Grant Agreement no. 777167

BOUNCE

Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back

Research and Innovation Action
SC1-PM-17-2017: *Personalised computer models and in-silico systems for well-being*

Deliverable: D4.1 Preliminary Factor Correlation Hypotheses

Due date of deliverable: (05-31-2018)
Actual submission date: (03-11-2019)

Start date of Project: 01 November 2017 Duration: 48 months
Responsible WP: ICCS

The research leading to these results has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777167		
Dissemination level		
PU	Public	
PP	Restricted to other programme participants (including the Commission Service)	X
RE	Restricted to a group specified by the consortium (including the Commission Services)	

0. Document Info

0.1 Author

Author	Company	E-Mail
Georgios Stamatakos	ICCS	gestam@central.ntua.gr
Eleni Kolokotroni	ICCS	ekolok@mail.ntua.gr
Evangelos C. Karademas	FORTH	karademas@uoc.gr
Akis Simos	FORTH	akis.simos@gmail.com
Paula Poikonen-Saksela	HUS	paula.poikonen-saksela@hus.fi
Ruth Pat-Horenczyk	HUJI	ruth.pat-horenczyk@mail.huji.ac.il
Chariklia Tziraki	HUJI	tziraki@gmail.com
Ilan Roziner	HUJI	ilanr@post.tau.ac.il
Ketti Mazzocco	IEO	ketti.mazzocco@unimi.it
Berta Sousa	CHAMP	berta.sousa@fundacaochampalimaud.pt
Susan Valerio	CHAMP	susan.valerio@research.fchampalimaud.org
Albino O. Maia	CHAMP	albino.maia@neuro.fchampalimaud.org

Reviewers: Lefteris Koumakis, Haridimos Kondylakis, Virginia Sanchini, Konstantinos Marias, Dimitra Dionysiou

0.2 Documents history

Document version #	Date	Change
V0.1	1 April 2018	Starting version, template
V0.2	7 April 2018	Definition of ToC
V0.3	24 May 2018	First complete draft
V0.4	26 May 2018	Integrated version (send to WP members)
V0.5	31 May 2018	Updated version (send PCP)
V0.6	5 June 2018	Updated version (sent to project internal reviewers)
Sign off	10 June 2018	Signed off version (for approval by PMT members)
V0.7	25 February 2019	Extended and modified version (with additional retrospective data)
V0.8	3 March 2019	Updated version (sent to project internal reviewers)
Sign off	5 March 2019	Signed off version (for approval by PMT members)
V1.0 final	11 March 2019	Approved Version to be submitted to EU

0.3 Document data

Keywords	breast cancer resilience in silico oncology in silico clinical psychology in silico modelling computer modelling cancer modelling
Editor Address data	Name: Georgios S. Stamatakos Partner: Institute of Communication and Computer Systems (ICCS), School of Electrical and Computer Engineering, National Technical University of Athens Address: 9, Iroon Polytechniou, Zografos, Greece Phone: + 30 210 772 2287 E-mail: gestam@central.ntua.gr
Delivery date	11 March 2019

I. Table of Contents

2. Executive Summary

The BOUNCE Project

Coping with breast cancer more and more becomes a major socio-economic challenge not least due to its constantly increasing incidence in the developing world. There is a growing need for novel strategies to improve understanding and capacity to predict resilience of women to the variety of stressful experiences and practical challenges related to breast cancer. This is a necessary step toward efficient recovery through personalized interventions. BOUNCE will bring together modelling, medical, and social sciences experts to advance current knowledge on the dynamic nature of resilience as it relates to efficient recovery from breast cancer. BOUNCE will take into consideration clinical, cancer-related biological, lifestyle, and psychosocial parameters in order to predict individual resilience trajectories throughout the cancer continuum and eventually increase resilience in breast cancer survivors and help them remain in the workforce and enjoy a better quality of life. BOUNCE will deliver a unified clinical model of modifiable factors associated with optimal disease outcomes and will deploy a prospective multi-centre clinical pilot at four major oncology centres (in Italy, Finland, Israel and Portugal), where a total of 660 women will be recruited in order to assess its clinical validity against crucial patient outcomes (illness progression, wellbeing, and functionality). The advanced computational tools to be employed will validate indices of patients' capacity to bounce back during the highly stressful treatment and recovery period following diagnosis of breast cancer. The overreaching goal of BOUNCE is to incorporate elements of a dynamic, predictive model of patient outcomes in building a decision-support system used in routine clinical practice to provide physicians and other health professionals with concrete, personalized recommendations regarding optimal psychosocial support strategies.

