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Cognitive functioning and depressive symptoms in Fabry disease: A follow-up study

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Abstract

Patients with Fabry disease (FD) have a high prevalence of depressive symptoms and can suffer from cognitive impairment, negatively affecting their life. The course of cognitive functioning and depressive symptoms in FD is unknown. The aim of this prospective cohort study was to describe changes in cognitive functioning and depressive symptoms and to identify related variables in patients with FD over 1 year. Assessments were conducted twice, using a neuropsychological test battery and the Centre of Epidemiological Studies Depression scale (CESD). Eighty-one patients were included of which 76 patients (94%) completed both assessments (age: 44 years, 34% men, 75% classical phenotype). A significant decrease in cognitive functioning was found in four patients (5%), with patients regressing from excellent to average/good. Changes were not related to sex, phenotype, stroke, IQ or CESD scores. CESD scores ≥16 were present in 29 patients (38%) at baseline. Using the reliable change index a decrease in CESD scores was found in six patients (8%). Decreased CESD scores were independently related to employing a positive and problem solving coping style and increased CESD scores to an avoiding and brooding coping style and worsening health perception. We found no major changes in cognitive functioning in patients with FD during 1 year follow-up making it an unsuitable outcome in FD treatment trials. Considering the high prevalence of persistent depressive symptoms, assessment of depressive symptoms should be part of routine follow-up. Altering coping styles and health perception may improve psychological well-being in FD.

KEYWORDS

cognitive functioning, coping, depressive disorder, depressive symptoms, Fabry disease, follow-up

1 | INTRODUCTION

In Fabry disease (FD; OMIM 301500), a rare X-inherited lysosomal storage disorder, mutations in the GLA-gene result in a deficiency of α-galactosidase A activity (enzyme commission no. 3.2.1.22). Consequently, globotriaosylceramide and related compounds accumulate in various cell types, which often results in damage to the kidneys, heart and brain.[1] Strong predictors of disease progression in FD are age, sex and phenotype: older men with a classical disease phenotype have the highest complication risk while young women with a non-classical disease phenotype often do not display organ involvement.[2]

Patients with FD are at risk for cognitive impairment[3-5] and depressive symptoms are present in a large proportion of patients.[3,6,7] People diagnosed with a major depressive disorder show more cognitive impairment compared to controls from the general population.[8] In FD, however, no relation between cognitive impairment and depressive symptoms could be established,[4,5,9] but cognitive impairment is associated with male sex, a classical phenotype, a lower IQ[4] and stroke.[4,5]

Previous work on depressive symptoms in FD has shown a relation to pain and social factors such as economic status.[3,6] Conversely, the relation of depressive symptoms to renal, cardiac or cerebral involvement is less prominent and patients' subjective health perception is probably more important.[3,6,7] Differences in coping, the process of cognitive and behavioural efforts to manage daily hassles and stressors,[10] might influence the impact of subjective health perception on the psychological well-being of FD patients. In a recent study, we found that patients' use of an avoiding and brooding coping style was related to more depressive symptoms while positivity and problem solving was related to less depressive symptoms.[7]

Since most studies on depressive symptoms and cognitive functioning in FD have been cross sectional, little is known about their course over time. Follow-up data on depressive symptoms and cognitive functioning provide insight in the course of FD and offer an opportunity to

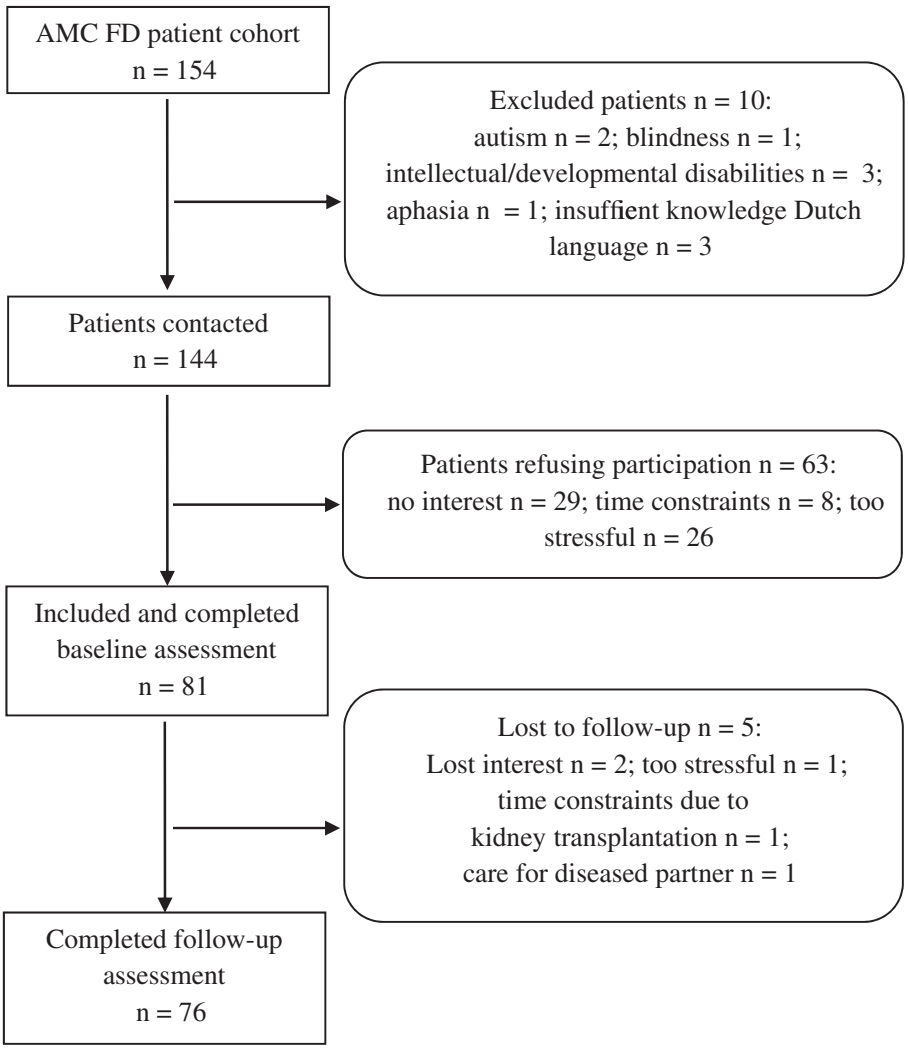

FIGURE 1 Flow chart of non-participants, in- and excluded patients and loss-to follow-up. AMC, Academic Medical Center; FD, Fabry disease

explore variables that might be related to changes. This knowledge can guide decisions of treating physicians, might be of interest for future trials designs (especially patient reported outcomes) and may identify modifiable variables to decrease depressive symptoms or prevent cognitive decline.

