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ORIGINAL ARTICLE

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Association between changes in pulmonary function and in patient reported outcomes during enzyme therapy of adult patients with late-onset Pompe disease

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Abstract

Pompe disease is a rare, progressive, and metabolic myopathy. Reduced pulmonary function is one of the main problems seen in adult patients with late-onset Pompe disease (LOPD). We aimed to explore the association between changes over time in pulmonary function and in patient-reported outcome measures (PROMs), in these patients treated with enzyme replacement therapy (ERT). This is a post hoc analysis of two cohort studies. Pulmonary function was assessed as forced vital capacity in the upright position (FVC_{up}). As PROMs, we assessed the physical component summary score (PCS) of the Medical Outcome Study 36-item Short-Form Health Survey (SF-36) and daily life activities (Rasch-Built Pompe-Specific Activity [R-PACT] scale). We fitted Bayesian multivariate mixed-effects models. In the models of PROMs, we assumed a linear association with FVC_{up}, and adjusted for time (nonlinear), sex, and age and disease duration at the start of ERT. One hundred and one patients were eligible for analysis. PCS and R-PAct were positively associated with FVC_{up}, while their relation with time was nonlinear (initial increase then decrease). A 1%-point increase in FVC_{up} is expected to increase PCS by 0.14 points (95% Credible Interval: [0.09;0.19]) and R-PACT by 0.41 points [0.33;0.49] at the same time point. In the first year of ERT, we expect a change of PCS and R-PAct scores by +0.42 and +0.80 points, and in the 5th year of +0.16 and +0.45, respectively. We conclude that the physical domain of quality of life and daily life activities improve when FVC_{up} increases during ERT.

KEYWORDS
enzyme replacement therapy (ERT), forced vital capacity (FVC), late-onset Pompe disease, patient-reported outcome measures

1 | INTRODUCTION

Pompe disease is a rare, inheritable, and progressive metabolic myopathy. It is caused by the partial or total deficiency of the lysosomal enzyme acid alpha-glucosidase, which is needed to break down glycogen. It causes a build-up of lysosomal glycogen and subsequent cellular damage in virtually all body tissues, particularly in the muscle.[1] Adult patients with late-onset Pompe disease (LOPD) present with progressive muscle weakness, limitations in motor function, and respiratory difficulties. Furthermore, patients' quality of life (QoL) has been shown to be reduced. In particular, the physical domains of QoL are affected, while the mental domains are less affected.[2–5]

The introduction of enzyme replacement therapy (ERT) with recombinant human alpha-glucosidase (alglucosidase alfa, Myozyme) for treating Pompe disease in 2006 has changed the lives of patients. In adult patients with LOPD, the initial placebo-controlled trial[6] and many subsequent observational studies have provided evidence of a beneficial effect of ERT on physical outcomes (motor performance, muscle strength, and pulmonary function), patient-reported outcomes, and survival.[4,6–11] The improvements in physical outcomes were most significant in the first 2–3 years after ERT. Fewer studies assessed the effect of ERT on patient-reported outcome measures (PROMs), showing that with ERT, the physical domains of QoL improved initially and then remained stable, while the mental fields of QoL did not change before and during ERT.[2,3,6,12]

PROMs are essential in evaluating the effects of (non-life-saving) treatments. However, the primary outcome measures in clinical trials for treating Pompe disease are usually forced vital capacity (FVC) and the six-minute walk test (6MWT). Furthermore, during clinical follow-up, there is often little time for collecting PROMs. In a situation where mainly physical outcomes are collected or evaluated, knowledge of how these are associated to the patient experience is essential.

Recently we found that physical outcome measures are associated with several patient-reported outcomes cross-sectionally at the start of ERT.[13] What we do not know yet is whether changes over time in these physical outcomes coincide with changes in PROMs during ERT. As an example of one of the two primary outcome measures in Pompe disease, it is especially interesting to explore the association between FVC and PROMs over time. It is often questioned how much benefit a patient experiences in response to an improvement in FVC. This question is more prominent than for the 6MWT, which is a measure of functioning, rather than impairment[14] and has a closer relation to certain items included in PROMs.

