Fatigue profiles under long term illnesses: prospective cohort study

DOCUMENT: SAR-2022-031-AH-v01

From: Felipe Figueiredo **To:** Alicia Hughes

2022-11-04

TABLE OF CONTENTS

Fatigue profiles under long term illnesses: prospective cohort study

Document version

Version	Alterations
01	Initial version

1 ABBREVIATIONS

- ANOVA: Analysis of Variance
- CBRQ: Cognitive and Behavioral Responses Questionnaire
- CFQ: Chalder fatigue scale
- CI: confidence interval
- FAQ: Fatigue Acceptance Questionnaire
- HADS: Hospital Anxiety and Depression Scale
- LTC: long term condition
- SD: standard deviation

2 CONTEXT

Fatigue is prevalent in LTCs and a high unmet need for patients.

Transdiagnostic theory assumes that heterogenous illnesses share underlying processes. A complex interaction between biological, affective, behavioural and cognitive factors can maintain symptoms across disorders which suggests they can be targeted similarly by similar interventions.

For many LTCs the biomedical aspects of fatigue are not well understood and there is a lack of efficacy for pharmacological interventions for fatigue.

2.1 Objectives

Estimate average fatigue predicted by cognitive and behavioral factors and sleep disturbance in participants with breast cancer, colorectal cancer, gynae cancer, prostate cancer, thyroid cancer, atrial fibrillation, heart failure, COPD, diabetes, multiple sclerosis, and stroke during 6 months of observation.

2.2 Data reception and cleaning

The original data base had 298 variables collected on 3384 observations. After the cleaning process 20 variables were included in the analysis. The total number of observations excluded due to incompleteness and exclusion criteria will be reported in the analysis.

3 METHODS

The methods of this analysis are fully described in the annex document **SAP-2022-031-AH-v02**.

4 RESULTS

4.1 Study population and follow up

After the cleaning process 20 variables were included in the descriptive analysis with 3384 observations.

Table 1 describes the study population epidemiological and clinical characteristics. The study population was similarly sampled from both genders, with approximately half males (47%) and females (53%). Average participant was 62 years old. Ethnicity was categorized into four groups, where the most frequently observed was group 1 at 92%.

The most frequent LTC observed was Diabetes at 15% prevalence, followed by MS (12%). COPD was observed in 6.6% participants. Oncologic-related LTC included Breast cancer, colorectal cancer, gynae cancer, prostate and thyroid cancer summing up to 33.3% of the study population. Cardiology-related LTC included Atrial fibrillation, heart failure, and stroke, comprising a sub-population of around 32.3% of the study population.

Table 1 *Population demographic and clinical characteristics.*

Characteristic	N = 3,384
Age, Mean (SD)	62 (14)
Missing	351
Gender, n (%)	
Male	1,429 (47%)
Female	1,614 (53%)
Missing	341

LTC, n (%)	
Breast Cancer	354 (10%)
Atrial Fibrillation	220 (6.5%)
Heart Failure	141 (4.2%)
Other Cardiology	240 (7.1%)
Colorectal Cancer	270 (8.0%)
COPD	223 (6.6%)
Diabetes	495 (15%)
Gynae Cancer	211 (6.2%)
HIV	88 (2.6%)
MS	398 (12%)
Prostate	260 (7.7%)
Psoriasis	121 (3.6%)
Stroke	296 (8.7%)
Thyroid Cancer	47 (1.4%)
15	20 (0.6%)
Ethncity (4 groups), n (%)	
1	2,785 (92%)
2	96 (3.2%)
3	84 (2.8%)
4	53 (1.8%)
Missing	366
Highest education qualification, n (%)	
None	200 (6.9%)
School (to the end of compulsory education)	723 (25%)
Tertiary (Secondary school to A-Levels)	417 (14%)
Vocational	532 (18%)
Higher (Undergraduate)	542 (19%)
Higher (Postgraduate)	488 (17%)
6	6 (0.2%)
11	1 (<0.1%)