The aim of this study was 2-fold: (a) to assess changes in both depressive symptoms and cognitive functioning after 1 year follow-up and (b) to explore disease related variables as well as coping styles in relation to changes in depressive symptoms and cognitive functioning.

2 | METHODS

2.1 | Study design and rationale

Baseline data on cognitive functioning and depressive symptoms have been published elsewhere.[4,7] The Amsterdam University Medical Center (location Academic Medical Center (AMC)) is the national referral centre for FD. All Dutch adult (≥18 years old) FD patients were screened for eligibility.[4] Eighty-one patients (52.6%) were assessed at baseline and after 1 year all included patients were approached for a follow-up assessment (Figure 1). Both baseline and follow-up assessment included the same neuropsychological tests and questionnaires. The baseline assessments were completed between July 2016 and May 2017 and the follow-up assessments between May 2017 and May 2018. Between baseline and follow-up, patients received care as usual.

This study did not include an intervention. However, some patients were referred to their general practitioners or to local psychologists as not communicating potentially relevant depressive symptoms (Center of Epidemiological Studies Depression scale (CESD) score ≥16) was considered unethical and potentially harmful, see Supplemental methods: Data collection and referral. Psychological interventions (pharmacological or non-pharmacological) between baseline and follow-up were registered.

A 1 year follow-up interval was chosen as (a) the course of depressive symptoms and cognitive functioning in FD is unknown as follow-up data are scarce,[9,11] and (b) this would be an achievable follow-up time for international trials, thus showing changes in cognitive functioning or depressive symptoms would provide evidence that these could potentially be used as a reliable outcome.

2.2 | Phenotype

Patients were phenotypically characterized as having classical or non-classical FD using preset criteria.[4,12] This study was conducted in accordance with the Declaration of Helsinki (1) and was approved by the local human ethics committee. All patients provided informed consent before inclusion.

2.3 | Neuropsychological test battery

The neuropsychological test battery consisted of 16 subtests representing the following cognitive domains: language, memory, visuospatial perception, attention and executive functioning and processing speed (Supplemental methods: Supplemental table 1). If available, different test versions were used for baseline and follow-up to minimize training effects. The neuropsychological test battery was composited by a licensed clinical neuropsychologist (*GJG*). Included subtests are commonly used in neuropsychological research in both the general population as well as in neurodegenerative diseases[13] and many have been used in earlier studies on cognitive functioning in patients with FD[3] (see Reference 4 for a more elaborate description of the subtests).

Raw test scores were converted to T-scores (mean of 50, standard deviation of 10) using normative data from Dutch healthy populations with a median sample size of 471 (range 121-1000). Most T-scores were adjusted for age, sex and education.

Additionally, the Dutch adult reading test (DART) provided an estimate of intelligence at baseline[14] and the test of memory malingering (TOMM) was used to assess malingering at baseline and follow-up.[15]

2.4 | Depressive symptoms

Depressive symptoms were measured using the CESD.[16] The CESD is a 20-item self-administered scale, has been validated in the Dutch population[17] and has previously been used in FD patients.[6] The total score ranges from 0 to 60 and scores ≥16 indicate the presence of depressive symptoms and that a depressive disorder may be present.[16,18]

2.5 | Coping

Coping was assessed using the Utrecht Coping List (UCL), a questionnaire consisting of 47 items which can be combined to seven subscales.[19] Since power was limited due to the sample size, we used an exploratory factor analysis to reduce the number of subscales to three. The three coping styles mainly employed in our FD population were: 'avoidance and brooding', 'positivity and problem solving' and 'seeking social support and comfort' (for more information on the exploratory factor analysis see

Reference 7). Scores per coping style were calculated for both baseline and follow-up using the Anderson-Rubin method.[20] This resulted in mean scores per coping style of 0 and a change in score of 1 per standard deviation increase or decrease. For both baseline and follow-up, most scores will range between −2 and 2 and higher scores indicate more employment of this coping style.

2.6 | Pain

Pain was quantified using the Brief Pain Inventory (BPI) severity subscale.[21] Pain score was averaged from four items: pain right now, average, worst and least pain. Each item ranged from 0 (absence of pain) to 10 (worst pain imaginable).

2.7 | Quality of life

Quality of life was assessed using the short-form 36 health survey (SF-36), which consists of 36 items.[22] It can be divided in eight different scales with scores ranging from 0-100 and higher scores indicating better functioning. For our analyses, we focused on the 'subjective health perception' scale and 'self-rated social functioning' scale.

2.8 | Clinical characteristics and complications

Kidney involvement was evaluated by calculating the estimated glomerular filtration rate (eGFR).[23] Left ventricular hypertrophy (LVH) was rated as present or absent on MRI or echocardiography (if MRI was unavailable).[24-26] Cardiac and renal complications were rated as present or absent. We created an ordinal scale rating cardiac and renal involvement (range 0-2): (0) No renal or cardiac involvement, (1) cardiac involvement (presence of LVH) and/or renal involvement (eGFR <60 mL/min/1.73 m^2) and (2) cardiac and/or renal complications (Supplemental methods: Clinical characteristics and complications).

