Late-onset Pompe disease primarily affects quality of life in physical health domains

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Abstract—*Objective:* To investigate quality of life in an international population of patients with late-onset Pompe disease. *Methods:* Data on quality of life (SF-36), age, sex, disease duration, wheelchair use, and use of artificial ventilation were collected for 210 adults with Pompe disease from Australia, Germany, the Netherlands, the United Kingdom, and the United States. SF-36 scores were compared between countries and related to patient characteristics. In addition, for the Dutch subgroup (n = 51), comparisons with the general population and 1-year follow-up assessments were performed. *Results:* No significant differences between countries were found for the four physical health scales. Mean scores on the vitality, role functioning-emotional, and mental health scale differed between countries, but these differences were not consistent. Wheelchair use was associated with lower physical and social functioning scores (B = −23.6 and −15.1, $p < 0.001$), and the use of artificial ventilation with lower physical functioning scores (B = −8.4, $p = 0.004$). Patients reported significantly poorer quality of life than the general population on the physical functioning, role functioning-physical, general health, vitality, and social functioning scales. No significant differences in SF-36 scores were found between the baseline and 1-year follow-up measurement. *Conclusions:* Patients with late-onset Pompe disease are, on average, markedly affected on the physical health domains of quality of life, but score only slightly lower than the general population on the mental health domains.

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Pompe disease is a hereditary lysosomal storage disorder with an incidence of 1:40,000 births.[1] Deficiency of the enzyme acid α-glucosidase leads to accumulation of glycogen and finally to destruction of muscle tissue. The clinical spectrum ranges from a rapidly progressive infantile form leading to death within the first year of life to a slowly progressive late-onset form of the disease that affects mobility and respiratory function.[2-4] Currently enzyme replacement therapy is under development for this so far untreatable disorder. Preliminary results for both infantile[5] and late-onset[6] patients are promising, and further clinical trials are underway.

Enzyme replacement therapy will be costly and it is expected that patients will need regular IV administrations for the rest of their lives. Careful evaluation of the therapeutic value is therefore important. Besides standardized clinical and laboratory measures, this evaluation should comprise the measurement of quality of life as an indicator of the effect of treatment on the well-being of patients. For this purpose, data obtained in a well-defined patient population before the onset of treatment are necessary. Such studies have not been carried out.

In this study we investigated the quality of life of patients with late-onset Pompe disease using the SF-36. Because the disease is rare, and new clinical trials on enzyme replacement therapy will very likely include patients from various countries, the study was conducted in an international population.

The aim of the present article is fivefold. First, we describe and compare quality of life of patients with late-onset Pompe disease from five different countries. Second, we present the psychometric properties of the SF-36 in this patient population, and third, we investigate the relationship between patient characteristics and quality of life. In the Dutch subgroup we then compare the quality of life of patients with late-onset Pompe disease with general population values and evaluate the changes in SF-36 scores over 1 year.

Methods. *Patients and procedures.* The study was part of an ongoing research project on the natural course of patients with late-onset Pompe disease. The medical ethics committee of Erasmus MC approved the project and all patients provided written informed consent. Patients were recruited through patient organizations affiliated with the International Pompe Association (IPA) in Australia, Germany, the Netherlands, the United Kingdom, and the United States. Inclusion criteria were a diagnosis of Pompe disease and an age above 2 years. For the SF-36 substudy patients younger than 18 years were excluded. All questionnaires were provided by our study center and distributed in a single mailing through the patient organizations in each country. The

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Table 1 *General characteristics of patients with late-onset Pompe disease from five countries*

	Australia	Germany	The Netherlands	United Kingdom	United States	Total	p*
n	14	48	51	20	77	210	
Mean age, y (SD)	46.8 (14.9)	46.2 (12.4)	50.6 (13.3)	49.6 (13.2)	47.4 (14.3)	48.1 (13.5)	0.52
% Women	64	51	63	42	52	54	0.48
Median disease duration, y (interquartile range)	12 (5–18)	9 (4–15)	12 (4–19)	12 (4–16)	11 (6–16)	11 (5–17)	0.43
% Wheelchair use	36	41	49	58	45	46	0.67
% Use of artificial ventilation	64	40	37	60	46	45	0.23

* p Value for between-country differences (analysis of variance and Kruskall-Wallis tests).

completed questionnaires were either sent directly to Erasmus MC or first collected by the local IPA representative. One year after the baseline measurement, the Dutch patients completed a follow-up questionnaire. To examine the test-retest reliability of the SF-36 in this population, a third assessment was performed within 1 month.