Missing	475
Current work status, n (%)	
0	38 (1.4%)
Employed	880 (32%)
Unemployed, looking for word	46 (1.7%)
Student, not in paid employment	12 (0.4%)
Homemaker, no working outside home	80 (2.9%)
Retired	1,441 (52%)
Disability/long term sick leave	149 (5.4%)
Other	106 (3.9%)
Missing	632
Marital status, n (%)	
Single	395 (13%)
Married/living together	2,045 (68%)
Divorced/separated	293 (9.8%)
Widowed	256 (8.6%)
5	1 (<0.1%)
Missing	394
Length of illness - Years, Mean (SD)	16 (87)
Missing	801
Length of illness - Months, Mean (SD)	12.5 (85.7)
Missing	1,269
Chalder fatigue total, Mean (SD)	17.2 (5.8)
Missing	294
HADS distress total, Mean (SD)	12 (7)
Missing	298
Fear Avoidance total, Mean (SD)	5.30 (2.49)
Missing	299
Symtom Focusing total, Mean (SD)	4.96 (3.01)
Missing	336
Embarrassment Avoidance total, Mean (SD)	4.2 (3.2)

Missing	337
Resting Behaviour total, Mean (SD)	3.11 (2.39)
Missing	341
All or nothing behaviour total, Mean (SD)	4.0 (3.0)
Missing	343
Damage beliefs total, Mean (SD)	5.52 (2.23)
Missing	322
Jenkins Sleep Questionnaire total, Mean (SD)	9 (6)
Missing	294
Chalder fatigue scale socre at 4 months follow-up, Mean (SD)	16.6 (6.1)
Missing	2,321

Fatigue had a bimodal distribution at baseline, with one larger group having CFQ scores between 11 and 12, and a second well defined group with scores ranging between 16 and 17 (Figure 1, first panel). After four months of follow-up this bimodal characteristic of the distribution almost disappears, where the group with higher scores became less distinguished from the rest of the higher-score population, while the most frequently observed scores accumulate between 13.2 and 16.2 (Figure 1, second panel).

The distribution at baseline is skewed to higher scores, whereas the distribution at 4 months of follow-up is more symmetric (Figure 1). Although the shape of the CFQ score distribution changed between baseline and four months, the range of observed scores, between 0 and 33, remained the same at both times. Average CFQ appears to drop from 17.2 (SD 5.8) at baseline to 16.5 (SD 4.5) at four months. This drop in average CFQ score appear to come from the higher scores at baseline that do not seem to correspond to a similar frequency of high scores at 4 months.