Stroke was diagnosed by a neurologist using a combination of clinical symptoms and MRI. The diagnosis depressive disorder was made by a patient's general practitioner, psychologist or psychiatrist and was extracted from clinical letters and verified during the interview phase of the baseline and follow-up assessment.

2.9 | Brain MRI

Brain involvement was rated on MRIs acquired during routine follow-up (Philips Ingenia, Philips Medical Systems, Best, The Netherlands), using a standardized protocol.[4] MRIs were rated by two neuroradiologists (*MRL* rated basilar artery diameter (BAD), *MGFL* rated white matter lesions (WMLs)). Deep and periventricular WMLs were rated using the Fazekas scale on FLAIR, resulting in a score ranging from 0 (no WMLs) to 6 (confluent deep and periventricular WMLs).[27] The BAD was calculated as a mean of measurements in three slices (caudal, intermediate, rostral) on axial T2.

2.10 | Statistical methods

R (version 3.5.1) was used for statistical analysis.[28] *P*-values <.05 were considered statistically significant unless stated otherwise.

Cognitive domain scores were calculated by averaging T-scores on tests measuring a similar cognitive domain, for the domains language, memory, visuospatial perception, attention and executive functioning and processing speed (Supplemental methods: Supplemental table 1).

Whole group baseline and follow-up CESD and neuropsychological test scores were compared using paired *t*-tests or the Wilcoxon signed rank-test. Effect sizes of differences between baseline and follow-up were evaluated using Cohen's d or a non-parametric equivalent.[29] In both, scores between 0.2 to 0.5, 0.5 to 0.8 and >0.8 indicate small, medium and large effects, respectively.

To evaluate if changes on individual patient level were reliable and clinically relevant we calculated a reliable change index (RCI) per patient for both the CESD score and the neuropsychological test results, with the latter adjusted for multiple testing. The RCI gives an indication whether the change within a patient is greater than what could be expected by measurement error alone[30] and is a reliable measure of change,[31] see Supplemental methods: Statistical methods.

At baseline, the following parameters independently correlated with cognitive impairment: male sex, a classical disease phenotype, a history of stroke and lower IQ as estimated with the DART.[4] We assessed whether changes in neuropsychological domain scores (T-scores follow-up minus T-scores baseline) were related to any of these variables using MANOVA's, Kruskal-Wallis tests and Kendall's Tau b. Considering the multiple relations tested we set the *P*-value at <.01.

For depressive symptoms, the following parameters were associated with a higher CESD score at baseline: avoidant and brooding coping scale score, positivity and problem solving coping scale score, BPI pain severity score and SF-36 health perception score.[7] Two multiple linear models were created. In model 1, changes in CESD scores (CESD score follow-up minus CESD score baseline) were related to changes in these variables. In extended model 2, changes in variables that were identified in an explorative analysis as potentially relevant in relation to CESD scores at baseline

TABLE 1 Patient characteristics at baseline

	All	Men		Women	
		Classical	Non-classical	Classical	Non-classical
Patients, n (%)	76	17 (22.4%)	9 (11.8%)	40 (52.6%)	10 (13.2%)
Age in years, mean (±SD)	44.3 (±14.3)	38.6 (±13.5)	60.5 (±10.2)	43.1 (±13.6)	43.9 (±13.0)
ERT at any time before baseline, n (%)	45 (59.2%)	17 (100.0%)	3 (33.3%)	24 (60.0%)	1 (5.0%)
Years treated with ERT, median (range)	8.8 (0.1-16.0)	12.4 (1.5-16.0)	12.5 (6.4-14.2)	8.1 (0.1-13.6)	0.3
Antidepressant use, n (%)	7 (9.2%)	1 (5.9%)	2 (22.2%)	3 (7.5%)	1 (10.0%)
Estimated IQ[a], median (range)	94 (68-133)	89 (83-114)	84 (68-133)	95 (82-121)	100 (84-121)
Years of education, mean (±SD)	13.8 (±3.0)	14.4 (±2.8)	13.6 (±5.2)	13.4 (±2.6)	14.9 (±1.8)
Unemployed, n (%)	28 (36.8%)	9 (52.9%)	3 (33.3%)	13 (32.5%)	3 (30.0%)
Unfit for work[b], n (%)	19 (25.0%)	7 (41.2%)	2 (22.2%)	9 (22.5%)	1 (10.0%)
Single[c], n (%)	28 (36.8%)	9 (52.9%)	3 (33.3%)	13 (32.5%)	3 (30.0%)
Left ventricular hypertrophy, n (%)	42 (55.3%)	13 (76.5%)	3 (33.3%)	22 (55.0%)	4 (40.0%)
eGFR in mL/min/1.73 m^2, median (range)	95.4 (11.4-141.0)	105.6 (25.4-141.0)	77.3 (11.4-109.9)	93.4 (45.6-131.1)	95.4 (73.6-118.3)
eGFR < 60 mL/min/1.73 m^2, n (%)	10 (13.2%)	2 (11.8%)	3 (33.3%)	5 (11.6%)	0 (0.0%)
Fazekas score[d], median (range)	1 (0-6)	0 (0-6)	1 (0-3)	1 (0-6)	0.5 (0-2)
BAD[d] in mm, median (range)	3.6 (2.5-5.6)	4.2 (3.1-5.6)	3.6 (3.3-4.3)	3.6 (2.5-5.6)	3.2 (2.5-3.6)
Complications, n (%)	27 (33.3%)	7 (41.2%)	6 (54.5%)	14 (32.6%)	0 (0.0%)
Cardiac, n (%)	14 (17.3%)	4 (23.5%)	4 (36.4%)	6 (14.0%)	0 (0.0%)
Renal, n (%)	4 (4.9%)	1 (5.9%)	2 (18.2%)	1 (2.3%)	0 (0.0%)
Stroke, n (%)	9 (11.8%)	2 (11.8%)	2 (22.2%)	5 (12.5%)	0 (0.0%)

Notes: Continuous variables are presented as median (range) or mean (±SD) and discrete variables as number (percentages).
Abbreviations: BAD, basilar artery diameter; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; IQ, intelligence quotient.
[a]The IQ-score was estimated using the Dutch Adult Reading Test.
[b]Includes three patients regarded partially unfit for work.
[c]Unmarried, divorced or widowed.
[d]MRIs were unavailable in seven patients (three non-classical men, four classical women) due to presence of an MRI non-compatible pacemaker or ICD (n = 6) and due to claustrophobia (n = 1).

were added.[7] These were: loneliness, SF-36 social functioning scores and cardiac and/or renal involvement.