Data collection. SF-36. Quality of life was assessed using the SF-36 health survey. The SF-36 comprises four physical health scales (physical functioning, role limitations due to physical problems, bodily pain, and general health perceptions) and four mental health scales (vitality, social functioning, role limitations due to emotional problems, and mental health). Items are summed per scale and transformed into scores between 0 and 100, with higher values representing better function.[7] The SF-36 has been used in many different conditions, including the lysosomal storage disorders Fabry and Gaucher disease.[8-11] The SF-36 was translated into more than 40 languages, which made it particularly appropriate for our international study population. In the present study, the following validated and cross-culturally adapted translations were used: Dutch, English (Australian), English (UK), English (US), and German.[12,13]

Other variables. In the baseline questionnaires, date of birth, year of diagnosis, sex, wheelchair use, and use of artificial ventilation were recorded. Duration of disease was obtained by subtracting year of diagnosis from date of questionnaire completion. Participants in the follow-up study among Dutch patients were further asked to indicate on a five-point scale whether their physical situation had improved a lot, improved a little, remained the same, deteriorated a little, or deteriorated a lot since the baseline measurement and to add a short explanation.

Statistical analysis. The returned questionnaire forms were scanned and the answers were automatically entered into a predesigned database by means of the Teleform program (Teleform version 8.2, Cardiff software Inc., CA). One investigator (M.L.C.H.) corrected the answers not recognized by the computer. For the SF-36 scores, missing data handling and checks on data quality were performed as recommended.[14] No inconsistencies occurred.

To examine the psychometric performance of the SF-36, we evaluated the internal consistency, test-retest reliability, and the percentage of floor and ceiling effects for each scale. Internal consistency was assessed by Cronbach's alpha and test-retest reliability by the intraclass correlation coefficient (ICC). Floor and ceiling effects were considered present when more than 20% of the participants had the lowest (0) or highest possible score (100) on a scale. Differences between countries in general characteristics were assessed by one-way analysis of variance (ANOVA) and Kruskal-Wallis tests. Differences in SF-36 scores between countries were tested by ANOVA. To compare quality of life in the Dutch subgroup with general population values, univariate analyses of variance with age and sex as covariates were performed. Values for the Dutch general population were obtained from a population-based study providing Dutch normative data for the SF-36.[15] The original data on quality of life, age, and sex were available for analysis (n = 1,742). To investigate the influence of patient characteristics on SF-36 scores, multiple regression analyses with disease duration, wheelchair use, use of artificial ventilation, age, and sex as independent variables were performed. To compare quality of life between patients with different degrees of disability, the total population was divided into four groups: patients who used neither a wheelchair nor artificial ventilation, patients who used only a wheelchair, patients who used only artificial ventilation, and patients who used both. The data were adjusted for age and sex. To compare the baseline and follow-up SF-36 scores in the Dutch subgroup paired samples t-tests were used. A p value < 0.05 was considered significant in all instances. All analyses were performed using SPSS for Windows (version 10.1, SPSS Inc., Chicago, IL).

Results. *Study population.* Of the 422 patients invited between May 2002 and May 2003, 237 participated in the study. The response rate was 100% in Australia, 77% in Germany, 70% in The Netherlands, 58% in the United Kingdom, and 44% in the United States. The SF-36 was completed by patients 18 years and older (n = 214). Two patients were excluded because too many SF-36 data were missing and two patients were excluded because they did not complete the SF-36 in their native language. The study population thus included 210 adult Pompe patients. The general characteristics of the respondents for each country are shown in table 1. Age, sex, duration of disease, wheelchair use, and use of artificial ventilation did not differ significantly among the five countries.

Psychometric properties of the SF-36. The percentage of missing values for each SF-36 scale in the total group of 210 participants was lowest for the mental health scale (0%) and highest for the role functioning-emotional scale (4.5%). Internal consistency of the eight SF-36 scales was good with coefficient alpha ranging from 0.78 to 0.92. Test-retest reliability was good for all scales (ICC 0.74 to 0.91) except for the role-functioning emotional scale (ICC = 0.37). Floor effects were present for the physical functioning (22%) and role functioning-physical (30%) scales. Ceiling effects were found for the role functioning-physical (30%), bodily pain (21%), role functioning-emotional (63%), and social functioning (20%) scales.

Differences between countries. Table 2 presents the mean SF-36 scores of late-onset Pompe patients from the five countries. No significant differences between countries were found for the four physical health scales. The mean scores on three of the four mental health scales differed between countries ($p = 0.01$ for vitality, $p = 0.03$ for role functioning-emotional, and $p = 0.04$ for mental health). Dutch patients tended to score higher on the mental health and vitality scales, while German patients had higher scores on the role functioning-emotional scale. There was, however, no consistent pattern of differences in SF-36 score among the five countries.

Comparison with general population. For the Dutch patients (n = 51), the adjusted mean SF-36 scores were

Table 2 *Mean SF-36 scores of patients with late-onset Pompe disease from five countries*

Scales	Australia (n = 14)	Germany (n = 48)	The Netherlands (n = 51)	United Kingdom (n = 20)	United States (n = 77)	Total (n = 210)	p*
Physical health							
Physical functioning	25.0	23.8	26.0	17.5	25.3	24.3	0.75
Role functioning-physical	46.2	52.3	49.5	32.0	44.0	46.2	0.44
Bodily pain	61.1	67.4	70.9	62.9	60.9	65.0	0.21
General health	46.5	48.6	50.8	51.3	45.8	48.2	0.73
Mental health							
Vitality	43.6	48.1	51.5	37.2	40.6	44.8	0.01
Social functioning	58.9	69.9	67.8	63.2	63.3	65.6	0.52
Role functioning-emotional	56.4	86.8	79.3	68.4	67.3	73.9	0.03
Mental health	67.1	64.7	75.5	66.8	71.5	70.2	0.04

* p Value for between-country differences (analysis of variance).

compared to the general population (figure 1). Overall, patients with late-onset Pompe disease reported significantly poorer quality of life on the physical functioning, role functioning-physical, general health, vitality, and social functioning scales ($p < 0.001$ on all scales). The difference was most profound for the physical functioning scale: the adjusted mean score of patients was 29.3 compared to 83.1 of the general population. No significant differences were found for the bodily pain, role functioning-emotional, and mental health scales.

Relationship between SF-36 scores and clinical characteristics. Figure 2 presents the adjusted mean SF-36 scores in four groups of patients with different degrees of

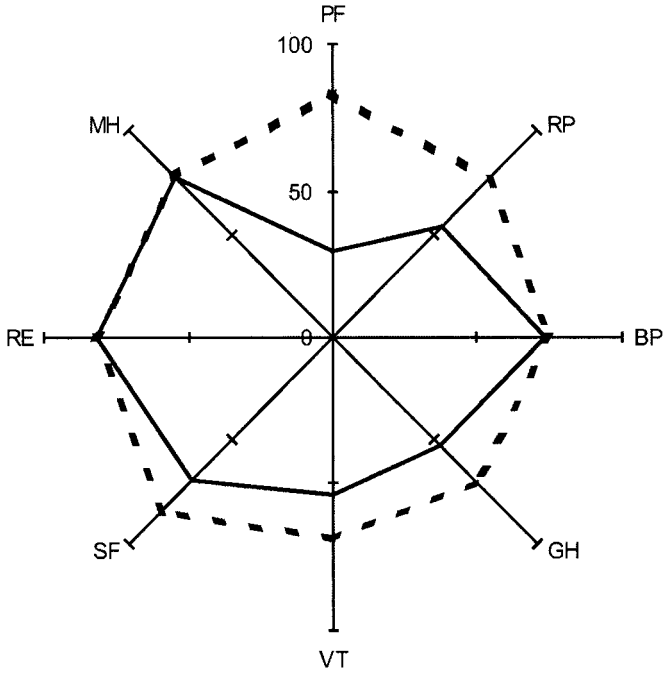

Figure 1. Quality of life in 51 Dutch late-onset Pompe patients compared to the Dutch general population. Solid line = Pompe (n = 51), dashed line = general population (n = 1,742). Values are mean scores for SF-36 scales, adjusted for age and sex. The center of the graph represents the lowest possible score on each scale. PF = physical functioning; RP = role functioning-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role functioning-emotional; MH = mental health.

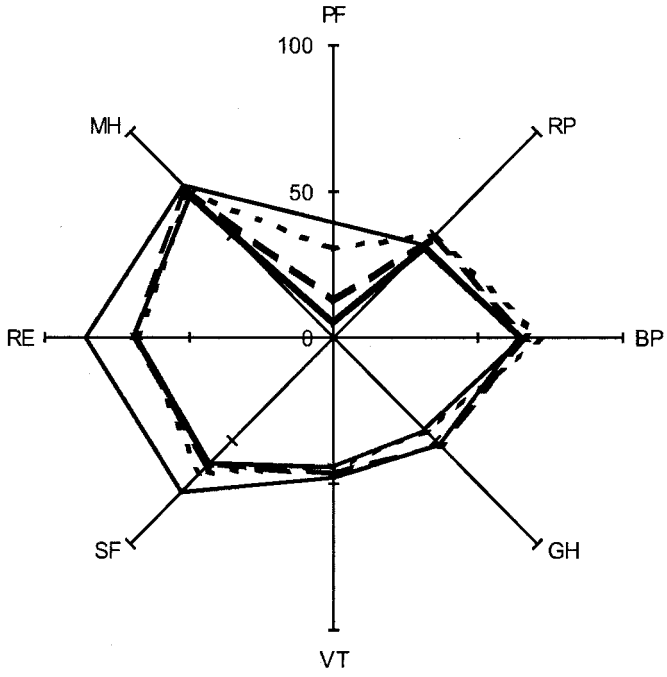

Figure 2. Quality of life in late-onset Pompe patients related to disability. Solid line = no wheelchair, no artificial ventilation (n = 74), dashed line = only wheelchair (n = 32), dotted line = only artificial ventilation (n = 35), thick black line = wheelchair and artificial ventilation (n = 56). Values are mean scores for SF-36 scales, adjusted for age and sex. The center of the graph represents the lowest possible score on each scale. Data on wheelchair and ventilator use were missing for 13 of the 210 participants. PF = physical functioning; RP = role functioning-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role functioning-emotional; MH = mental health.

disability, as defined by wheelchair use and use of artificial ventilation. The groups differed only on the physical functioning, social functioning, and role functioning-emotional scales. Multivariate regression analyses showed that patients who needed a wheelchair scored on average 23.6 points lower on the physical functioning scale and 15.1 points lower on the social functioning scale than patients who did not need a wheelchair (B = −23.6 and −15.1, $p < 0.001$). The use of artificial ventilation was associated with lower physical functioning scores (B = −8.4, $p = 0.004$). Independent from wheelchair use and use of artificial ventilation, a longer disease duration was associated with lower physical functioning scores (B = −0.5, $p = 0.01$), but with higher role functioning-physical scores (B = 1.0, $p = 0.04$) and higher mental health scores (B = 0.5, $p = 0.02$).

Follow-up. Of the 51 Dutch patients who started the study, 38 completed the 1-year follow-up questionnaire. One of the patients had died between the baseline and follow-up measurement; for the other nonresponders at follow-up the reason was not recorded. Age, sex, duration of disease, wheelchair use, and dependency on artificial ventilation did not differ significantly between patients who participated at the 1-year follow-up (n = 38) and those who did not (n = 13).

Twenty-seven of the 38 participants indicated deterioration in their physical situation over the last year, as measured on the five-point scale. None of the participants reported improvement. Most patients (n = 15) reported increased muscle weakness or a diminished walking ability. Of this group, seven patients also mentioned deterioration in pulmonary function. Three patients experienced deterioration in pulmonary function but not in skeletal muscle function. No significant differences in scores were found for any of the SF-36 scales between baseline and 1-year follow-up, whether including all patients or only the 27 who indicated deterioration in their clinical condition.

Discussion. Although Pompe disease is rare, we obtained data from 210 patients from five countries. We found that late-onset Pompe patients scored low on the physical health scales of the SF-36, while their scores on the mental health scales remained relatively high.

The SF-36 was chosen as a measure of quality of life because it is widely used in a variety of health conditions, and validated translations were available in several languages. Because the instrument had not been used before in late-onset Pompe disease, an evaluation of its psychometric properties in this population was indicated. We found good internal consistency on all scales and good test-retest reliability on all but one scale. In combination with a low percentage of missing values these findings suggest that the SF-36 is a useful instrument for the assessment of quality of life in patients with late-onset Pompe disease. Floor effects were found for the physical functioning and role functioning-physical scales and ceiling effects for the role functioning-physical, bodily pain, role functioning-emotional, and social functioning scales. Comparable percentages of floor and ceiling effects on these scales were also reported for other patient populations.[16,17] These effects make the scales less responsive to changes at the ends of the scale, which should be kept in mind when studying very healthy or very ill patients.

Before further interpreting the results, the composition of the study population should be discussed. The recruitment of patients through patient organizations is a potential source of selection bias, as this group may be particularly motivated and perhaps more severely affected. However, it should be noted that our study population covers the entire range of disease severity, from mildly affected to fully wheelchair and ventilator dependent. Furthermore, despite differences in response rate, general patient characteristics were comparable across countries.

No significant between-country differences were found for the physical health scales. Although the scores on some of the mental health scales differed between countries, these differences were not consistent in direction and magnitude. We therefore conclude that this international sample of 210 patients can be considered as one reference group for future studies.

Patients with late-onset Pompe disease in the Dutch subgroup reported significantly poorer quality of life compared to the general population on all physical health scales except bodily pain and on the scales vitality and social functioning. The mental health and role functioning-emotional scores of the patients were equivalent to the scores of the general population. This can be explained by the fact that in late-onset Pompe disease, limitations in daily activities develop over a long period. During this period patients may have adapted to the situation and adjusted their expectations ("response shift").[18,19] Given the comparability between the patient populations from different countries, we conclude that the results in the Dutch subgroup can be generalized to the international population of patients with late-onset Pompe disease.

The SF-36 physical functioning scale clearly discerned the four patient groups with different disability status. In contrast, the role functioning-physical, bodily pain, general health, vitality, and mental health scales did not differ between groups. On the role functioning-emotional and social functioning scales, patients who did not use a wheelchair or artificial ventilation scored relatively high and could be discerned from the three groups of patients using one or both of these aids. Among these last three groups no difference in score was found, suggesting that the extent of disability does not influence the SF-36 scores on these domains. Together with the independent positive effect of disease duration on the role functioning-physical and mental health domains, this may be another indication of adaptive coping behavior in this patient population.

No significant differences in SF-36 scores were found between the baseline and the 1-year measurement in the group who indicated a change in their overall physical situation. This could mean that the

changes in physical situation were not accompanied by a change in quality of life. Another possibility is that the changes in physical situation were accompanied by a change in quality of life, but that the SF-36 was not able to capture these changes. The fact that the SF-36 did not show a difference from the baseline measurement on physical functioning, although on this domain a relevant change was reported, supports the second explanation. The SF-36 is a generic measure of quality of life and apparently does not cover all aspects relevant for late-onset Pompe disease. We therefore recommend adding symptom-specific quality of life scales. Domain-specific scales such as fatigue, depression, and handicap scales may also be relevant when the aim is to measure the impact of the disease on a patient's well-being.

On balance, patients with late-onset Pompe disease score markedly low on the physical health scales of the SF-36. At the same time they function relatively well on the mental health domains of quality of life, probably as a result of adaptive coping with the disease. The international patient population in the present study is a suitable reference group for future studies in late-onset Pompe disease. In these future studies, symptom-specific instruments should supplement the SF-36 in the measurement of quality of life.

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