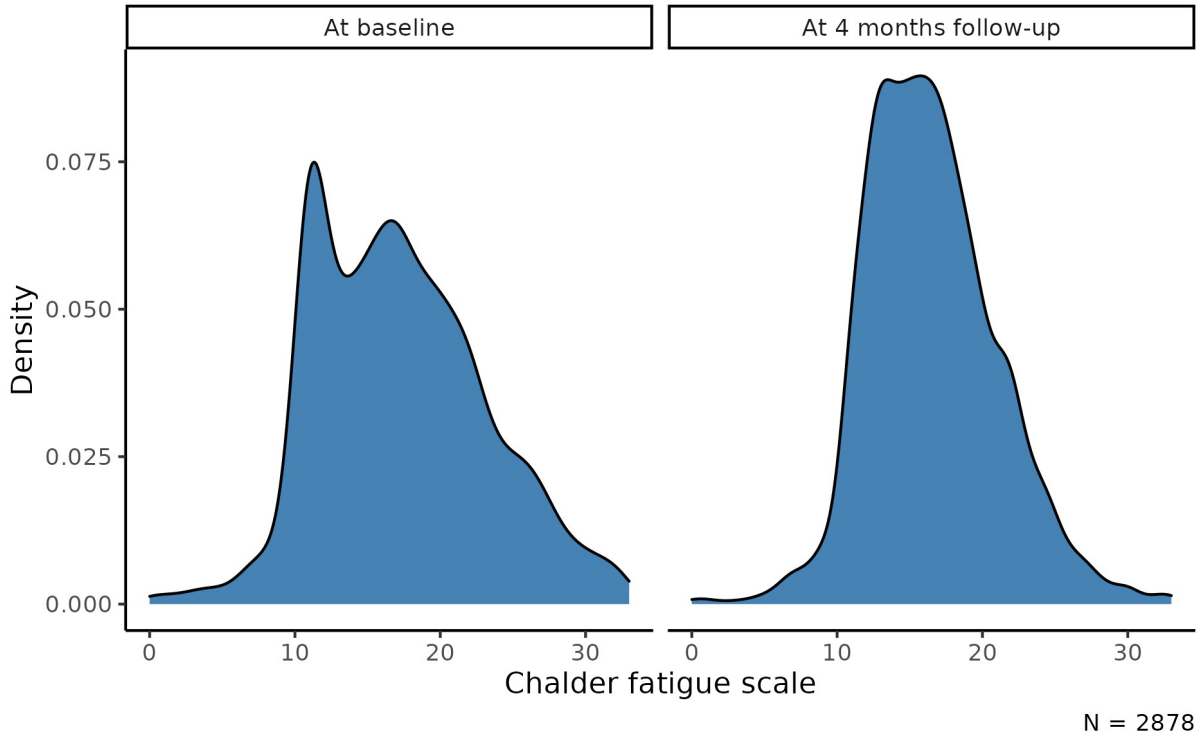

Figure 1 *Distribution density of CFQ of study participants at baseline and at end-point.*

Individual changes in CFQ score are shown in Figure 2. Despite a small decrease in the average score there is no obvious upward or downward trend that can be observed in the individual score changes between time points, but a regression to the mean where most participants that exhibited more extreme values at baseline displayed scores appear to fall between 10 and 25 (this can also be seen in Figure 1, second panel).

As there were more participants at the higher extreme scores at baseline than lower extremes, it is noticeable that there are more individuals at the higher end of the fatigue spectrum at baseline converging to more intermediate scores, when compared to individuals at the lower extreme scores, which can be seen in both Figures 1 and 2.

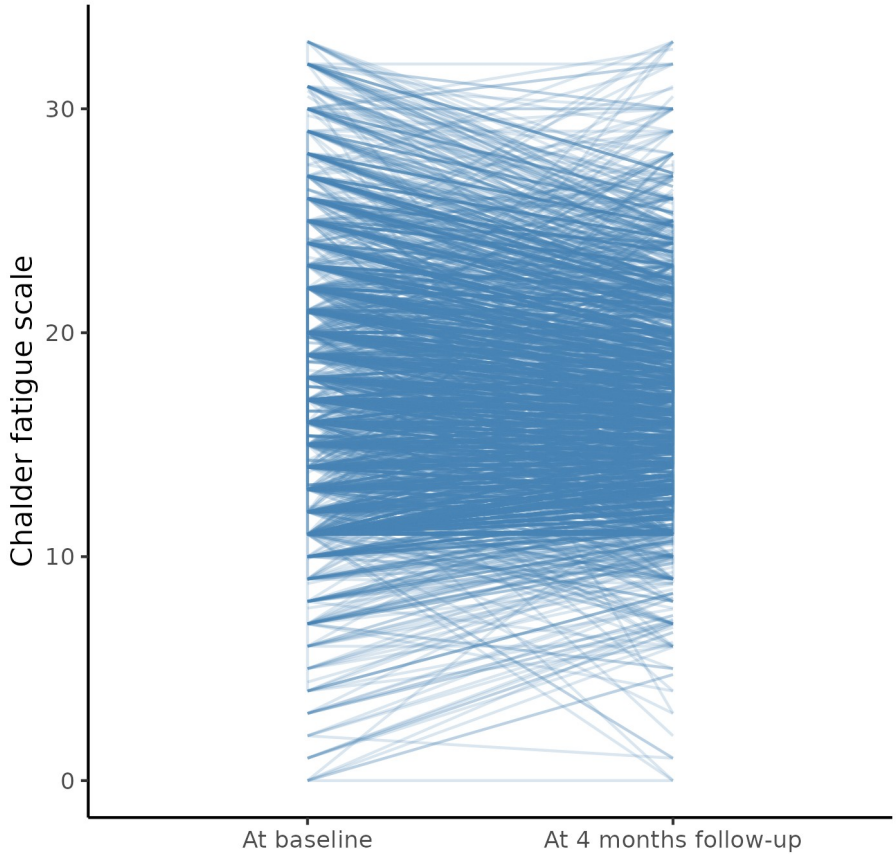

Figure 2 *Change in CFQ of study participants between baseline and end-point.*

4.2 Average CFQ at four months of follow up

After the treatment of missing values (see appendix 8.2) the models in this analysis were adjusted using 14 variables on 2878 observations from individual participants, where fatigue was measured at two time points.

The average CFQ can be predicted by both resting and all of nothing behaviors (Table 2, no LTC), when controlling for age, sex, HADS distress and fatigue at baseline. When, in addition to those we also control for the effect of the various LTC under study, the average CFQ score of the above predictors remain significant (Table 2, LTC controlled), and fear avoidance and Jenkins sleep now have a detectable effect.