To evaluate the potential effects of patients lost to follow-up we used multiple imputation by chained equations (package: mice[32]) to impute missing data and reran several analyses. The results presented in this study are the original unimputed data.

For additional information on the RCI, assumption testing multiple linear models and multiple imputation, please see Supplemental methods: Statistical methods.

3 | RESULTS

3.1 | Patient participation

No differences with respect to age, sex, phenotype, Fazekas score and stroke were found between the 81 included patients and the 73 non-participants (Figure 1) at baseline.[4] Seventy-six patients (93.8%) completed the follow-up assessment after a mean interval of 1.1 (±0.1) year (Figure 1). The five patients lost to follow-up assessment did not differ in age, sex, cognitive domain scores and CESD-score at baseline and were excluded from all analyses.

3.2 | Patient characteristics

Of the 76 patients completing both assessments 26 were men (34.2%), 57 had a classical phenotype (75.0%) and mean age was 44.3 years (Table 1).

During follow-up three patients experienced a stroke, two of which had had one or more strokes in the past. Six patients developed a new cardiac complication. No new renal events occurred. Eight patients were started on enzyme replacement therapy between baseline and follow-up.

TABLE 2 Comparison baseline and follow-up T-scores neuropsychological tests and domains

Neuropsychological tests and domains	Baseline T-score	Follow-up T-score	Median or mean change score (95% CI for mean scores)	*P*-value	Effect size[a]	Reliable decrease, n (%)
Language	49.5 (32-63)	51.5 (33.5-65.0)	2	0.093	0.14	
BNT	49 (37-63)	53 (37-63)	4	0.370	−0.07	2 (2.6%)
WAIS-IV: S	50 (27-72)	53 (27-72)	3	0.140	−0.12	3 (4.0%)
Memory	53.9 (±9.5)	53.4 (±9.4)	−0.5 (−1.9 to 0.8)	0.422	−0.09	
RAVLT ir	51.8 (±11.4)	55.9 (±11.5)	4.1 (2.2 to 6.0)	<0.001	0.48	0 (0.0%)
RAVLT dr	52.4 (±10.5)	54.9 (±10.5)	2.5 (0.6 to 4.3)	0.008	0.31	3 (3.9%)
RBMT ir	56.3 (±11.0)	51.5 (±11.2)	−4.8 (−6.7 to −2.8)	<0.001	−0.56	6 (7.9%)
RBMT dr	55.0 (±11.5)	51.1 (±12.1)	−3.9 (−6.2 to −1.7)	<0.001	−0.40	8 (10.5%)
Visuospatial perception	55 (32.5-67.0)	54 (28.0-65.5)	−1	0.406	0.07	
WAIS-IV: BD	50.1 (±10.9)	50.9 (±11.6)	0.8 (−1.0 to 2.5)	0.375	0.10	4 (5.3%)
JLO	61 (29-61)	61 (30-61)	0	0.266	−0.09	3 (3.9%)
Processing speed	54.1 (±8.1)	53.8 (±8.4)	−0.3 (−1.5 to 0.9)	0.599	−0.06	
TMT A	54.1 (±9.5)	53.8 (±9.9)	−0.3 (−2.7 to 2.1)	0.806	−0.03	5 (6.6%)
Stroop W	55.5 (34-79)	55.5 (30-93)	0	0.018	−0.19	7 (9.2%)
Stroop C	51.3 (±11.8)	52.0 (±10.5)	0.8 (−0.8 to 2.3)	0.322	0.11	3 (3.9%)
Attention and executive functioning	49.0 (±7.5)	50.0 (±8.6)	1.0 (−0.1 to 2.1)	0.07	0.21	
TMT B	51 (-1-74)	52 (−10 to 70)	1	0.389	0.07	4 (5.3%)
Stroop CW	50 (32-84)	51.5 (25-76)	1.5	0.022	0.19	3 (3.9%)
Fluency A	49.7 (±11.3)	50.1 (±11.4)	0.4 (−1.7 to 2.6)	0.706	0.04	2 (2.6%)
Fluency O	47.4 (±11.3)	47.6 (±12.9)	0.3 (−2.0 to 2.5)	0.828	0.03	4 (5.3%)
Fluency L	46.5 (±10.0)	49.4 (±11.4)	3.0 (1.3 to 4.7)	<0.001	0.40	1 (1.3%)

Notes: T-scores are presented as median (range) or mean (±SD). Reliable decrease is presented as n (%) with n = 75 at WAIS-IV: S and WAIS-IV: BD and n = 76 at the other tests. *P*-values <.01 were considered statistically significant.

Abbreviations: BD, Block Design; BNT, Boston Naming Test; CI, confidence interval; dr, delayed recall; Fluency A, Animal; Fluency L, Letter; Fluency O, Occupation; ir, immediate recall; JLO, Judgement of Line Orientation; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test; Stroop C, Colour; Stroop CW, Colour-Word; Stroop W, Words; TMT, Trail Making Test; WAIS-IV: S, Wechsler Adult Intelligence Scale IV: Similarities.

[a]For normally distributed data Cohen's d was calculated and in case of non-normality a non-parametric equivalent.

3.3 | Follow-up cognitive functioning

There were no signs of underachievement in any of the patients based on the TOMM score. The Rey Auditory Verbal Learning Test immediate recall, delayed recall and the letter fluency T-scores increased between baseline and follow-up, while the Rivermead Behavioural Memory Test immediate recall and delayed recall decreased (Table 2). Effect sizes were small to medium.