Therefore, we aimed to assess the association over time between pulmonary function (forced vital capacity in the upright seated position [FVC_{up}]) and two patient-reported outcomes in patients with LOPD who were receiving ERT. Specifically, we were interested in the association over time of FVC_{up} with (1) the physical domain of QoL (PCS), and (2) the ability to carry out daily life activities (R-PAct). We linked data from two cohort studies for this analysis.[15,16]

2 | METHODS

2.1 | Data

We used data from two prospective observational cohort studies to investigate the association between the outcomes.[15,16] The studies are conducted at the Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center in Rotterdam, the national referral center for Pompe disease in the Netherlands.

FVC in the upright seated position (FVC_{up}) was assessed during clinical follow-up every 3–12 months before and after the start of ERT since January 2005.[17] It was measured using spirometry. The results were expressed as the percentage of the predicted normal values based on the subjects' age, sex, race, and height.[18,19] This means that an FVC_{up} value of 100% corresponds to the mean FVC measurement in a healthy population.

PROMs were collected annually through an ongoing international questionnaire study: the IPA/Erasmus MC Pompe survey,[16] but also partly alongside the clinical follow-up. QoL was assessed using the widely used Medical Outcome Study 36-item Short-Form Health Survey (SF-36) versions 1 and 2.[20] Two summary scores can be derived from the SF-36: the physical component summary measure (PCS) and the mental component summary measure (MCS). The MCS has been shown not to be affected in Pompe disease and was not associated with FVC_{up} at baseline.[3,13] Thus it is not chosen here as an

outcome. Norm-based PCS scores were calculated using the Dutch 1998 norm-based scoring ensuring the comparability of the results for both versions of the SF-36 (SF-36 version 1.0 until 2009 and version 2.0 after that).[21] The PCS scores range from 0 to 100, with higher values indicating better QoL, and a value of 50($\pm$5) corresponding to a healthy population.

As second PROM, we chose the only available Pompe-specific instrument: the Rasch-Built Pompe-Specific Activity (R-PAct) scale,[22] which assesses the patient's ability to carry out daily life activities. The R-PAct scale consists of 18 items that address daily life activities, each with three response options (0 = unable to perform; 1 = able to perform, but with difficulty; 2 = able to perform without difficulty). Only when all items have been answered a centile metric score (0–100) is calculated,[22] with higher values indicating better general well-being. A value of 100 corresponds to a situation in which no limitations have been reported.

The databases for the current study were locked at the end of December 2018. We included only adult patients residing in the Netherlands who were followed in both longitudinal studies, received ERT and had their FVC_{up} assessed during ERT. We excluded patients who lacked key information for the model (i.e., missing disease duration, age, sex, and/or date of measurement). The time frame for analysis was the period during which a patient received ERT. This was operationalized starting 4 months before ERT (to ensure there were sufficient "baseline" data points) until the last measurement available for each patient during ERT (excluding any data points after stopping ERT).

The ethics committee of the Erasmus MC University Medical center (METC) approved both studies. All participants provided written informed consent for the study as well as the use of their data in post hoc analyses such as those in this study.

2.2 | Analysis

Continuous variables are presented as median and total range, while categorical variables are presented as frequency and percentage.

FVC_{up} and PROMs were collected repeatedly over time. To explore the association between FVC_{up} and the PCS and R-PAct, while taking into consideration the inter-correlation of these outcomes, multivariate mixed-effects models were fitted. These models are an extension of the univariate mixed-effects models and can handle multivariate longitudinal outcomes. They allow for potential missing values in the outcomes and the fact that measurements may not be taken at the same time points.

The multivariate mixed-effects models fitted here consist of two sub-models: the first describes the progression of FVC_{up} over time, and the second describes the progression of the PROM over time and its association with FVC_{up}. All models included natural cubic splines of time since the start of ERT (i.e., the time of the measurement in years since start of ERT) with two degrees of freedom to account for the potential nonlinear evolutions of FVC_{up}, PCS, and R-PAct over time. In the specification of the splines, boundary knots were placed at 0 (i.e., at the start of ERT also, called "baseline") and at 15.29 years (maximum observed time), and the internal knot was placed at the median time of measurement (2.78 for the PCS and 5.0 for the RPAct). Splines were also used in the random-effects part to capture the correlation structure among the follow-up visits flexibly.

The model for FVC_{up} included the natural cubic splines of time since the start of ERT and the patients' disease duration at the start of ERT. As mentioned above, FVC_{up} was expressed as the percentage of predicted values adjusted for age, sex, race, and height. Thus, the model of FVC_{up} did not include these.