All things constant, an increase of one point in the fear avoidance scale has an effect of an increase of 0.05 (95% CI 0.01, 0.10; p=0.014) in the fatigue score. Similarly both resting and all or nothing behaviors are associated with an increase around 0.06 and the effect size of the Jenkins sleep scale is an increase of 0.03 (95% CI 0.01, 0.05; p=0.003).

Table 2 *Relationship between predictors and change in fatigue scores after four months of follow-up.*

Characteristic	Beta	95% CI[1]	p-value	Beta	95% CI[1]	p-value
	No LTC			LTC controlled		
Fear Avoidance total	0.04	-0.01 to 0.09	0.087	0.05	0.01 to 0.10	**0.014**
Symtom Focusing total	-0.04	-0.09 to 0.01	0.097	-0.03	-0.07 to 0.02	0.216
Embarrassment Avoidance total	0.03	-0.01 to 0.08	0.152	0.00	-0.04 to 0.04	0.966
Resting Behaviour total	0.12	0.07 to 0.18	**<0.001**	0.06	0.01 to 0.11	**0.022**
All or nothing behaviour total	0.09	0.05 to 0.14	**<0.001**	0.06	0.02 to 0.10	**0.004**
Damage beliefs total	0.01	-0.05 to 0.06	0.795	0.05	0.00 to 0.10	0.059
Jenkins Sleep Questionnaire total	0.02	0.00 to 0.04	0.132	0.03	0.01 to 0.05	**0.003**

[1]CI = Confidence Interval

Adding the LTC of individual participants as a control variable improved the model (see section 8.3 in the appendix), by slightly reducing variance in estimation of both predictors that were consistently detectable in both models (resting behavior and all or nothing behavior). The CI around other estimates appear to have similar sizes in both models, which means that the uncertainty around these estimates were similar as well.

The inclusion of LTC as a controlling variable also changes the estimate of effect predictors appear to have in end of study fatigue. The estimates for both fear avoidance and Jenkins sleep scale have shifted from no association towards a positive association, so there is evidence that higher values for these variables would predict higher levels of fatigue at four months. The estimates for both resting and all or nothing behaviors have decreased and, while still positively associated with fatigue, there is evidence that patients with differing LTC of the patient on average have lower fatigue.

Additionally this provides evidence that different LTC impact the end fatigue score with varying effects. For example, consider the profile of a 62 years old female with average characteristics presented in Table 1, including a baseline CFQ of 17. The model in Table 2 predicts she would have a different fatigue score at 4 months of follow-up according to the LTC for which she was being treated. If she had a heart failure, the predicted CFQ would be 15.0, while if she had experienced a stroke her predicted score would be 17.1. If she were being treated for MS her fatigue score would be 18.2.

It is worth noticing that, while the uncertainty around the estimate of damage beliefs was kept largely at the same level, the CI shifted to the positive side. This may indicate that a higher powered study might be able to provide evidence of the association between this variable and fatigue. This could be confirmed in future independent studies.

5 OBSERVATIONS AND LIMITATIONS

Recommended reporting guideline

The adoption of the EQUATOR network (http://www.equator-network.org/) reporting guidelines have seen increasing adoption by scientific journals. All observational studies are recommended to be reported following the STROBE guideline (von Elm et al, 2014).

6 CONCLUSIONS

The CFQ fatigue score was tracked for individual participants over the study period to identify prognostic factors that could predict change. Factors identified as such were fear avoidance (effect size 0.05), resting behavior (effect size 0.06), all or nothing behavior (effect size 0.06) and Jenkins sleep scale (effect size 0.03). The LTC is a predictor of changes in fatigue scores, with specific LTCs contributing varying effects.

7 REFERENCES

- **SAP-2022-031-AH-v02** – Analytical Plan for Fatigue predicted by cognition, behavior and sleep disturbance factors: prospective cohort study

8 APPENDIX

8.1 Exploratory data analysis

The distribution of ages of both men and women recruited show similar ranges, similar widths and have peak frequency at the similar average age (Figure A1, Table 1).