Deliverable D4.1

The present document reflects the work done within the framework of Task 4.1 of the BOUNCE project and aims at demonstrating certain preliminary factor correlation results based on retrospective data provided by BOUNCE partners as well as the conceptual resilience modelling approaches proposed by consortium members. A brief outline of the process of provision of inhomogeneous data related to resilience by the clinical centres participating in BOUNCE is provided. Indicative tabulations of data are included. Relevant existing data exploitation tools are listed. A literature survey on pertinent factor correlations with special focus on the aims of the studies and the methodologies and the associations identified is summarized. A number of representative correlation analyses using retrospective BOUNCE data are presented. These analyses have led to an in depth quantitative exploitation and exploration of the retrospective data domain provided by two participating clinical centres. The results produced are essentially consistent with pertinent literature. The entire process has offered the opportunity for an excellent familiarization with the handling of basic data types to be also generated and analysed in the prospective BOUNCE pilot study. More importantly, the correlation analyses performed have generated valuable hints which will partly guide the data analysis and interpretation of the prospective pilot study. An abstract conceptual approach to the quantification of resilience as a function of the biomedical, the psychosocial and the functional statuses of the patient is briefly outlined. Subsequently, a preliminary framework of factor correlation hypotheses is presented. An outline of the temporal data mining approach adopted is also provided. The main mid- and long-term goal is to contribute to the personalization, concretization and optimization of recommendations regarding psychosocial support strategies. Following the conclusions, a number of appendices include representative data sharing agreements and the descriptions of the inhomogeneous data provided by the participating clinical centres.

3 [I]. Introduction [Code Letter: I]

The primary aim of the document is to report on the work related to the preliminary hypotheses regarding the bio-medical, psycho-social and functional factors affecting the resilience of a person affected by breast cancer. It essentially refers to the task T4.1 of the BOUNCE project. The main mid- and long-term goal of the whole endeavour is to contribute to the personalization, concretization and optimization of recommendations regarding psychosocial support strategies. The present document is structured as follows.

Chapter 4 [R] provides a brief outline of the retrospective data originating from the following four clinical centres: Helsinki University Hospital Comprehensive Cancer Centre (HUS, Helsinki, Finland) , Hebrew University School of Social Work and Social Welfare (HUJI, Jerusalem, Israel) , European Institute of Oncology (IEO, Milan, Italy) and the Champalimaud Clinical Centre (CHAMP, Lisbon, Portugal). Certain indicative aspects of the retrospective data collection procedure are presented through the paradigm of the work done in IEO. These include among others inclusion and exclusion criteria and statistical considerations of the analysis design. Ethical aspects are also addressed. A list of relevant existing tools for the exploitation of various classes of inhomogeneous data such as the ALGA questionnaire, profiling the patient's cognitive and psychological status and the Distress Thermometer is also included.

Chapter 5 [A] provides the results of a number of indicative preliminary analyses of retrospective data having been provided by participating clinical centres so far. The analyses refer to the datasets provided by both HUS, HUJI and CHAMP. It is noted that the IEO retrospective data had not been provided by the time of deliverable preparation. Correlations and statistical analysis among various factors at various time points have been identified and are presented through the use of correlation matrices and other visualization means. Additionally, a concise summary of pertinent literature focusing on the associations among various BOUNCE related factors observed so far is included in an appendix.

In order to convey the idea that resilience should be ideally viewed as a uniquely measurable quantity, an abstract conceptual approach to the quantification of resilience as a function of the biomedical, the psychosocial and the functional statuses of the patient is proposed through the use of a simple table (Chapter 6 [Q]). The values or categorizations of the three statuses of the patient can generally refer to the same and/or different time points.

Chapter 7 [H] presents a refined framework of factor related hypotheses regarding resilience. First, an overview of the factors included in the prospective pilot study is provided. Subsequently, a basic theoretical background is outlined. In order to fulfil the main aim of this study, two "prediction" models are proposed; an overall/general one, and a resilience-trajectory specific one.

Chapter 8 [M] outlines the temporal data mining procedures including time series prediction, classification of temporal data, temporal cluster analysis, temporal pattern discovery and associations rules.

Following the conclusions (Chapter 9 [C]), a number of appendices include representative data sharing agreements and the descriptions of the inhomogeneous data provided by the participating clinical centres.

4 [R]. Description of the Retrospective Data [Code Letter: R]

R1 Sources of Retrospective data

Data sharing agreements between each retrospective data providing clinical organization and the modelling partners have been formulated. This has been achieved following a strict and lengthy procedure so that all ethical and legal constraints imposed by each clinical organization and the European regulations could be met. Representative data sharing agreements are included in Appendix P.APPENDIX 1 (P.APPENDIX 1A and P.APPENDIX 1A). P.APPENDIX 1A contains the data sharing agreement between the Helsinki University Hospital Comprehensive Cancer Centre (HUS) and the Institute of Communication and Computer Systems (ICCS), National Technical University of Athens. P.APPENDIX 1B contains the data sharing agreement between the Hebrew University School of Social Work and Social Welfare and the Institute of Communication and Computer Systems (ICCS), National Technical University of Athens. Both agreements have been signed by the involved parties and the corresponding data has been provided. However, due to internal delays originating from the complicated approval processes followed by the ethical and the legal committees of the European Institute of Oncology (IEO) located in Milan and the Champalimaud Clinical Centre (CHAMP) located in Portugal, the signing of the respective agreements has not taken place as yet and therefore, the data has not yet been provided. This is expected to take place within June 2018. Nevertheless, descriptions of the data to be provided have been made available to the consortium.

P.APPENDIX 2 contains the descriptions of the retrospective data originating from the four clinical centres participating in BOUNCE. More precisely,
P.Appendix 2A contains the HUS retrospective data description and the respective coding,
P.Appendix 2B contains the HUJI retrospective data description and the respective coding,
P.Appendix 2C contains the IEO retrospective data description,
P.Appendix 2D contains the CHAMP retrospective data description and the respective coding.