The models for the PCS and the RPAct contained the natural cubic splines of time since the start of ERT, disease duration at the start of ERT, age at the start of ERT, sex, and the association with FVC_{up}. We did not adjust for other physical outcomes like the 6MWT. Because FVC_{up} is a time-dependent variable, it can be included in the PROM models in different ways. In particular, the estimated value or the slope of FVC_{up} at a specific time point could be associated with the PROMs at that same time point. Alternatively, the history of the FVC_{up} outcome can be used by including the area under the curve (whole or partial) in the models. Combinations of the aforementioned association structures are also possible. In the PCS and R-Pact models, we included the estimated value of FVC_{up} and the area under the curve (AUC) of FVC_{up} and we assumed a linear association of the PROM with both of them. For the AUC we considered three different timeframes: the entire area from the start of ERT, the area the last 12 months, and the area the last 6 months.

Disease duration was calculated from symptom onset. Disease duration and age at the start of ERT were standardized, that is, every value is subtracted by the mean value across all patients and divided by the standard deviation. This was done to improve the performance of the models.

The models were fitted using a Bayesian approach and we assumed noninformative priors for the parameters of the models. The assumptions of the multivariate mixed-effects models were checked with residual plots.

Analyses were performed with the statistical program R (version 4.2.0) and STAN (version 2.23.1). In Table S3, we provide the R packages that we have used.

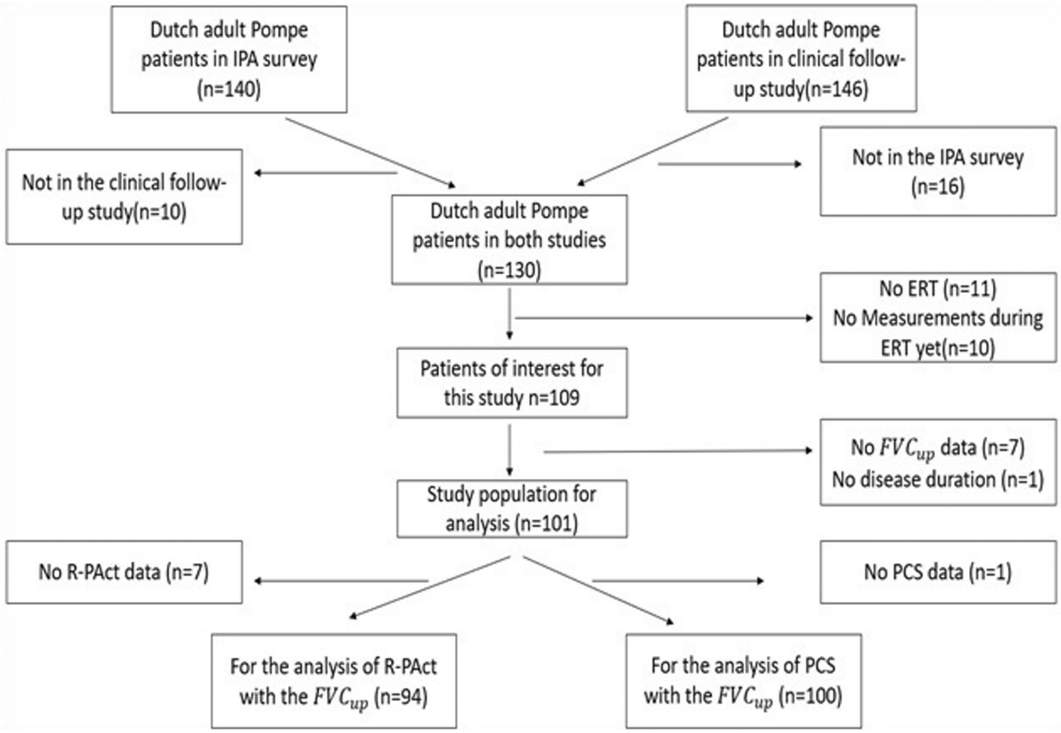

FIGURE 1 Flowchart of the study population. ERT, enzyme replacement therapy; FVCup, forced vital capacity in the upright-seated position; PCS, the Physical Component Summary score; R-Pact, the Rasch-Built Pompe-Specific Activity scale; n: number of patients.