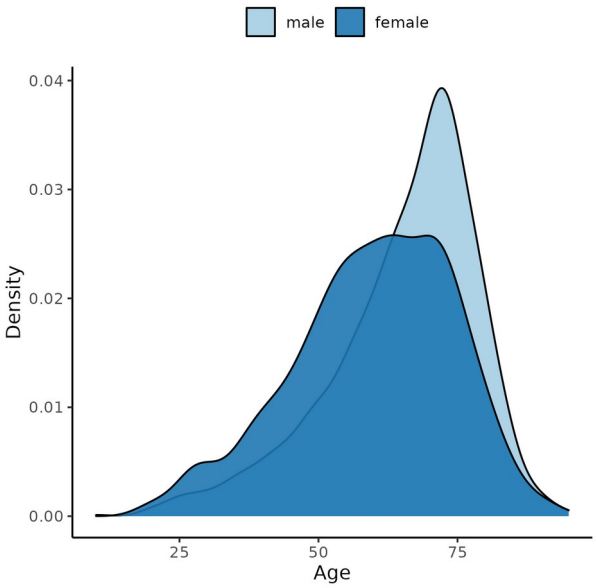

Figure A1 *Distribution of age in the study population.*

8.2 Missing data treatment

8.2.1 Missing data in original dataset

Data does not appear Missing Completely At Random (p <0.001).

Only the CFQ score at 4 months of follow up met the criteria for missing data imputation (Table A1, Figure A2).

Table A1 *Missingness in raw data.*

variable	n_miss	pct_miss
cfq_total_4months	2321	68.59
age	351	10.37
cbrq_all_nothing_total	343	10.14

gender	341	10.08
cbrq_resting_behav_total	341	10.08
cbrq_embar_avoid_total	337	9.959
cbrq_symp_focus_total	336	9.929
cbrq_damage_total	322	9.515
cbrq_fear_avoid_total	299	8.836
hads_distress_total	298	8.806
cfq_total	294	8.688
jenkins_total	294	8.688
id	0	0
group	0	0

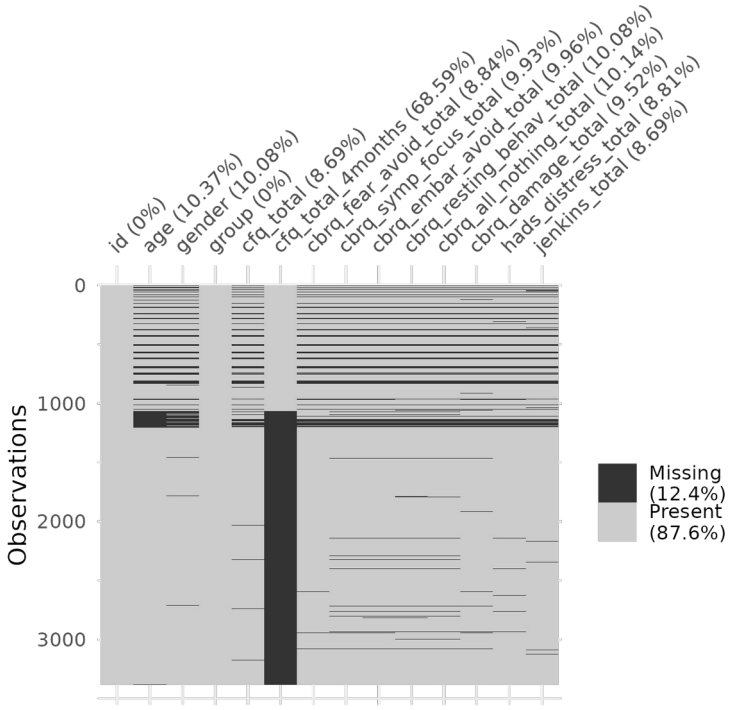

Figure A2 *Missingness in raw data.*

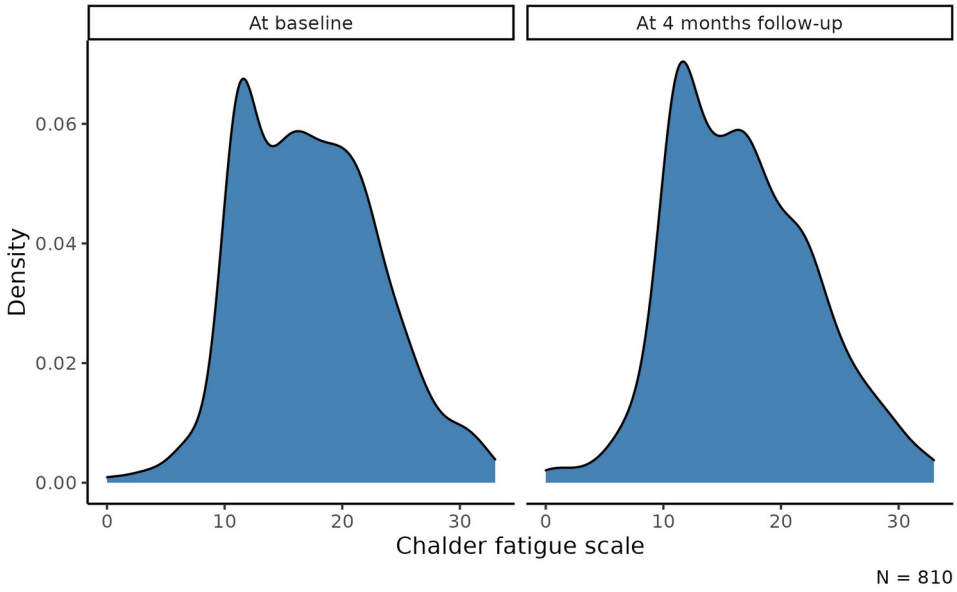

Figure A3 *Distribution density of CFQ of study participants at baseline and at end-point, before imputation.*

Fatigue had a bimodal distribution at baseline, which was described in the main report (Figure 1). After four months of follow-up this bimodal characteristic of the distribution almost disappears, where the group with higher scores became less distinguished from the rest of the higher-score population, while the most frequently observed scores still accumulate between 11 and 12.

This distribution in Figure A3 is presumed to reflect the best approximation of the true CFQ at end of study available and was used as reference for the evaluation of imputation methods in the next sections.

8.2.2 Imputation with the mean

Following the plan described in **SAP-2022-031-AH-v02** the missing data in CFQ scores at 4 months of follow-up had undergone imputation using the mean. The aim of the imputation was to achieve an imputed distribution similar to the distribution in the RAW data (Figure A3), while not biasing the relationship between baseline and follow-up values.

The imputation with the mean severely biases the relationship between CFQ scores at both time points (Figure A4), while also producing an unreasonable distribution of scores (Figure A5). The imputation with the mean was thus rejected.

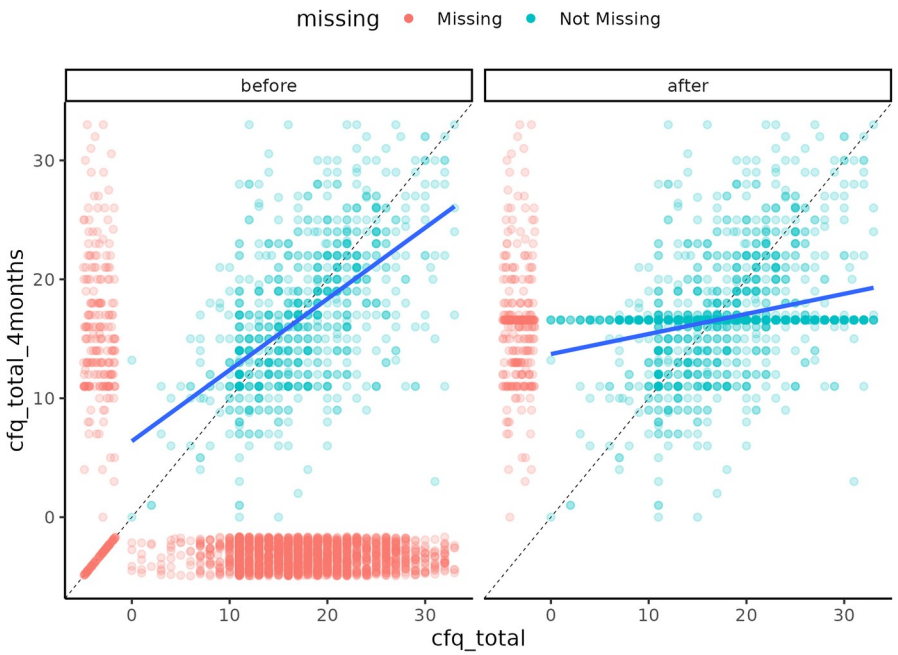

Figure A4 *Relationship between baseline and end-point CFQ of study participants, before and after imputation with the mean.*