R2. Methodology of Retrospective Data Collection

R2.1. Introduction

In this chapter, several indicative aspects of the retrospective data collection procedure are presented through the paradigm of the European Institute of Oncology (IEO). Similar procedures have been adopted by the other clinical partners (HUS, HUJI and CHAMP). In particular, excerpts from the formulation of the IEO data based study description document are presented. The Appendix "R2. APPENDIX" appearing at the end of this chapter presents several existing tools quantifying various BOUNCE related factors. Similar procedures for data collection and management have been followed with respect to retrospective data sets from the other clinical sites.

R2.2. Objectives

The main objective of the BOUNCE-IEO data based study is to collect clinical, biological, psychological and social parameter data able to describe a preliminary resilience trajectory. This study is part of the BOUNCE project. Data collected in the present observational retrospective study are used to build a predictive computer model that will subsequently be tested in a future prospective study. The advanced computational tools to be employed will validate indices of patients' capacity to bounce back during the highly stressful treatment and recovery period following diagnosis of breast cancer. The present study represents a preliminary phase, which is necessary in order to properly design the core of the prospective BOUNCE pilot study that will be deployed in the four clinical cancer centres participating to the European project.

R2.2.1 Primary Endpoint of the Analysis of Retrospective Data

The primary endpoint of this analysis is to survey, in existing breast cancer patient cohorts, the biological, sociodemographic, functional and psychological variables that could influence resilience processes. Biological variables refer to the cancer type, treatment characteristics and medical outcomes. For a detailed list of biological variables, see Table R2.1. Functional variables refer to lifestyle aspects such as sleep, diet habits, and physical activity, that have an impact on the overall functioning (Table R2.2). Sociodemographic data refers sociological (e.g. marital status) and demographic (e.g. age) characteristics (Table R2.3). Finally, psychological variables refer to emotional, cognitive and relational aspects of an individual (Table R2.4).

The aforementioned retrospective data will be collected from existing registries. By harmonizing on the BOUNCE consortium level and factoring all mentioned variables and the interaction between them, an in-silico resilience model will be built by using a partial set of these variables as correlates and predictors of resilience. In the context of a theoretical perspective, these variables will be included in the predictive model, which will be tested in the pilot study. Pertinent literature is provided in the sub-section "R2.9 References".

R2.3. Methods and Study Design

The particular data set has originated from an observational retrospective design: it looks backwards to medical, functional, demographic, and psychometric data collected and stored in the IEO databases and examines the correlation between biological and psychological factors. The data pertains to all the IEO breast cancer patients treated with curative intent until 2017.

All the psychological, functional and biomedicall data that will be extracted from the existing databases is listed in Table R2.1, Table R2.2, Table R2.3 and R2.4.

TABLE R2.1: Medical data (see also appendix P.Appendix 2C for a more precise description of the data provided by IEO)

TNM stage
Nodal status
Date of first diagnostic sampling
Surgery type and side
Menopausal status
Early age menstruation
Nulliparous or pregnancy
Breastfeeding
Family history for tumours
Tumour biology (estrogen, progesterone and HER2 receptor expression, grade and state, vascular invasion, margins)
Ki67
Basic laboratory tests (CBC, Hb, creatinine, bilirubin CRP, ALT)
Imaging results (mammography, CT, ultrasound)
Genetic risk factors
RMI, mammography, echography
Amount of counselling (and support sessions) received during cancer treatment
Psychotropic medication
Disease free survival
Type and duration of treatment (chemotherapy/HT/RT)

TABLE R2.2: Health behaviors data (see also appendix P.Appendix 2C for a more precise description of the data provided by IEO)

Frequency and amount of alcohol consumption
Frequency and type of physical activity
Nutrition and diet

TABLE R2.3: Quality of life related data (see also appendix P.Appendix 2C for a more precise description of the data provided by IEO)

Sexual activity
Sleep
Pain
Fatigue

TABLE R2.4: Functional data (see also appendix P.Appendix 2C for a more precise description of the data provided by IEO)

Return to work
Activities of daily living

Age
Height
Weight (BMI)
Education
Socioeconomic status
Marital status
Number of children

Occupational status
Past/current smoking

TABLE R2.5: Demographic data (see also appendix P.Appendix 2C for a more precise description of the data provided by IEO)

TABLE R2.6: Psychological and Psychosocial data (see also appendix P.Appendix 2C for a more precise description of the data provided by IEO)

Quality of life
Distress
Profile of Mood and emotional state
Resilience
Psycho-cognitive profile

The biological and demographical variables are retrieved from the institutional database for breast cancer patients. The psychological, functional and psychosocial variables are retrieved from databases of specific psychological studies conducted in IEO on breast cancer patients. In "R2. APPENDIX" within this chapter a list of tools and measures applicable to the collected psychological and functional data is provided.

R2.4. Patient Selection: Criteria for Patient Eligibility / Ineligibility

R2.4.1 Participants Population

The goal is to collect as many data sets as possible, in order to obtain the most accurate/representative sample.

Data collection will regard breast cancer patients treated with curative intent until 2017 at the European Institute of Oncology.