For baseline and follow-up raw scores and T-scores, please see Supplemental results: Supplemental tables 4 to 7.

Four patients (5.3%) showed reliable decrease in cognitive functioning, two women and one man with classical disease and one woman with non-classical disease (age range: 19-41 years). Changes were from excellent to good/average and from good to average. None had a history of stroke or extensive WMLs. Follow-up CESD scores were similar in two patients (+0 and +1) and increased in two others (+6, +11).

3.4 | Variables related to cognitive changes

We found no significant relations between changes on neuropsychological domain scores and sex, phenotype, a history of stroke, estimated IQ, baseline Fazekas scores or changes in CESD scores (Supplemental results: Supplemental table 2).

TABLE 3 Depressive symptoms and psychological follow-up

	All	Men		Women	
		Classical	Non-classical	Classical	Non-classical
Baseline					
CESD, median (range)	11 (0-44)	11 (0-40)	12 (0-23)	12.5 (0-44)	7.5 (0-20)
CESD ≥ 16, n (%)	29 (38.2%)	7 (41.2%)	3 (33.3%)	16 (40.0%)	3 (30.0%)
Depressive disorder[a], n (%)	22 (28.9%)	3 (17.6%)	3 (33.3%)	12 (30.0%)	4 (40.0%)
Antidepressant use, n (%)	7 (9.2%)	1 (5.9%)	2 (22.2%)	3 (7.5%)	1 (10.0%)
Follow-up					
CESD, median (range)	8 (0-38)	6 (0-37)	11 (1-30)	9 (0-38)	5 (1-24)
CESD ≥ 16, n (%)	22 (29.3%)	5 (29.4%)	2 (25.0%)	12 (30.0%)	3 (30.0%)
Newly diagnosed depressive disorder[b], n (%)	6 (7.9%)	3 (17.6%)	0 (0.0%)	3 (7.5%)	0 (0.0%)
Psychological counselling after baseline, n (%)	18 (23.7%)	4 (23.5%)	1 (11.1%)	13 (32.5%)	0 (0.0%)
New antidepressant use, n (%)	1 (1.3%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Notes: Continuous variables are presented as median (range) and discrete variables as number (percentages).
Abbreviation: CESD, Center for Epidemiologic Studies Depression scale.
[a](History of) depressive disorder as diagnosed by a psychologist, psychiatrist or general practitioner.
[b]Newly diagnosed depressive disorder by a psychologist, psychiatrist or general practitioner.

3.5 | Follow-up CESD scores

At baseline, 29 patients (38.2%) scored ≥16 on the CESD and 22 patients (28.9%) had a history of depressive disorder (Table 3). Eighteen patients (23.7%) had psychological counselling between baseline and follow-up, mostly from the group scoring above the CESD cut-off at baseline (51.7%, n = 15). Between baseline and follow-up, a new depressive disorder was diagnosed in six patients (7.9%) by their general practitioner or psychologist/psychiatrist. Five of these patients scored above the CESD cut-off at the baseline assessment and were subsequently referred to their general practitioner or psychologist/psychiatrist for further analyses. One patient had a CESD score of 15 at the baseline assessment and sought help with increasing depressive symptoms between baseline and follow-up. At follow-up 22 patients (29.3%) scored above the CESD cut-off.

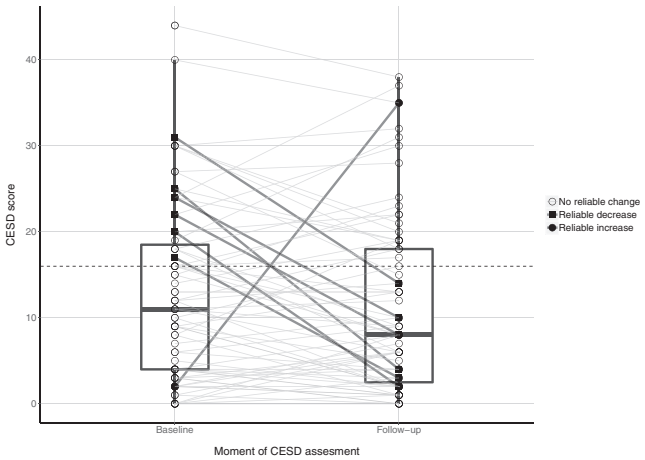

FIGURE 2 Changes in CESD scores between baseline and follow-up. The CESD scores at baseline and follow-up are visualized using two boxplots showing the median, interquartile range and total range. A scatterplot is projected over the boxplots with patients divided by the presence or absence of reliable change. Thick grey lines display the change in score in patients with reliable change, thin grey lines display change in scores in the remaining patients. There is considerable overlap in CESD scores, resulting in overlap within the scatters. CESD, Center for Epidemiologic Studies Depression scale

3.6 | Changes in CESD scores

Overall, no significant difference was found when comparing CESD scores between baseline and follow-up ($P = .096$, effect size: 0.14).

A change in CESD score of 13.6 points was calculated as reliable change. Six patients showed reliable decrease of the CESD score and 1 patient showed reliable increase (Figure 2). All six patients showing reliable decrease had a CESD score >16 at baseline and <16 at follow-up. Of the six patients with a new diagnosis of depressive disorder between baseline and follow-up, one had a reliable decrease in CESD score (−17 points) with CESD scores changes in the other five ranging from −9 to +8 points.

TABLE 4 Summary of multiple linear regression model relating change in CESD score to potentially relevant variables

	Model 1				Model 2			
Independent variables	***B* (95% CI)**	**SE *B***	***β***	***P*-value**	***B* (95% CI)**	**SE *B***	***β***	***P*-value**
Change in BPI severity	−0.11 (−1.30 to 0.88)	0.55	−0.04	.7050	0.02 (−2.21 to 3.34)	0.57	0.00	.9762
Change in SF-36 health perception	−0.13 (−0.26 to −0.00)	0.07	−0.22	.0452	−0.09 (−0.22 to 0.08)	0.07	−0.12	.3330
Change in avoidance and brooding	3.02 (0.51 to 5.53)	1.26	0.27	.0192	2.84 (0.17 to 5.43)	1.32	0.25	.0372
Change in positivity and problem solving	−4.37 (−6.94 to −1.79)	1.29	−0.40	.0012	−4.14 (−6.95 to −1.61)	1.34	−0.40	.0021
Loneliness at follow-up					0.76 (−4.78 to 6.05)	2.71		.8145
Change in SF-36 social functioning					−0.05 (−0.14 to 0.04)	0.05	−0.14	.2699
Cardiac and/or renal involvement								
eGFR < 60 mL/min and/or presence of LVH at baseline					−3.11 (−6.98 to 0.77)	1.94		.1140
Cardiac or renal complications at baseline					−2.71 (−7.48 to 2.07)	2.39		.2618
Intercept	−1.24				0.57			
F-value	6.52			.0002	3.72			.0012
R^2	27.4% (11.9 to 44.0)				31.4% (14.1 to 43.7)[a]			
Adjusted R^2	23.7%				23.4%			

Abbreviations: B, beta coefficients; β, standardized beta coefficients for continuous variables; BPI, Brief Pain Inventory; CESD, Centre for Epidemiologic Studies Depression scale; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; SE, standard error; SF-36, Short Form-36 Health Survey.

[a]Bootstrapping for 95%CI was performed without 'Loneliness at follow-up' due to lack of variation in this variable.

3.7 | Variables related to the CESD change score

We created two multiple linear models evaluating potentially relevant variables in relation to the change in CESD scores. Model 1 significantly explained 27.4% of the variance in change scores (95%CI: 11.9-44.0%, $F(4,69) = 6.52$, $P = .0002$) (Table 4). CESD score changes were negatively related to changes in SF-36 health perception scores and changes in positivity and problem solving scores, meaning that an increase in SF-36 health perception and more use of positivity and problem solving between baseline and follow-up were related to a decrease in CESD scores during follow-up. CESD scores changes were positively related to changes in avoidance and brooding scores, meaning that more use of avoidance and brooding during follow-up was related to an increase in CESD scores during follow-up.

None of the added variables in model 2 were significantly related to changes in CESD scores (Table 4). Model 1 was preferred over model 2 as it was simpler and explained an equal amount of the variance (after adjusting R^2 for number of variables).

In sensitivity analyses, removing two influential patients, the relation between the change in CESD score and the change in the SF-36 health perception score became less prominent (*B*: −0.09, 95%CI: −0.21 to 0.03, $P = .14$) (Supplemental results: Assumption checking and sensitivity analyses).

We found no differences in the change in CESD scores between patients that did and did not receive psychological counselling between evaluations, regardless of whether their baseline score was above the cut-off (≥16).

3.8 | Missing data and multiple imputation

Using imputed data, we compared baseline and follow-up cognitive domain scores and reran the multiple linear models relating variables to changes in CESD scores (Supplemental results: Multiple imputation). Results were highly similar to the non-imputed analyses (Tables 2 and 4).

4 | DISCUSSION

This is the largest longitudinal cohort study to date following the short-term course of cognitive and psychological functioning in patients with FD. While cognitive impairment is present in FD patients,[3-5] we found no major changes in cognitive functioning during 1 year of follow-up and did not identify factors related to changes in cognitive functioning. Changes in depressive symptoms were more variable and were related to changes in use of coping styles, and to patients' own health perception.

Four patients (5%) showed a reliable decrease in cognitive functioning according to our preset criteria. Most T-scores in these four patients decreased from excellent to good/average. In addition, the patient characteristics of these four patients did not correspond with our previously hypothesized risk groups (e.g. only one man with a classical phenotype, no patients with stroke or severe WMLs). We hypothesize that the decrease in these patients is not directly related to FD itself; however, the low number of patients with reliable decrease prevents strong conclusions. The only previously published follow-up study of cognitive functioning in FD also showed no cognitive decline after 8 years, but was hampered by size ($n = 14$) and loss to follow-up.[9] The methodology applied here is sensitive enough to detect short-term changes as exemplified by a trial evaluating the effect of deep brain stimulation in patients with Parkinson's disease in which 34% of included patients showed a reliable decrease in cognitive functioning over 1 year using similar criteria.[33]

Twenty-nine patients (38%) had depressive symptoms at baseline and six patients (8%) showed a reliable decrease in depressive symptoms between baseline and follow-up. Six patients were diagnosed with a new depressive disorder between baseline and follow-up by their general practitioner or psychologist/psychiatrist, five of which were referred after discussing their increased CESD scores. This could be explained by depressive disorder being under-diagnosed in FD, which has been suggested in FD.[6] Surprisingly, we found no differences in changes in CESD scores between patients that were counselled between baseline and follow-up for depressive symptoms and those that were not. Our findings might reflect general findings of depressive symptoms in a chronic disease population: remission may occur but depressive symptoms are generally more persistent in patients with a chronic disease when compared to those without.[34] Nevertheless, improvement may be achieved using a patient or disease adapted approach. In a small longitudinal study in FD patients, a sustained decrease in depressive symptoms was achieved after employing individually tailored psychological interventions.[11] In contrast to the intervention study, we did not employ a standardized referral or intervention for all patients. Rather, as Dutch FD patients are spread throughout the country they were referred to local healthcare practitioners. Since depressive symptoms may thus persist for prolonged periods of time, patients with FD might need specialized psychological interventions since rare inherited metabolic diseases present unique problems[35,36] ideally offered by psychologists embedded in multidisciplinary care teams.[37]