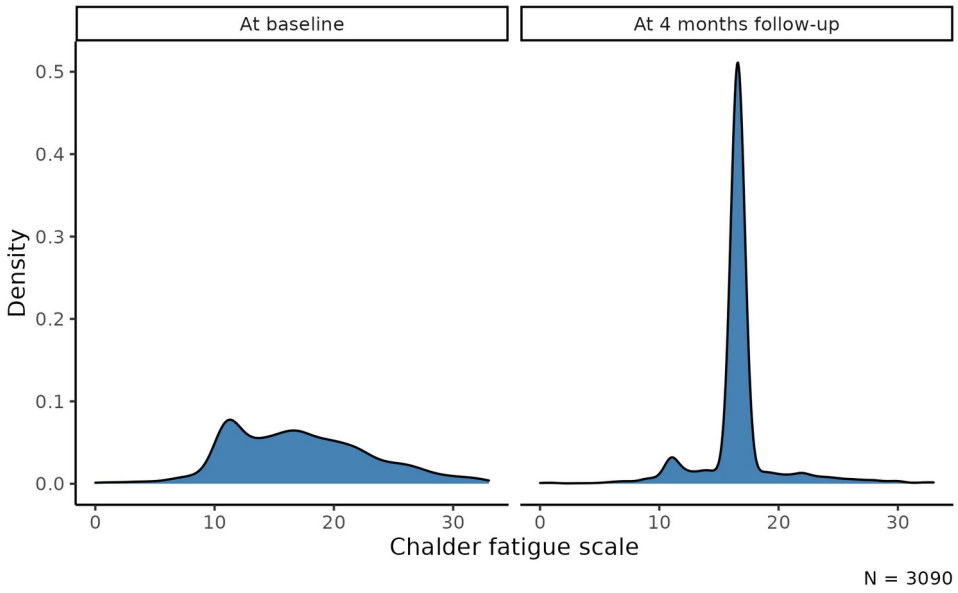

Figure A5 *Distribution density of CFQ of study participants at baseline and at end-point, before and after imputation with the mean.*

8.2.3 Imputation with linear models

We planned models of end of study CFQ based on combinations of baseline CFQ, age, sex and LTC. The simple linear regression on baseline CFQ did not provide enough variance around the regression line, and adding either age or sex decreased the number of observations imputed due to the missing values in those variables (LTC did not have any missing values). The best compromise between bias and loss was a model with baseline CFQ and the LTC. Figure A6 shows the resulting data.

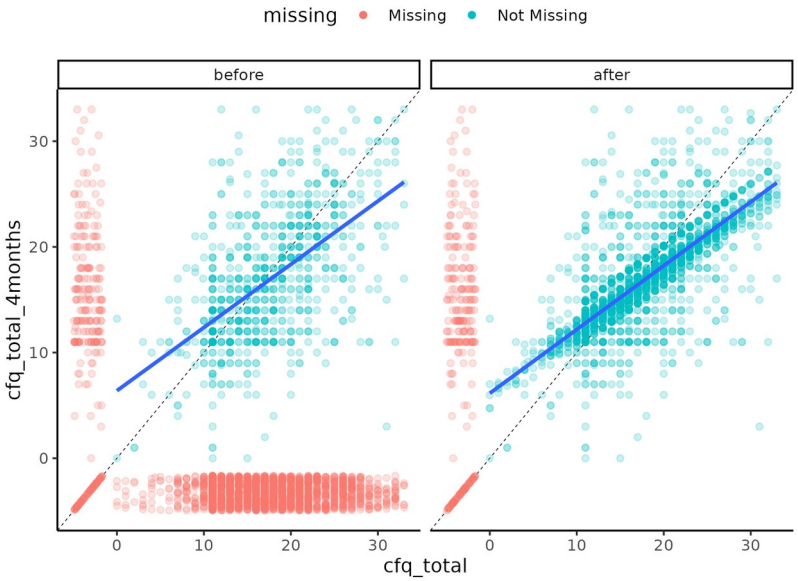

Figure A6 *Relationship between baseline and end-point CFQ of study participants, before and after imputation with linear models.*

8.3 Modeling strategy

Table A2 shows the estimates to all variables included in the models that were displayed in Table 2, including the controlling variables.

Table A2 *Alternative version of Table 2, displaying all parameters.*

Characteristic	Beta	95% CI[1]	p-value	Beta	95% CI[1]	p-value
	No LTC	LTC controlled		No LTC	LTC controlled	
(Intercept)	7.0	6.3 to 7.6	**<0.001**	6.4	5.7 to 7.1	**<0.001**
Chalder fatigue total	0.53	0.51 to 0.56	**<0.001**	0.53	0.51 to 0.55	**<0.001**
Age	-0.01	-0.02 to -0.01	**<0.001**	0.00	-0.01 to 0.01	0.505
Gender						

Male	—	—		—	—	
Female	-0.03	-0.25 to 0.19	0.768	-0.22	-0.45 to 0.01	0.064
Fear Avoidance total	0.04	-0.01 to 0.09	0.087	0.05	0.01 to 0.10	**0.014**
Symtom Focusing total	-0.04	-0.09 to 0.01	0.097	-0.03	-0.07 to 0.02	0.216
Embarrassment Avoidance total	0.03	-0.01 to 0.08	0.152	0.00	-0.04 to 0.04	0.966
Resting Behaviour total	0.12	0.07 to 0.18	**<0.001**	0.06	0.01 to 0.11	**0.022**
All or nothing behaviour total	0.09	0.05 to 0.14	**<0.001**	0.06	0.02 to 0.10	**0.004**
Damage beliefs total	0.01	-0.05 to 0.06	0.795	0.05	0.00 to 0.10	0.059
Jenkins Sleep Questionnaire total	0.02	0.00 to 0.04	0.132	0.03	0.01 to 0.05	**0.003**
HADS distress total	0.01	-0.01 to 0.03	0.250	0.01	-0.01 to 0.03	0.183
LTC						
Breast Cancer				—	—	
Atrial Fibrillation				-2.0	-2.5 to -1.5	**<0.001**
Heart Failure				-1.5	-2.1 to -0.97	**<0.001**
Other Cardiology				-0.41	-0.92 to 0.09	0.108
Colorectal Cancer				-1.0	-1.5 to -0.58	**<0.001**
COPD				-0.18	-0.68 to 0.33	0.494
Diabetes				-0.70	-1.1 to -0.30	**<0.001**
Gynae Cancer				-0.64	-1.1 to -0.17	**0.007**
HIV				-1.2	-1.9 to -0.54	**<0.001**
MS				1.6	1.2 to 2.0	**<0.001**
Prostate				-0.24	-0.74 to 0.26	0.342
Psoriasis				0.27	-0.29 to 0.84	0.344
Stroke				0.54	0.08 to 1.0	**0.022**
Thyroid Cancer				-1.0	-2.0 to -0.09	**0.031**
15				8.2	6.9 to 9.5	**<0.001**

[1]CI = Confidence Interval

Models with interactions between LTC and other factors were assessed, but both interactions with all factors and interactions with each single factor resulted in singular matrices for the resulting models, thus making these models uninterpretable. Even after aggregating the LTCs into clinically relevant groups was attempted in order to reduce the number of parameters in the model, such as “Cancer (all types)”, “Cardiology (all

types)", "HIV", "Diabetes", "COPD", "MS", "Psoriasis" and "Other" did not result in non-singular models. The only choice that produced an interpretable model was "Cancer", "Cardiology" and "Other", but this choice was deemed too restrictive for the purpose of this analysis, relative to the original design of the study and was discarded. This way the original encoding of the LTCs in the raw data was used for the main analysis and conclusion, thus preserving the original design of the study.

Table A3 shows the ANOVA comparison between the simpler model (not controlled by LTC) and the full model. Controlling for LTC gives a model significantly more explanatory than the simpler one.

Table A3 *Statistical adjustment for the inclusion of control variables. m0 = No LTC, m1 = LTC controlled*

model	npar	AIC	BIC	logLik	deviance	Chisq	Df	Pr(>Chisq)
m0	14	14058	14142	-7015	14030	NA	NA	NA
m1	28	13635	13802	-6789	13579	451.4	14	<0.001

8.4 Availability

All documents from this consultation were included in the consultant's Portfolio.

The portfolio is available at:

https://philsf-biostat.github.io/SAR-2022-031-AH/

8.5 Analytical dataset

Table A4 shows the structure of the analytical dataset.

Table A4 *Analytical dataset structure (continued below)*

id	age	gender	group	cfq_total	cfq_total_4months	cbrq_fear_avoid_total	cbrq_symp_focus_total	cbrq_embar_avoid_total
1								
2								
3								
…								
N								

cbrq_resting_behav_total	cbrq_all_nothing_total	cbrq_damage_total	hads_distress_total	jenkins_total

Due to confidentiality the data-set used in this analysis cannot be shared online in the public version of this report.