0.0011720	0.0001823	0.0000673	-0.0001740	0.0003901	-0.0000250	-0.0000420
Age	-0.0012750	0.0000011	-0.0000010	-0.0000130	-0.0000006	-0.0000079	0.0000066	-0.0000078	0.0000195	-0.0000280	-0.0000300	0.0000911	0.0000331	0.0000290	0.0000002	-0.0000190	0.0000010	0.0000095
CVD co-morbidity	0.0008523	0.0000050	0.0000020	0.0000004	-0.0000070	-0.0001500	-0.0001020	0.0000029	-0.0000280	0.0071900	0.0001539	0.0001192	0.0000166	0.0002332	0.0000239	-0.0001690	-0.0000053	0.0001453
Other co-morbidity	-0.0049280	-0.0000030	-0.0000960	-0.0000210	-0.0000048	-0.0006360	-0.0002450	-0.0002490	-0.0000300	0.0001539	0.0098630	0.0004256	-0.0007850	-0.0004940	0.0005407	0.0001252	-0.0000074	0.0002297
Current smoker	-0.0068270	-0.0000240	0.0000161	-0.0000250	-0.0000160	-0.0000410	-0.0004120	-0.0011720	0.0000911	0.0001192	0.0004256	0.0057430	-0.0004020	0.0003934	-0.0006680	-0.0000170	-0.0000038	0.0000165
Sex	-0.0058710	-0.0000110	-0.0001100	0.0002469	0.0000608	-0.0002130	-0.0001360	0.0001823	0.0000331	0.0000166	-0.0007850	-0.0004020	0.0062980	-0.0005500	-0.0000880	-0.0000950	0.0000070	-0.0001050
BMI (high vs normal)	-0.0008890	-0.0000200	-0.0000480	-0.0000260	-0.0000250	0.0002069	0.0002080	0.0000673	0.0000290	0.0002332	-0.0004940	0.0003934	-0.0005500	0.0092850	0.0016900	-0.0008750	-0.0000120	0.0001457
BMI (low vs normal)	-0.0035210	0.0000070	-0.0000110	-0.0001040	0.0000395	0.0005667	0.0004469	-0.0001740	0.0000002	0.0000239	0.0005407	-0.0006680	-0.0000880	0.0016900	0.0091780	0.0000211	-0.0000071	-0.0002710
mMRC	-0.0122200	0.0000035	0.0000269	-0.0000450	0.0000130	-0.0006370	-0.0002120	0.0003901	-0.0000190	-0.0001690	0.0001252	-0.0000170	-0.0000950	-0.0008750	0.0000211	0.0174500	-0.0000570	-0.0000620
SGRQ	-0.0002420	0.0000002	-0.0000004	-0.0000024	0.0000006	-0.0000690	-0.0000190	-0.0000250	0.0000010	-0.0000053	-0.0000074	-0.0000038	0.0000070	-0.0000120	-0.0000071	-0.0000570	0.0000056	-0.0000250
Prior exac.	-0.0031080	0.0000018	-0.0000220	-0.0000410	0.0000079	-0.0000410	-0.0002860	-0.0000420	0.0000095	0.0001453	0.0002297	0.0000165	-0.0001050	0.0001457	-0.0002710	-0.0000620	-0.0000250	0.0054700

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire

Table A24 Covariance matrix (outpatient visits)