R2.4.2 Inclusion Criteria

To be eligible for inclusion in the study, each patient must fulfill the following criteria:

- *Patient has provided in the past a written informed consent for using her data for research*
- *Female 40-65years of age at the time of recruitment of diagnosis*
- *Histologically confirmed invasive early or locally advanced operable breast cancer*
- *Tumour stage I, II and III*
- *Patients receiving any type of systemic treatment regardless of treatment type*

R2.4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded:

- *Presence of distant metastases*
- *History of another malignancy or contralateral invasive breast cancer within the last five years except cured basal cell carcinoma of skin or carcinoma in situ of the uterine cervix*
- *History of early onset (i.e., before 40 years of age) mental disorder (i.e., schizophrenia, psychosis, bipolar disorder, major depression) or severe neurologic disorder (i.e., neurodegenerative disorder, dementia)*
- *Serious other uncontrolled concomitant diseases such as clinically significant (i.e. active) cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease or cardiac arrhythmia not well controlled with medication) or myocardial infarction within the last 12 months.*
- *Major surgery (except breast surgery) within 4 weeks prior to study entry or lack of complete recovery from the effects of major surgery*
- *Treatment for invasive cancer*
- *Treatment for any major illness in the last half year*

R2.5. Procedures to Register a Patient

Not applicable

R2.6. Statistical Procedures

R2.6.1 Statistical Considerations on the Design

Preliminary correlations between heterogeneous information sets related to resilience will be extracted and hypotheses to be used as input to the model will be defined. Biological, clinical treatment, psychological, lifestyle, social and environmental data will be considered. Concrete hypotheses will be formulated based on the correlations to be extracted. To this end both retrospective data from the BOUNCE clinical partners and literature information will be exploited. A broad palette of statistical and machine learning techniques will be used in order to identify risk factors for poor resilience and hidden correlations among data. A methodological approach is described below.

- Univariate (e.g. t-test, chi-squared test, Mann–Whitney U test, Spearman's rank correlation coefficient etc.) and multivariate techniques (e.g. logistic regression, correlation-based feature selection, sequential forward selection, sequential backward elimination, decision trees, naive Bayes etc.) will be performed to identify features of importance.
- Intelligent pattern recognition analysis of an individual's context will be applied to allow the identification of established behaviours and, eventually, cause and effect relationships.
- Given the sequential nature of recorded data, association analysis techniques, able to handle both co-occurrence and dynamic relationships in multivariate time series data, will be utilized.
- Temporal data mining will enable the identification of dynamic patterns or predictive rules in long-term trajectories and, eventually, will allow drawing conclusions regarding the associations between the patient's context - indicating resilience to BC - and the clinical health outcomes, and vice versa. A brief presentation of this approach is provided in chapter 8 [M].

- The identification of groups of patients with similar characteristics will be investigated based upon classification and clustering analysis (e.g.random forests and supporing vector machines, hierarchical clustering, k-means,).

R2.6.2 Sample Size Considerations

The design of the particular retrospective study has an observational character focusing on a specific disease i.e. breast cancer. The aim is to analyse the relationships between biological, psychological and social factors and their influence on resilience among breast cancer patients. Given the number and the heterogeneity of the clinical centres involved in the BOUNCE project, it is not possible to predict a priori the optimal sample size. The goal is to collect as many data sets as possible, in order to obtain the most representative sample.

R2.7. Case Report Forms and Data Management

The particular observational study will be conducted according to the ICH Good Clinical Practice (GCP) guidelines. ICH stands for International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Case Report Forms (CRF) will not be registered, as they have already been collected in the past; they will only be reviewed when necessary.

The European Institute of Oncology Data Management Office will be responsible of the study database and data management.

Keeping accurate and consistent records is essential to a cooperative study. Data must be submitted according to the protocol requirements for ALL patients and participants, including patients deemed to be ineligible.

R2.7.1 Data Collection

The European Institute of Oncology is responsible for collecting and maintaining the documentation for this IEO data based study study as described in the next points. Clinical and biological data extracted and anonymized, will be inserted in the main database.

R2.7.2 Investigators' File

The European Institute of Oncology should keep documentation about this study in an investigators' file, which should include the following documents:

- Protocol and Appendices
- Amendments
- Signed Protocol Signature Pages
- Ethics Committee Approval of Protocol, Amendments
- Correspondence with Ethics Committee

- Agreement with the European Institute of Oncology
- Correspondence with the European Institute of Oncology Data Management Center
- CV of Principal Investigator and co-Investigators
- Authorization Log
- Patient Identification Log
- ICH GCP guidelines/Declaration of Helsinki and Updates

R2.7.2.1 Patient Identification Log

As per GCP, patients have the right to confidentiality. Therefore, no patients' names will be used in any documentation transmitted to and from the European Institute of Oncology.

Items that are used to identify a patient include year of birth and registration number. The local data manager will keep an identification log for all patients entered in this study according to the GDPR legislation. This will include:

- Patient's name
- Patient's initials
- Registration number
- Date of birth
- Date of registration

R2.7.2.2 Authorization Log

The Principal Investigator should identify the other members of the Clinical Study Team who are supervised by the Principal Investigator. This Log should be faxed to the European Institute of Oncology prior to the first patient registration and whenever the information contained in it is updated.

R2.8. Regulatory Approval Procedures

R2.8.1 Ethics Committee

The protocol has been submitted for approval by the Ethics Committee of the Istituto Europeo di Oncologia (IEO).

R2.8.2 Ethical Issues and Data Privacy

The present study has been devised to comply with both national (i.e., GCPs) and international declarations (i.e. Declaration of Helsinki) regulating proper ethical research involving human subjects. By signing the corresponding protocol, the investigator declares to conduct the study in accordance with these regulations and norms.

The study design follows a risk minimization and a benefit maximization requirement, thus promoting non-maleficence and active beneficence towards the category of research participants that are

investigated in the BOUNCE project: breast cancer women. First of all, retrospective data research is important to design the next study more accurately, thus allowing the maximization of the chances of actually predicting resilience. Moreover, it is harmless to patients, as it makes use of material that exists already and does not require further procedures to patients.

R2.9 References

Beck, J. G., Grant, D. M., Read, J. P., Clapp, J. D., Coffey, S. F., Miller, L. M., & Palyo, S. A. (2008). The Impact of Event Scale-Revised: Psychometric properties in a sample of motor vehicle accident survivors. Journal of anxiety disorders, 22(2), 187-198.

Bonanno, G. A., Galea, S., Bucciarelli, A., & Vlahov, D. (2007). What predicts psychological resilience after disaster? The role of demographics, resources, and life stress. Journal of Consulting and Clinical Psychology, 75(5), 671–682. https://doi.org/10.1037/0022-006X.75.5.671

Brady, M. J., Cella, D. F., Mo, F., Bonomi, A. E., Tulsky, D. S., Lloyd, S. R., ... & Shiomoto, G. (1997). Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. Journal of Clinical Oncology, 15(3), 974-986.

Breast Cancer Research Foundation. (n.d.). Retrieved from https://bcrfcure.org/breast-cancer-statistics

Bruenig, D., Mehta, D., Morris, C. P., Harvey, W., Lawford, B., Young, R. M., & Voisey, J. (2017). Genetic and serum biomarker evidence for a relationship between TNFα and PTSD in Vietnam war combat veterans. Comprehensive psychiatry, 74, 125-133.

Cella, D. (1997). Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University, Evanston IL, Version 4.

Cosco, T. D., Howse, K., & Brayne, C. (2017). Healthy ageing, resilience and wellbeing. Epidemiology and Psychiatric Sciences, 26(6), 579–583. https://doi.org/10.1017/S2045796017000324

Deshields, T. L., Heiland, M. F., Kracen, A. C., & Dua, P. (2016). Resilience in adults with cancer: development of a conceptual model. Psycho-Oncology, 25(1), 11–18. https://doi.org/10.1002/pon.3800

Drageset, S., Lindstrøm, T. C., & Underlid, K. (2010). Coping with breast cancer: between diagnosis and surgery. Journal of Advanced Nursing, 66(1), 149–158. https://doi.org/10.1111/j.1365-2648.2009.05210.x

Felger, J. C., Li, Z., Haroon, E., Woolwine, B. J., Jung, M. Y., Hu, X., & Miller, A. H. (2016). Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Molecular psychiatry, 21(10), 1358.

Goldberg DP, Gater R, Sartorius N, Üstün TB, Piccinelli M, Gureje O, Rutter C. (1997). The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med, 27: 191–7.

E. O. R. T. C. (n.a.) EORTC QLQ–BR23.

E.O.R.T.C. (1993). EORTC QLQ-30.

Extermann, M., Overcash, J., Lyman, G. H., Parr, J., & Balducci, L. (1998). Comorbidity and functional status are independent in older cancer patients. Journal of Clinical Oncology, 16(4), 1582-1587.

Friborg, O., Hjemdal, O., Rosenvinge, J. H., & Martinussen, M. (2003). A new rating scale for adult resilience: What are the central protective resource behind healthy adjustment? International Journal of Methods in Psychiatric Research, 12(2), 65-76.

Gorini, A., Mazzocco, K., Gandini, S., Munzone, E., McVie, G., & Pravettoni, G. (2015). Development and psychometric testing of a breast cancer patient-profiling questionnaire. Breast Cancer : Targets and Therapy, 7, 133–146. http://doi.org/10.2147/BCTT.S80014

Graffigna, G., Barello, S., Bonanomi, A., & Lozza, E. (2015). Measuring patient engagement: development and psychometric properties of the Patient Health Engagement (PHE) Scale. Frontiers in Psychology, 6, 274. http://doi.org/10.3389/fpsyg.2015.00274

Bonanno, G. A., Galea, S., Bucciarelli, A., & Vlahov, D. (2007). What predicts psychological resilience after disaster? The role of demographics, resources, and life stress. Journal of Consulting and Clinical Psychology, 75(5), 671–682. https://doi.org/10.1037/0022-006X.75.5.671

Brady, M. J., Cella, D. F., Mo, F., Bonomi, A. E., Tulsky, D. S., Lloyd, S. R., ... & Shiomoto, G. (1997). Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. Journal of Clinical Oncology, 15(3), 974-986.

Breast Cancer Research Foundation. (n.d.). Retrieved from https://bcrfcure.org/breast-cancer-statistics

Bruenig, D., Mehta, D., Morris, C. P., Harvey, W., Lawford, B., Young, R. M., & Voisey, J. (2017). Genetic and serum biomarker evidence for a relationship between TNFα and PTSD in Vietnam war combat veterans. Comprehensive psychiatry, 74, 125-133.

Cella, D. (1997). Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University, Evanston IL, Version 4.

Cosco, T. D., Howse, K., & Brayne, C. (2017). Healthy ageing, resilience and wellbeing. Epidemiology and Psychiatric Sciences, 26(6), 579–583. https://doi.org/10.1017/S2045796017000324

Deshields, T. L., Heiland, M. F., Kracen, A. C., & Dua, P. (2016). Resilience in adults with cancer: development of a conceptual model. Psycho-Oncology, 25(1), 11–18. https://doi.org/10.1002/pon.3800

Drageset, S., Lindstrøm, T. C., & Underlid, K. (2010). Coping with breast cancer: between diagnosis and surgery. Journal of Advanced Nursing, 66(1), 149–158. https://doi.org/10.1111/j.1365-2648.2009.05210.x

Felger, J. C., Li, Z., Haroon, E., Woolwine, B. J., Jung, M. Y., Hu, X., & Miller, A. H. (2016). Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Molecular psychiatry, 21(10), 1358.

Goldberg DP, Gater R, Sartorius N, Üstün TB, Piccinelli M, Gureje O, Rutter C. (1997). The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med, 27: 191–7.

E. O. R. T. C. (n.a.) EORTC QLQ–BR23.

E.O.R.T.C. (1993). EORTC QLQ-30.

Extermann, M., Overcash, J., Lyman, G. H., Parr, J., & Balducci, L. (1998). Comorbidity and functional status are independent in older cancer patients. Journal of Clinical Oncology, 16(4), 1582-1587.

Friborg, O., Hjemdal, O., Rosenvinge, J. H., & Martinussen, M. (2003). A new rating scale for adult resilience: What are the central protective resource behind healthy adjustment? International Journal of Methods in Psychiatric Research, 12(2), 65-76.

Gorini, A., Mazzocco, K., Gandini, S., Munzone, E., McVie, G., & Pravettoni, G. (2015). Development and psychometric testing of a breast cancer patient-profiling questionnaire. Breast Cancer : Targets and Therapy, 7, 133–146. http://doi.org/10.2147/BCTT.S80014

Graffigna, G., Barello, S., Bonanomi, A., & Lozza, E. (2015). Measuring patient engagement: development and psychometric properties of the Patient Health Engagement (PHE) Scale. Frontiers in Psychology, 6, 274. http://doi.org/10.3389/fpsyg.2015.00274

Lawton, M.P., and Brody, E.M. "Assessment of older people: Self-maintaining and instrumental activities of daily living." Gerontologist 9:179-186, (1969).

Mendoza, T. R., Wang, X. S., Cleeland, C. S., Morrissey, M., Johnson, B. A., Wendt, J. K. and Huber, S. L. (1999), The rapid assessment of fatigue severity in cancer patients. Cancer, 85: 1186–1196. doi:10.1002/(SICI)1097-0142(19990301)85:5<1186::AID-CNCR24>3.0.CO;2-N.

Michels, F. A., Latorre, M. D. R., & Maciel, M. D. S. (2010). Validation, reliability and comprehension of the IBCSG quality of life questionnaire specific to breast cancer. Appl. cancer res, 30(4), 348-352.

Mitchell, A. J., Baker-Glenn, E. A., Granger, L., & Symonds, P. (2010). Can the Distress Thermometer be improved by additional mood domains? Part I. Initial validation of the Emotion Thermometers tool. Psycho-Oncology, 19(2), 125-133.

O'Donnell, E., D'Alton, P., O'Malley, C., Gill, F., & Canny, Á. (2013). The distress thermometer: a rapid and effective tool for the oncology social worker. International journal of health care quality assurance, 26(4), 353-359.

Paykel, E. S. (1997). The interview for recent life events. Psychological medicine, 27(2), 301-310

Parker G, Tupling H, Brown L. (1979). A parental bonding instrument. Br J Med Psychol, 52:1–10

Spielberger CD, Jacobs G, Russell S, Crane R. (1983). Assessment of Anger: the State-Trait Anger Scale. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Inc.; Palo Alto, CA.

Takeuchi, H., Kawanaka, H., Fukuyama, S., Kubo, N., Hiroshige, S., & Yano, T. (2017). Comparison of the prognostic values of preoperative inflammation-based parameters in patients with breast cancer. PloS one, 12(5), e0177137.

WHO. (n.d.). Retrieved from https://www.who.int/cancer/detection/breastcancer/en/

Wills, T. A., & Bantum, E. O. (2012). Social Support, Self-Regulation, and Resilience in Two Populations: General-Population Adolescents and Adult Cancer Survivors. Journal of Social and Clinical Psychology, 31(6), 568–592. https://doi.org/10.1521/jscp.2012.31.6.568

Zigmond, AS; Snaith, RP (1983). "The hospital anxiety and depression scale". Acta Psychiatrica Scandinavica. 67 (6): 361–370. doi:10.1111/j.1600-0447.1983.tb09716.x. PMID 6880820.

Holmes, K. (2006). Adolescent resilience: The influence of family relationships and their impact on resilient outcomes. ETD Collection for Fordham University, AAI3223401.

Van Schoors, M., Caes, L., Verhofstadt, L. L., Goubert, L., & Alderfer, M. A. (2015). Systematic review: Family resilience after pediatric cancer diagnosis. Journal of pediatric psychology, 40(9), 856-868.

R2.APPENDIX

Several Existing Tools Quantifying Various BOUNCE Related Factors

It is noted that part of the tools will also be used in the prospective BOUNCE study. References are linked to the section "R2.9 References" above.

Activities of Daily Living Index (Externmann et al., 1998)

This is a standardised measure of biological and psychosocial functioning.

ALGA (Gorini et al., 2013, 2015)

ALGA's main aim is to provide an accurate profile of the patient's cognitive and psychological status helping the physician shape their language and messages to maximize the patient's understanding of their management options. The 29 items questionnaire is divided in eight key factors: global self-rated health, perceived physical health, anxiety, self-efficacy, cognitive closure, memory, body image, and sexual life.

The Brief Fatigue Inventory (BFI) (Mendoza, 1999)

A measure to rapidly assess the severity and impact of fatigue in cancer patients. Its 9 items investigate three factors: Fatigue right now: Usual fatigue in last 24 hours: Worst fatigue in last 24 hours.

The Distress Thermometer (O'Donnell et al., 2013)

This is a simple, self-report, pencil and paper measure consisting of a line with a 0-10 scale anchored at the zero point with "No distress" and at scale point ten with "Extreme distress". Patients are given the instruction, "How distressed have you been during the past week on a scale of 0-10"? Patients indicated their level of distress with a mark on the scale. Patients scoring 4 or above were regarded as requiring intervention. It includes a problem checklist. The patient is asked to identify those problems from the checklist which are contributing to their score.

Emotion Thermometer (Mitchell et a., 2010)

It is a simple five-dimensional screening tool in the form of four predictor domains (distress, anxiety, depression, anger) and one outcome domain (need for help).

The EORTC QLQ-BR23 (E.O.R.T.C.)

It is a breast-specific module of the EORTC QLQ that comprises of 23 questions to assess body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss.

The EORTC QLQ-C30 (E.O.R.T.C., 1993)

It is a questionnaire developed to assess the quality of life of cancer patients. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.

The FACIT Measurement System (Cella, 1997)

It is a 16-item questionnaire of health-related quality of life (HRQOL) questionnaires targeted to the management of chronic illness.

Family Resilience Measure (FaRe)

This questionnaire developed by IEO assesses family resilience in a systemic approach and is composed of 24 items divided into four factors: Communication and Cohesion, Perceived Social Support, Perceived Family Coping, Religiousness and Spirituality.

Functional Assessment of Cancer Therapy-Breast (FACT-B) (Brady et al., 1997)

A 44-item self-report instrument designed to measure multidimensional quality of life (QL) in patients with breast cancer, developed with an emphasis on patients' values and brevity.

General Health Questionnaire (Goldberg, 1997)

It is a screening device detecting the risk of developing mild short-term psychiatric disorders or to detect recent psychic well-being. It investigates the area of somatic symptoms, anxiety, social disorders, and depression.

Hospital Anxiety and Depression scale (HADs) (Zigmond & Snaith, 1983)

It is a fourteen item scale, seven of the items relate to anxiety and seven relate to depression. The anxiety and depressive subscales are also valid measures of severity of the emotional disorder.

The IBCSG Quality of Life Core Questionnaire (Michels et al., 2010)

It is used to evaluate selected components of HRQoL. The questionnaire is a breast cancer specific questionnaire, designed to cross-culturally measure quality of life on and off different treatment regimens. It consists of 10 single-item visual analogue scales.

The Impact of Event Scale–Revised (IES-R) (Beck et al., 2008)

A 22-item self-report measure that assesses subjective distress caused by traumatic events. The tool assesses intrusive thinking, behavioural avoidance of traumatic event and hyper arousal symptoms.

Instrumental Activities of Daily Living Scale (Lawton & Brody, 1963)

It assesses everyday functional competence, specifically developed for an older population of patients.

Interview for recent life events (Paykel, 1997)

This semi-structured interview covers a comprehensive range of recent life events, their timing and other important qualities. 63 event-specific variables are included. These are divided into nine categories of life events: work; education; finance, health, bereavement, migration, courtship and cohabitation; legal; family and social relationships.

The Parent Bonding Instrument (Parker et al., 1979)

The PBI is a 25 items questionnaire that estimates the parental style as reported by the son or daughter. It investigates two attributes of parenting behaviour: care and overprotection.

Patient Health Engagement Scale (Graffigna et al., 2015)

It is a brief instrument of 5 items. This questionnaire is a measure of patient engagement.

Profile of Mood States (Baker et al., 2002)

The Profile of Mood States is a self-report questionnaire aiming to assess transient distinct mood states through 37-items divided in six factor-based subscales: Tension–Anxiety, Depression– Dejection, Anger–Hostility, Fatigue–Inertia, Vigor– Activity, and Confusion– Bewilderment.

Resilience Scale for Adults (RSA) (Friborg et al., 2003)

The RSA is a self-report scale for measuring protective resilience factors (intrapersonal and interpersonal) that promote the adaptation of adversity. The resilience factors are divided into 6 subscales: Perception of self. Planned future. Social competence, Structured style. Family cohesion and Social resources.

State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983)

It is a 40 item questionnaire that assesses trait and state anxiety. It is used in clinical settings to diagnose anxiety and to discriminate between anxiety as a symptom and anxiety as a habitual way of responding to external stimuli.