3 | RESULTS

3.1 | Study population

There were 140 Dutch adult patients with LOPD in the IPA/Erasmus MC Pompe survey and 146 in the clinical follow-up study (Figure 1). After excluding patients who were not in both datasets, and those who, during our follow-up, either never received ERT or did not have any measurements since starting ERT, 109 patients were eligible for this study. Finally, we excluded patients who lacked key information required in the model, resulting in an overall study population of 101 patients: 100 for the analysis of FVC_{up} with the PCS and 94 for the analysis of FVC_{up} with the R-PAct. For the first analysis, we had 2015 FVC_{up} measurements and 944 PCS measurements; for the second analysis, we had 1990 FVC_{up} measurements and 927 R-PAct measurements. Measurements were more frequent in the first years of follow-up: 50% of PCS and R-PAct measurements took place in the first 2.8 and 5.0 years of ERT, and 75% of PCS and R-PAct measurements in the first 6.4 and 8.5 years of ERT, respectively.

Table 1 shows the demographic and clinical characteristics of the study population. Of all 101 Pompe patients, 55.4% were women, the median age was 50 years at the start of ERT and 33 years at the start of symptoms, 30.7% were wheelchair dependent, and 24.8% were ventilator dependent. Most patients had the common IVS-I mutation (95%) on one allele. The median total follow-up time in the study was 9.3 years (range: 0.5–15.4). During our follow-up, 12 patients died while receiving regular ERT infusions, and five died after stopping ERT. Eight further patients, who were alive at the end of follow-up, stopped ERT. The median time between the start of ERT and stopping ERT or death of these 25 patients was 5.7 years.

3.2 | Associations of FVC_{up}, time, and confounders in the model with the PCS and R-PAct

The models for FVC_{up} and the PROMs (which include FVC_{up} as an explanatory variable) were fitted to the data simultaneously (i.e., the estimates for FVC_{up} feed into the PROM models). Residuals plots showed that all the assumptions of the models are valid. In the underlying models, FVC_{up} was negatively associated with time (nonlinear) and with the standardized disease duration at the start of ERT. FVC_{up} remained approximately stable during the first 5 years of ERT and decreased after that (Figures S1 and S3).

In the PCS and R-PAct models, none of the possible scenarios of the area under the curve (AUC) of FVC_{up}

TABLE 1 Characteristics of the study population.

Demographic and clinical characteristics	Patients ($n = 101$)
Women: number (%)	56 (55.4)
Age at start of symptoms in years: median (range)	33 (2–62)
Age at start of ERT: median (range)	50 (19–76)
Disease duration at start of ERT in years: median (range)	13.8 (0.85–50.3)
Wheelchair dependent at start of ERT: number (%)	31 (30.7)
Fully: number (%)	8 (7.9)
Partially: number (%)	23 (22.8)
Respiratory support at start of ERT: number (%)	25 (24.8)
Invasive: number (%)	2 (2)
Noninvasive: number (%)	23 (22.8)
Most frequent allele 1: number (%)	
c-32-13T>G(IVS1-13T>G)	96 (95.0)
Most frequent allele 2: number (%)	
c.525delT	46 (45.6)
Patients died or stopped ERT: number (%)	25 (24.8)
Dead: number (%)	17 (16.8)
Died during ERT: number	12
Died after stop ERT: number	5
Alive after stop ERT: number (%)	8 (7.9)
Time between start ERT and stop/death[a]: median years after ERT (range)	5.7 (0.6–12.1)
Total follow-up time in years[b]: median (range)	9.3 (0.5–15.4)

Note: *n*, number of patients.

Abbreviation: ERT, enzyme replacement therapy.

[a]Time until stop or, if not stopped, time until death.

[b]It is calculated as the time of the last measurement minus the time of the first measurement of any outcome that the subject has.

had a clear importance for the PROMs (the estimated coefficients for the AUC were close to zero and their 95% credible intervals included zero: for the entire AUC, the AUC in the last 12 months and the AUC in the last 6 months these were 0 [0, 0.01], 0 [−0.11, 0.11], and −0.01 [−0.23, 0.21], respectively for the PCS model. In the R-PAct model they were 0.01 [0, 0.01], 0.33 [−0.03, 0.69], and 0.17 [−0.01, 0.34], respectively). Therefore, this variable was omitted from the models.

The PCS and R-PAct were positively associated with the estimated value of FVC_{up} at time *t*. Specifically, for a hypothetical 1%-point increase in FVC_{up}, the PCS score is expected to be 0.14 points higher (95% Credible Interval (Crl): [0.09, 0.19]) and the R-PAct 0.41 points higher [0.33, 0.49], accounting for time (i.e., when the time-point is the same), sex, age, and disease duration at the start of ERT. In the absence of any changes in FVC_{up}, the PCS and R-PAct had a nonlinear association with time, increasing in the first 5 years after starting ERT, followed by a decrease (Figures S2 and S4). The R-PAct was also negatively associated with the standardized age at the start of ERT and positively associated with sex (men having 5.7 (95% Crl: [2.03, 9.57]) points higher R-PAct scores than women). The PCS was not found to be associated with age and sex.

Tables S1 and S2 provide the estimated parameters of the multivariate mixed-effects models. Figures S1–S4 illustrate the model estimates of FVC_{up}, PCS, and R-PACT over time for a fictitious "average" patient (i.e., a patient with the median values of the variables in the dataset underlying the specific model). All the outcomes had nonlinear patterns over time.

3.3 | Effect of simultaneous changes in FVC_{up} and time on PROMs

If FVC_{up} improves, it is expected from the above models that PCS and R-PAct scores improve. However, when FVC_{up} changes in a time period, time will also negatively affect the PROMs. To illustrate the relationship of the PROMs with both FVC_{up} and time, we provide Table 2 and Figures 2 and 3.

Table 2 shows the estimated change in a patient's PCS/RPACT score in the hypothetical scenario where FVC_{up} improves by 1%-point in a specific year after the start of ERT (until year 9). After 6–7 years of ERT, we see that the scores decrease rather than increase because, at that point, the negative effect of time on the PROM is larger than the positive effect of increasing FVC_{up} by 1% point.

Figures 2 and 3 depict the association of the estimated PROMs with FVC_{up} for an "average" female subject (i.e., with median standardized age and median standardized disease duration at the start of ERT) at different time points. The straight lines in the graphs reflect the linear relationship of the PROMs with FVC_{up} (slope 0.14 for the PCS and 0.41 for the R-PAct). The shaded areas in the graphs are the 95% credible intervals. As a 95% credible interval, we interpret the 95% probability that the true value falls in this area given the data and the a-priori distributions assumed for the parameters of the models. The lines for the different time-points seem very similar but are, in fact, somewhat higher in each subsequent year after the start of ERT until around 5 years after starting ERT, after which the lines are a bit lower each year. Again, this shows the negative effect of time on the PROMs.

In the Supporting Information, we provide the two formulas for estimating the change in the patient's PCS and R-PAct score, given a certain change in FVC_{up} and in time.

Time change (in years since start of ERT)	ΔFVC_{up}(*pp*)	ΔPCS	ΔRPACT
0–1	1	0.42	0.80
1–2	1	0.40	0.76
2–3	1	0.34	0.69
3–4	1	0.27	0.59
4–5	1	0.16	0.45
5–6	1	0.03	0.28
6–7	1	−0.13	0.07
7–8	1	−0.31	−0.17
8–9	1	−0.49	−0.41

Note: ΔPCS, change in the estimated Physical Component Summary score; ΔRPACT, change in the estimated Rash-built Pompe Activity score; ΔFVC_up (pp), change in percentage points of forced vital capacity in upright position.

TABLE 2 Expected change in the estimated PCS and R-PAct scores for a 1%-point increase in FVC_{up} per year since starting ERT.

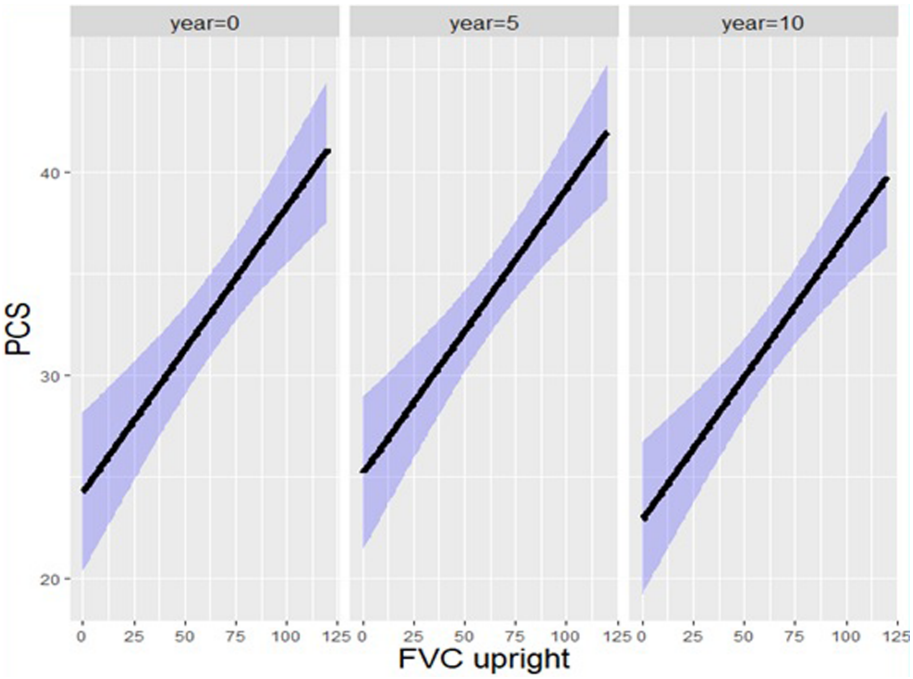

FIGURE 2 Plot of the estimated PCS scores with the FVCup values at different time points since starting ERT for an "average"* patient. PCS, Physical component summary score; FVCup, forced vital capacity in upright position expressed as percentage of the predicted normal values; average* patient, a female patient with median standardized age at start of ERT (0.1; equivalent to unstandardized age 51.39 years old) and median standardized disease duration at start of ERT (−0.26; equivalent to unstandardized disease duration at start of ERT 13.9 years); year, the time since starting ERT (year = 0). The shadowed area is the 95% credible interval. This graph shows the model estimated PCS scores for an average patient in certain years since the start of ERT, depending on the FVC_{up} value. At baseline (year 0), given an FVC_{up} of 75% this fictitious patient would be estimated to have a PCS score of approximately 35, but in year 5 of ERT this would be approximately 36 for the same FVC_{up} value, and 33 in year 10. By assuming a different value of FVC_{up}, for example, 76% we will have at year 0, 5, and 10 a PCS score of approximately 35, 35, and 36, respectively.

4 | DISCUSSION

To our knowledge, this is the first study exploring the association of PROMs with FVC_{up} over time in adult patients with LOPD receiving ERT. We found a positive association of the physical domain of QoL (i.e., PCS) and daily life activities (i.e., R-PAct) with FVC_{up} (coefficients 0.14 and 0.41, respectively). This indicates that during ERT, a patient perceives benefit of an improvement in FVC_{up} in terms of his/her physical component of QoL and his/her ability to carry out daily life activities. However, the PROMs were also nonlinearly associated with time since

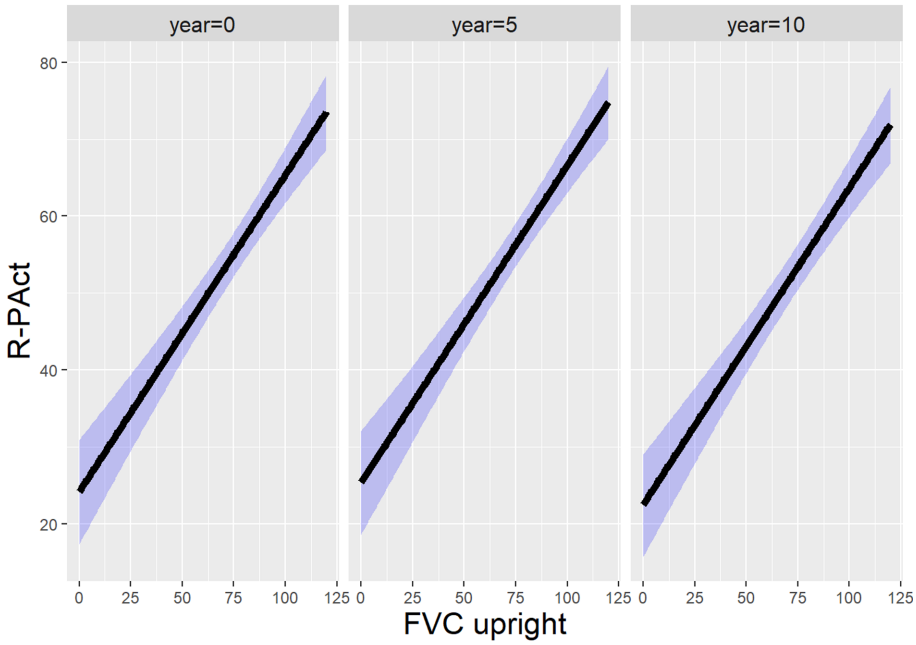

FIGURE 3 Plot of the estimated R-PAct scores with the FVCup values at different time points since starting ERT for an "average"* patient. R-PAct: Rasch-Built Pompe-Specific Activity (R-PAct) scale; FVCup: forced vital capacity in upright position as the percentage of the predicted normal values; average* patient: a female patient with median standardized age at start of ERT (0.1; equivalent to unstandardized age 50.5 years old) and median standardized disease duration at start of ERT (−0.42; equivalent to unstandardized disease duration at start of ERT 11.2 years); year: the time since starting ERT (year = 0). The shadowed area is the 95% credible interval. This graph shows the model estimated PCS scores for an average patient in certain years since the start of ERT, depending on the FVC_{up} value. At baseline (year 0), given an FVC_{up} of 75% this fictitious patient would be estimated to have a R-PAct score of approximately 55, but in year 5 of ERT this would be approximately 56 for the same FVC_{up} value, and 53 in year 10. By assuming a different value of FVC_{up}, for example, 76% we will have at year 0, 5, and 10 a R-PAct score of approximately 56, 57, and 54, respectively.

the start of ERT, decreasing after an initial increase. Due to this, the positive effect of an improvement in FVC_{up} can be overshadowed by the negative effect of time, when moving further away from the start of ERT.

The positive association between FVC_{up} and PROMs answers our research question whether patients perceive a benefit from an improvement in this outcome. Nevertheless, a large part of the changes in PROMs that we observed in our population are not explained by changes in FVC but by time. The effect of time in our model captures the progression of other aspects of the disease, such as deteriorating muscle strength, reduced distance walked, fatigue, and so on, as well as, partly, aging. We could not add these different aspects in the model for reasons explained further below. The nonlinear association of FVC_{up} and PROMs with time since starting ERT that we describe in this study was also reported in our previous studies.[2,15,23] For the FVC_{up} this was also described in other cohort studies.[5,8–11,24]

To illustrate the simultaneous effect of FVC_{up} and time together on the PROMS, we showed a hypothetical scenario in which FVC_{up} increased 1%-point per year in a specified year. The 1%-point increase is relatively high compared to what we currently know of the effect of ERT at group level.[4–6,8–11,15,23,24] Nevertheless, there are individual patients in our cohort who improve 1%-point in a year, especially in the early years of treatment, and new and improved treatments may have a larger effect on FVC_{up}.[25] After 6–7 years of ERT, we found that a 1%-point increase in FVC_{up} cannot weight up against the negative effect of time, and we expect the PROMs, to decline even if FVC_{up} improves 1%-point.

In addition to the associations with the FVC_{up} and time, the R-PAct was negatively associated with the standardized age at the start of ERT meaning that older patients have lower R-PAct values. Also, it was associated with sex: men had almost 6 points higher R-PAct scores than women at any time point. In our previous study[15] evaluating the effects of ERT after 5 years of treatment, subgroup analyses indicated that the R-PAct scores improved more in men than in women. Neither study had sufficient power to assess the effect of gender plus its interaction with time on the R-PAct. For FVC_{up} a negative association was found with the standardized disease duration at the start of ERT, indicating that with a longer disease duration FVC_{up} is expected to be further reduced, which makes sense for a progressive disease.

For this analysis, we used a unique and large dataset obtained by matching clinical follow-up and survey data. This provided data on 101 patients who were followed for a median of 9.3 years and had over 900 PROM assessments and around 2000 FVC_{up} measurements. The larger number of FVC_{up} measurements compared to the PROMs was mainly due to the fact that the clinical follow-up was scheduled more often than the PROM questionnaires. The number of patients and measurements that we could include in our study is large for this rare disease. Nevertheless, for statistical analyses, the number of patients was not that large and limited the number of confounders that we could correct for. Specifically, it was not possible to include the simultaneous effects of other outcomes, such as the distance walked or fatigue, on the PROMs. Hence, we cannot disentangle whether a specific outcome is the main driver of the beneficial effect of ERT, or that this is a combination of different factors.

Another concern is that the number of patients reduced with longer follow-up both because of reasons related to the disease (e.g., deteriorating status) and not related to the disease (e.g., recently diagnosed). This could result in biased estimates.

Nevertheless, our estimated multivariate mixed-effects models fitted under the Bayesian framework, for the PCS, R-PAct, and FVC_{up} over time reproduced a pattern comparable to our previous studies on the same cohorts where we used univariate linear mixed-effects models[2] and piece-wise linear regression[15] and thereby seem robust. These newly developed models are not easily applicable, and we are working on a R package for future researchers to fit such models. They are appropriate for analyzing two and more longitudinal outcomes simultaneously and estimating their relationship.

In this study, we did not evaluate the correlation of FVC_{up} with two further PROMs also available from the IPA/Erasmus MC Pompe survey: the mental component summary measure (MCS) of the SF-36 and participation (Rotterdam Handicap Scale, RHS). The MCS has been shown not to be affected in adult patients with LOPD and was not associated to FVC_{up} at baseline.[2,3,6,13] Therefore, it was not included in this study. The RHS remains of interest in addition to the PCS and the R-PAct.

4.1 | Clinical and research implications

The positive association we found between FVC_{up} and the PROMs suggests that a patient perceives a benefit of a change in FVC_{up}. However, this association does not give proof of a causal effect. As mentioned earlier, we cannot disentangle the effects of FVC on the PROMS from the effects of other health domains like muscle strength and fatigue. Also, we do not know how much of the waning effect of ERT with time is a result of disease progression, aging, or both.

In order to disentangle these processes further and get more insight into how ERT improves PROMs, we will need both larger datasets as well as more complex models. The only way to increase the number of patients is by creating follow-up studies that cross the national boundaries. The Pompe Survey, which was used in this study as the source of the PROMs, is in fact an international cohort study including more than 400 patients. This study should be expanded with clinical data to allow further progression of research on the effect of ERT and the correlation between outcome measures. This would require sharing and merging clinical follow-up data from clinics in other countries with this survey.

The fact that a patient perceives a benefit of an improvement in FVC_{up} indicates that FVC_{up} remains a useful endpoint in trials, and helps un interpret studies which have not been able to include PROMs. It obviously remains important to include PROMs in studies on the effects of treatment, but there are often limits to what can be assessed. Finally, given that patients experience benefit of an improvement in FVC_{up} in terms of their PROMs raises a new question: how much should FVC_{up} improve (e.g., in a clinical trial) to be clinically relevant. This study has shown that there is a correlation between FVC_{up} and the reports of patients (PROMs), suggesting that we might be able to deduce a minimum level of change that is relevant for a patient (MCID) that could be used to interpret the results of trials or in clinical evaluation. As a next step in research it is important to unravel the minimal clinically important difference (MCID) of FVC_{up}, that is, is the smallest change in a treatment outcome that an individual patient would identify as important.[26]

5 | CONCLUSION

We conclude that during treatment with ERT, adult patients with LOPD perceive a benefit of an improvement in pulmonary function in their physical component of QoL and their ability to carry out daily living activities. An improvement in FVC_{up} is therefore beneficial. As the next step in this research, we aim to investigate how much FVC_{up} should increase to be clinically relevant, by estimating the minimal clinically important difference (MCID) for FVC_{up} that can be used for clinical decision-making.

AUTHOR CONTRIBUTIONS

Study concept and design: Michelle E. Kruijshaar, Nadine A. M. E. van der Beek, Ans T. van der Ploeg. *Statistical analysis*: Aglina Lika, Eleni-Rosalina Andrinopoulou,

Dimitris Rizopoulos. *Analysis and interpretation of data*: Aglina Lika, Eleni-Rosalina Andrinopoulou, Dimitris Rizopoulos, Michelle E. Kruijshaar, Nadine A. M. E. van der Beek, Ans T. van der Ploeg. *Original draft preparation*: Aglina Lika, Michelle E. Kruijshaar. *Critical revision of manuscript for intellectual content*: Eleni-Rosalina Andrinopoulou, Dimitris Rizopoulos, Michelle E. Kruijshaar, Nadine A. M. E. van der Beek, Ans T. van der Ploeg. The author(s) read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Ans T. van der Ploeg received funding for research from Sanofi-Genzyme. Also, she has received funding for clinical trials and as an advisor from Sanofi-Genzyme, Amicus, Spark and Denali under agreements with Erasmus MC University Medical Center and the relevant industry.

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Aglina Lika, Dimitris Rizopoulos, Eleni-Rosalina Andrinopoulou, and Michelle Kruijshaar declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available to protect subject privacy.

ETHICS STATEMENT

Both studies in this article were approved by the ethics committee of the Erasmus MC University Medical Center and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to their inclusion. Consent included the use of data for research purposes, including investigating the course of disease and effects of ERT over time, and linking clinical and patient reported outcomes. Consent for publication is not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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