	Intercept	Time (log years)	Moderate exac. count	Severe exac. count	FEV ₁ % predicted	Dyspnea (most days vs none)	Dyspnea (several days vs none)	Cough and sputum	Age	CVD co-morbidity	Other co-morbidity	Sex	Current smoker	BMI (high vs normal)	BMI (low vs normal)	mMRC	SGRQ	Prior exac.
Intercept	0.3999300	0.0005560	-0.0001510	0.0021260	-0.0008500	-0.0286500	-0.0352200	0.0020600	-0.0035210	0.0037140	-0.0065340	-0.0185300	-0.0157100	-0.0041190	-0.0084200	-0.0442000	-0.0006750	-0.0084160
Time (log years)	0.0005560	0.0005441	0.0000167	-0.0000520	-0.0000005	0.0006241	0.0003688	0.0001159	0.0000041	0.0000054	-0.0000270	-0.0000710	-0.0000250	-0.0000580	0.0000107	-0.0000350	-0.0000017	0.0000249
Moderate exac. count	-0.0001510	0.0000167	0.0001667	-0.0001630	-0.0000001	-0.0002600	-0.0001170	-0.0000370	0.0000008	0.0000396	-0.0002950	0.0000301	-0.0003440	-0.0001130	-0.0000610	0.0001228	-0.0000003	-0.0000300
Severe exac. count	0.0021260	-0.0000520	-0.0001630	0.0020130	0.0000153	0.0000843	-0.0000090	0.0000641	-0.0000390	-0.0001190	-0.0000630	-0.0000470	0.0006148	-0.0001960	-0.0003260	-0.0001050	-0.0000120	-0.0001990
FEV₁ % predicted	-0.0008500	-0.0000005	-0.0000001	0.0000153	0.0000160	0.0001184	0.0000544	-0.0000270	-0.0000018	-0.0000250	-0.0000130	-0.0000400	0.0001419	-0.0000650	0.0001086	0.0000320	0.0000021	0.0000231
Dyspnea (most days vs none)	-0.0286500	0.0006241	-0.0002600	0.0000843	0.0001184	0.0489900	0.0365600	-0.0041980	0.0000145	-0.0006840	-0.0013690	-0.0004630	-0.0003190	0.0002253	0.0016450	-0.0013330	-0.0001700	-0.0003390
Dyspnea (several days vs none)	-0.0352200	0.0003688	-0.0001170	-0.0000090	0.0000544	0.0365600	0.0412100	-0.0005600	0.0000485	-0.0006020	-0.0004250	-0.0007950	0.0000053	0.0005747	0.0011650	-0.0005580	-0.0000560	-0.0007840
Cough and sputum	0.0020600	0.0001159	-0.0000370	0.0000641	-0.0000270	-0.0041980	-0.0005600	0.0147200	-0.0000200	-0.0000390	-0.0005080	-0.0027150	0.0005160	0.0003459	-0.0004750	0.0008070	-0.0000680	-0.0000700
Age	-0.0035210	0.0000041	0.0000008	-0.0000390	-0.0000018	0.0000145	0.0000485	-0.0000200	0.0000536	-0.0000960	-0.0000850	0.0002434	0.0001034	0.0000884	-0.0000140	-0.0000620	0.0000026	0.0000128
CVD co-morbidity	0.0037140	0.0000054	0.0000396	-0.0001190	-0.0000250	-0.0006840	-0.0006020	-0.0000390	-0.0000960	0.0174800	0.0007264	0.0005326	-0.0001570	0.0004505	0.0001809	0.0001613	-0.0000250	0.0005167
Other co-morbidity	-0.0065340	-0.0000270	-0.0002950	-0.0000630	-0.0000130	-0.0013690	-0.0004250	-0.0005080	-0.0000850	0.0007264	0.0185600	0.0010220	-0.0019050	-0.0014010	0.0015620	0.0003520	-0.0000096	0.0005798
Current smoker	-0.0185300	-0.0000710	0.0000301	-0.0000470	-0.0000400	-0.0004630	-0.0007950	-0.0027150	0.0002434	0.0005326	0.0010220	0.0157300	-0.0010710	0.0010070	-0.0017430	0.0002734	-0.0000035	0.0000644
Sex	-0.0157100	-0.0000250	-0.0003440	0.0006148	0.0001419	-0.0003190	0.0000053	0.0005160	0.0001034	-0.0001570	-0.0019050	-0.0010710	0.0245900	-0.0015380	-0.0000900	-0.0004240	0.0000273	-0.0000270
BMI (high vs normal)	-0.0041190	-0.0000580	-0.0001130	-0.0001960	-0.0000650	0.0002253	0.0005747	0.0003459	0.0000884	0.0004505	-0.0014010	0.0010070	-0.0015380	0.0388200	0.0044430	-0.0019120	-0.0000280	0.0006994
BMI (low vs normal)	-0.0084200	0.0000107	-0.0000610	-0.0003260	0.0001086	0.0016450	0.0011650	-0.0004750	-0.0000140	0.0001809	0.0015620	-0.0017430	-0.0000900	0.0044430	0.0184500	0.0000636	-0.0000290	-0.0007420
mMRC	-0.0442000	-0.0000350	0.0001228	-0.0001050	0.0000320	-0.0013330	-0.0005580	0.0008070	-0.0000620	0.0001613	0.0003520	0.0002734	-0.0004240	-0.0019120	0.0000636	0.0587500	-0.0001590	-0.0003410
SGRQ	-0.0006750	-0.0000017	-0.0000003	-0.0000120	0.0000021	-0.0001700	-0.0000560	-0.0000680	0.0000026	-0.0000250	-0.0000096	-0.0000035	0.0000273	-0.0000280	-0.0000290	-0.0001590	0.0000142	-0.0000600
Prior exac.	-0.0084160	0.0000249	-0.0000300	-0.0001990	0.0000231	-0.0003390	-0.0007840	-0.0000700	0.0000128	0.0005167	0.0005798	0.0000644	-0.0000270	0.0006994	-0.0007420	-0.0003410	-0.0000600	0.0151700

BMI, body-mass index; CVD, cardiovascular disease; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire