Analytical Plan for Fatigue predicted by cognition, behavior and sleep disturbance factors: prospective cohort study

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Document version

Version	Alterations
01	Initial version
02	Added missing data imputation

1 ABBREVIATIONS

- CBRQ: Cognitive and Behavioral Responses Questionnaire
- CFQ: Chalder fatigue scale
- CI: confidence interval
- FAQ: Fatigue Acceptance Questionnaire
- HADS: Hospital Anxiety and Depression Scale
- LTC:
- 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 Hypotheses

Across LTCs increased fatigue severity will be associated with (at baseline) and predicted by (at follow-up) increased fear avoidance, symptom focusing, damage beliefs, embarrassment avoidance, all-or-nothing behaviour, and poor sleep quality.

More variance in fatigue severity will be accounted for by these trans-diagnostic factors than by the type of LTC and other clinical or socio-demographic factors.

3 DATA

3.1 Raw data

The original data base had 298 variables collected on 3384 observations.

3.2 Analytical dataset

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. Table 1 shows the structure of the analytical dataset.

Table 1 *Analytical dataset structure after variable selection and cleaning. (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

All variables in the analytical set were labeled according to the raw data provided and values were labeled according to the data dictionary for the preparation of production-quality results tables and figures.

4 STUDY PARAMETERS

4.1 Study design

Prospective cohort with measurements at baseline and after 4 to 6 months.

4.2 Inclusion and exclusion criteria

N/A

4.3 Exposures

Predictors in the model will include Fear avoidance, Symptom focusing, Embarrassment avoidance, Resting behavior, All or nothing behavior, Damage beliefs and Jenkins Sleep Scale.

4.4 Outcomes

Specification of outcome measures (Zarin, 2011):

1. (Domain) Fatigue
2. (Specific measurement) CFQ score
3. (Specific metric) End value
4. (Method of aggregation) Mean

Primary outcome

Average CFQ score in participants at end of observation.

4.5 Covariates

Estimates will be controlled for age, gender, Fatigue severity at baseline and Distress (combined score on the Hospital Anxiety and Depression Scale).

5 STATISTICAL METHODS

5.1 Statistical analyses

5.1.1 Descriptive analyses

The epidemiological profile of the study participants will be described. Demographic and clinical variables will be described as mean (SD) or as counts and proportions (%), as appropriate. The distributions of participants' characteristics will be summarized in tables and visualized in exploratory plots.

5.1.2 Inferential analyses

All inferential analyses will be performed in the statistical models (described in the next section).

5.1.3 Statistical modeling

A longitudinal analysis will be conducted to estimate the average CFQ scores at end of observation by tracking the states at each repeated observation of individuals. Mixed linear regression models will be used to track changes in scores from baseline for all individuals, using the patient ID as a random factor.

Two different but complementary models are planned. A simpler unadjusted model will include all predictors listed in section 4.3, and the fully adjusted model will include all control variables listed in section 4.5, besides the predictors.

5.1.4 Missing data

Missing data imputation was performed in the dataset previous to the procedures described in in this document, whenever a variable had over 25% missing data. Methods that will be considered include imputation with the mean, median and with linear regression models. Assessment of missing data imputation methods will be based on the comparison of the distribution of available data and imputed data, to decrease the risk of bias due to the imputation. If linear regression models are used, we plan to use models that include fatigue at baseline as well as combinations of age, sex and LTC to allow for the resulting variability to reflect baseline, demographic and clinical characteristics. The distribution of Missingness Completely At Random will be tested with Little's test.

All evaluations will be performed as complete case analyses.

5.2 Significance and Confidence Intervals

All analyses will be performed using the significance level of 5%. All significance hypothesis tests and confidence intervals computed will be two-tailed.

5.3 Study size and Power

N/A

5.4 Statistical packages

This analysis will be performed using statistical software R version 4.2.1.

6 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).

7 REFERENCES

- **SAR-2022-031-AH-v01** – Fatigue predicted by cognition, behavior and sleep disturbance factors: prospective cohort study
- Zarin DA, et al. The ClinicalTrials.gov results database – update and key issues. N Engl J Med 2011;364:852-60 (https://doi.org/10.1056/NEJMsa1012065).
- Gamble C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337–2343 (https://doi.org/10.1001/jama.2017.18556).
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014 Dec;12(12):1495-9 (https://doi.org/10.1016/j.ijsu.2014.07.013).

8 APPENDIX

This document was elaborated following recommendations on the structure for Statistical Analysis Plans (Gamble, 2017) for better transparency and clarity.

8.1 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/