Potential factors of interest for psychological interventions in patients with FD are coping styles. A decrease in depressive symptoms was independently related to an increased use of positivity and problem solving while an increase in depressive symptoms was independently related to increased avoidance and brooding. While causality cannot be inferred from this study and these relations might be bi-directional, similar relations between coping styles and depressive symptoms have been published for other chronic disorders.[38-40] Moreover, coping intervention studies show potential to improve outcomes in chronic illnesses[41] and could therefore also be investigated in the FD population. In addition, adjusting perception of illness, referring to a patients' interpretation of a diseases' causes, symptoms, consequences, timeline and controllability (locus of control)[42] can be useful, as has been shown in patients with myocardial infarction.[43]

Strengths of this study include the large sample size, the use of established neuropsychological tests, the low loss-to follow-up and the evaluation of the effects of patients lost to follow-up using imputed data. This study has several limitations. First, interpretation of the results is limited by the lack of a control group. Despite using large normative samples to evaluate neuropsychological test results, the effects of repeated testing (such as learning effects) could not be fully controlled for, although parallel test versions were used if available. Second, depressive symptoms were assessed using the CESD without simultaneous assessment of the DSM-V criteria for depressive disorder. Therefore, we were unable to analyse whether increased CESD scores reflected a current depressive disorder or were increased due to chronic pain or anxiety.[44] Third, the effect of enzyme replacement therapy and other medications such as antidepressants on depressive symptoms or cognitive functioning in FD is unknown. Considering the indication bias in cohort studies (more severely affected patients will generally receive more and earlier treatment), we expected no verifiable effect of these treatments and regarded the analyses as unreliable and therefore did not include these in this study. Nevertheless, despite treatment with both enzyme replacement therapy and antidepressants,

cognitive impairment was clearly present and depressive symptoms were widespread and persistent.[3,4,7] Fourth, since time of day was not standardized and seasonal affective disorder was not controlled for, we cannot rule out their effects on the neuropsychological test results.[45,46] As patients were assessed after 1 year, meaning that their baseline and follow-up assessment were both in the same season, the effect of seasonal affective disorder on the changes in neuropsychological test results are expected to be small. Lastly, there is some evidence that both cognitive impairment and depressive symptoms might be already present in paediatric FD patients.[47,48] Since we did not include patients <18 years old in our study population, we cannot exclude that early neuro- and psychologic development is affected in FD. Future studies should evaluate these early life effects of FD as this might also be important in relation to the timing of interventions to reduce or prevent depressive symptoms and cognitive impairment.

To conclude, no major changes in cognitive functioning were found over 1 year follow-up and we did not identify patients at risk for cognitive decline. Hence, we do not recommend the use of cognitive functioning as a functional outcome for intervention trials in patients with FD. The fact that depressive symptoms may persist for longer periods of time, mandates assessment of depressive symptoms during routine follow-up. Future studies should explore whether individually tailored psychological interventions focused on combining adjustment of coping styles and illness perception in FD patients improve depressive symptoms.

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CONFLICT OF INTEREST

S. K., G. J. G., M. G. F. L., M. R. L. and M. G. W. D. reports no competing interests.

C. E. M. H. is involved in pre-marketing studies with Genzyme, Protalix and Idorsia. Financial arrangements are made through AMC Research BV. No fees, travel support or grants are obtained from Pharmaceutical Industries. She reports no non-financial competing interests.

M. L. is involved in pre-marketing studies with Genzyme, Protalix and Idorsia. Financial arrangements are made through AMC Research BV. No fees, travel support or grants are obtained from Pharmaceutical Industries. She reports no non-financial competing interests.

I. N. v. S. chairs a steering committee for CSL Behring and received departmental honoraria for serving on scientific advisory boards for CSL Behring and Baxter. All lecturing and consulting fees for INS were donated to the Stichting Klinische Neurologie, a local foundation that supports research in the field of neurological disorders. He reports no non-financial competing interests.

AUTHOR CONTRIBUTIONS

Simon Körver: study design, acquisition, analysis and interpretation of data, first draft of manuscript.

Gert J. Geurtsen: study design, interpretation of data, study supervision, critical revision of manuscript.

Carla E. M. Hollak: study concept, study design, interpretation of data, study supervision, critical revision of manuscript.

Ivo N. van Schaik: study supervision, critical revision of manuscript.

Maria G. F. Longo: acquisition and interpretation of data, critical revision of manuscript.

Marjana R. Lima: acquisition and interpretation of data, critical revision of manuscript.

Marcel G. W. Dijkgraaf: statistical support, critical revision of manuscript.

Mirjam Langeveld: interpretation of data, study supervision, critical revision of manuscript.

INFORMED CONSENT

This study was approved by the Human Research Ethics Committee of the AMC (2016_060). All participants provided informed consent prior to inclusion. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

DATA AVAILABILITY STATEMENT

The data sets generated and analyzed during the current study are not publicly available. Because of the rarity of the disease, even anonymized data can be linked to a specific individual. In case of a specific scientific question, requests to make parts of the data set available will be reviewed.

REFERENCES

1. Zarate YA, Hopkin RJ. Fabry's disease. *Lancet*. 2008;372:1427-1435.
2. Arends M, Wanner C, Hughes D, et al. Characterization of classical and nonclassical Fabry disease: A multicenter study. *J Am Soc Nephrol*. 2017;28:1631.
3. Bolsover FE, Murphy E, Cipolotti L, Werring DJ, Lachmann RH. Cognitive dysfunction and depression in Fabry disease: a systematic review. *J Inherit Metab Dis*. 2014;37:177-187.
4. Körver S, Geurtsen GJ, Hollak CEM, et al. Predictors of objective cognitive impairment and subjective cognitive complaints in patients with Fabry disease. *Sci Rep*. 2019;9:188.

5. Loeb J, Feldt-Rasmussen U, Madsen CV, Vogel A. Cognitive impairments and subjective cognitive complaints in Fabry disease: A nationwide study and review of the literature. *JIMD Rep*. 2018;41:73-80.
6. Cole AL, Lee PJ, Hughes DA, Deegan PB, Waldek S, Lachmann RH. Depression in adults with Fabry disease: a common and under-diagnosed problem. *J Inherit Metab Dis*. 2007;30:943-951.
7. Körver S, Geurtsen GJ, Hollak CEM, et al. Depressive symptoms in Fabry disease: the importance of coping, subjective health perception and pain. *Orphanet J Rare Dis*. 2020;15:28.
8. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med*. 2014;44:2029-2040.
9. Lelieveld IM, Bottcher A, Hennermann JB, Beck M, Fellgiebel A. Eight-year follow-up of neuropsychiatric symptoms and brain structural changes in Fabry disease. *PLoS One*. 2015;10:e0137603.
10. Park CL. Meaning, coping, and health and well-being. In: Folkman S, ed. *The Oxford Handbook of Stress, Health, and Coping*. Oxford, UK: Oxford Library of Psychology; 2011:227-241.
11. Ali N, Gillespie S, Laney D. Treatment of depression in adults with Fabry disease. *JIMD Rep*. 2018;38:13-21.
12. Smid BE, van der Tol L, Cecchi F, et al. Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. *Int J Cardiol*. 2014;177:400-408.
13. Salmon DP, Bondi MW. Neuropsychological assessment of dementia. *Annu Rev Psychol*. 2008;60:257-282.
14. Schmand B, Bakker D, Saan R, Louman J. The Dutch reading test for adults: a measure of premorbid intelligence level. *Tijdschr Gerontol Geriatr*. 1991;22:15-19.
15. Rees LM, Tombaugh TN, Gansler DA, Moczynski NP. Five validation experiments of the test of memory malingering (TOMM). *Psychol Assess*. 1998;10:10-20.
16. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
17. Bouma J, Ranchor AV, Sanderman R, Van Sonderen E. *Het meten van symptomen van depressie met de CES-D. Een handleiding*. Groningen, the Netherlands: UMCG; 2012.
18. Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for depression in the general population with the center for epidemiologic studies depression (CES-D): a systematic review with meta-analysis. *PLoS One*. 2016;11:e0155431.
19. Schreurs PJ, Tellegen B, Willige GV. Gezondheid, stress en coping: de ontwikkeling van de Utrechtse coping-lijst [Health, stress and coping: The development of the Utrechtse Coping Scale]. *Gedrag Tijdschr Psychol*. 1984;12:101-117.
20. Grice JW. Computing and evaluating factor scores. *Psychol Methods*. 2001;6:430-450.
21. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore*. 1994;23:129-138.
22. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-483.
23. KDIGO. *Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements. Kidney Disease: Improving Global Outcomes (KDIGO)*. CKD Work Group; 2013:1-150. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf.
24. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1-39.e14.
25. Myerson SG, Bellenger NG, Pennell DJ. Assessment of left ventricular mass by cardiovascular magnetic resonance. *Hypertension*. 2002;39:750-755.
26. Petersen SE, Aung N, Sanghvi MM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Res*. 2017;19:18.
27. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149:351-356.
28. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018.
29. Field A. Non-parametric tests. *Discovering Statistics using R*. London: Sage; 2012:653-695.
30. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59:12-19.
31. Frerichs RJ, Tuokko HA. A comparison of methods for measuring cognitive change in older adults. *Arch Clin Neuropsychol*. 2005;20:321-333.
32. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;1(3):1–67.
33. Odekerken VJJ, Boel JA, Geurtsen GJ, et al. Neuropsychological outcome after deep brain stimulation for Parkinson disease. *Neurology*. 2015;84:1355.
34. Stegenga BT, Kamphuis MH, King M, Nazareth I, Geerlings MI. The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47:87-95.
35. von der Lippe C, Diesen PS, Feragen KB. Living with a rare disorder: a systematic review of the qualitative literature. *Mol Genet Genomic Med*. 2017;5:758-773.
36. von der Lippe C, Frich JC, Harris A, Solbraekke KN. Experiences of being heterozygous for Fabry disease: a qualitative study. *J Genet Couns*. 2016;25:1085-1092.
37. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metabol*. 2018;123:416-427.
38. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. *Perspect Psychol Sci*. 2008;3:400-424.
39. Penley JA, Tomaka J, Wiebe JS. The association of coping to physical and psychological health outcomes: a meta-analytic review. *J Behav Med*. 2002;25:551-603.
40. Visser MM, Heijenbrok-Kal MH, Spijker AV, Oostra KM, Busschbach JJ, Ribbers GM. Coping, problem solving, depression, and health-related quality of life in patients receiving outpatient stroke rehabilitation. *Arch Phys Med Rehabil*. 2015;96:1492-1498.
41. de Ridder D, Schreurs K. Developing interventions for chronically ill patients: is coping a helpful concept? *Clin Psychol Rev*. 2001;21:205-240.

42. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res*. 2006;60:631-637.
43. Sararoudi RB, Motmaen M, Maracy MR, Pishghadam E, Kheirabadi GR. Efficacy of illness perception focused intervention on quality of life, anxiety, and depression in patients with myocardial infarction. *J Res Med Sci*. 2016;21:125-125.
44. Carleton RN, Thibodeau MA, Teale MJN, et al. The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor structure. *PLoS One*. 2013;8:e58067.
45. Blatter K, Cajochen C. Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. *Physiol Behav*. 2007;90:196-208.
46. Merikanto I, Lahti T, Castaneda AE, et al. Influence of seasonal variation in mood and behavior on cognitive test performance among young adults. *Nordic J Psychiatry*. 2012;66:303-310.
47. Bugescu N, Alioto A, Segal S, Cordova M, Packman W. The neurocognitive impact of Fabry disease on pediatric patients. *Am J Med Genet B Neuropsychiatr Genet*. 2015;168b:204-210.
48. Bugescu N, Naylor PE, Hudson K, Aoki CD, Cordova MJ, Packman W. The psychosocial impact of Fabry disease on pediatric patients. *J Pediatr Genet*. 2016;5:141-149.

SUPPORTING INFORMATION

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

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