5[A]. Preliminary Correlation Analyses using the Retrospective BOUNCE Data [Code Letter: A]

A1 Preliminary Correlation Analysis with Retrospective data: The HUS Dataset

A1.1 Dataset description

The data following anonymization has been provided by Dr. Paula Poikonen-Saksela, Helsinki University Hospital Comprehensive Cancer Center, Finland within the framework of the BOUNCE EU funded project. The study details and outcome have been previously described [Saarto et al. 2012]. A short summary is provided here.

Researchers involved in the data collection: Tiina Saarto, Heidi Penttinen, Carl Blomqvist, Leena Vehmanen, Meri Utriainen et al

Aim: The study aimed at determining whether physical exercise training improves the quality of life (QoL) and physical fitness of breast cancer survivors.

Patients: The multiscale data used in the present work originates from a cohort of 573 patients enrolled by the Departments of Oncology at Helsinki, Tampere and Turku University Hospitals, for the purposes of BREX (BReast cancer and EXercise) study. The BREX study was a large open randomized clinical study of breast cancer survivors participating in a physical exercise intervention, shortly after adjuvant treatment, i.e. during the rehabilitation period. Patients were randomized into an exercise or a control group, 12-months after adjuvant treatments.

Inclusion criteria included: (1) histologically-proven invasive breast cancer T1-4N0-3M0; (2) pre- or post-menopausal breast cancer patient treated with adjuvant chemotherapy or radiotherapy within 4 months, or patient who has started adjuvant endocrine therapy (antiestrogens, aromatase inhibitors, LHRH agonists, or combinations) no less than 4 months earlier; (3) age between 35 and 68 years; and (4) signed informed consent prior to beginning specific protocol procedures.

Exclusion criteria included: (1) male gender; (2) prior malignancy except basal cell carcinoma or in situ cervix carcinoma; (3) haematogenous metastases (M1); (4) no systemic adjuvant therapy; (5) post-menopausal women with antiestrogens as the only adjuvant treatment (with/without radiotherapy); (6) pregnancy or recent lactation (<1 year); (7) severe cardiac disease (New York Heart Association class III or greater), myocardial infarction within 12 months, uncontrolled hypertension; (8) verified osteoporosis (proximal femur or lumbar spine t-score ≥ –2.5 or fracture without trauma); (9) concomitant medications affecting calcium and bone metabolism such as bisphosphonates, calcitonin, parathormone (PTH), selective estrogen receptor modulators (SERMs), oral corticosteroids (over 6 months), anticonvulsants (fenytoin, carbamatsebin) and prolonged heparin therapy; (10) other diseases affecting calcium and bone metabolism, such as hyperthyroidism, newly diagnosed hypothyroidism, primary hyperparathyroidism, renal failure, chronic hepatic diseases, organ transplant; (11) other serious illness or medical condition which could be contraindication for exercise; (12) patient not capable of training (severe knee arthritis, severe ligament or cartilage injuries at lower extremities); (13) residence more than one hour from the exercise centre; (14) competitive athlete.

Sample: Data are provided at baseline and after 3, 6, 12, 18, 24, 30 and 36 months. The HUS retrospective data include:

- **Clinical data:** age, WHO class, menstruation after chemotherapy, menopausal status, menopause age, BMI, weight, height, bone mineral density, total kolesterol levels, Blood Glucose, Blood Pressure, pulse, any other disease also psychiatric, basic health status, disability status, physical pain

- **Breast and treatment data:** tumour size, pT, pN, histological type, metastatic lymph modes, receptor status (estrogen, progesterone), Her2 expression, type of breast surgery, type of axillary operation, type of treatment (herceptin, chemotherapy, radiotherapy, endocrine treatment)

- **SocioDemographics:** years of education, marital status, number of children, employment status, reason for not working

- **History and Life Style:** competing athlete, smoking, frequency and amount of alcohol consumption, reduced fat in the diet, increased vegetables, increased the amount of exercise etc.

- **Physical performance and activity:** mean figure 8 running, mean 2-km walking test, leisure time physical activity, self-reported physical activity, MET (metabolic equivalent)

- **Psychosocial self-report questionnaires:**

  - **EORTC QLQ- C30:** A questionnaire of 30 items developed to assess the quality of life of cancer patients. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.

  - **EORTC QLQ- BR23**: It is a breast-specific module of the EORTC QLQ that comprises of 23 questions to assess body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss.

  - **WHQ** women's health questionnaire: It contains 37 items distributed among nine domains: depressed mood, somatic symptoms, memory/concentration, vasomotor symptoms, anxiety/fear, sexual behaviour, sleep problems, menstrual symptoms and attractiveness.

  - **FACIT-F** - Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire: It is a 13-item compilation of general questions that measures an individual's level of fatigue during their usual daily activities over the past week.

  - **BDI** - Beck Depression Inventory short form: Finnish modified version of Beck's 13-item depression scale (**R-BDI**). The short form of Beck Depression Inventory is a screening instrument for assessing depressive symptomatology among the following domains: mood, pessimism, sense of failure, dissatisfaction, guilt, self-hate, suicide, social withdrawal, indecisiveness, body image, work inhibition, fatigue and appetite.

    A detailed listing of the data descriptions that were disseminated by HUS to BOUNCE partners is attached in P. APPENDIX 2A. The time points that each type of data were collected are summarized in the following Table A1.

TABLE A1 Time availability of HUS retrospective data.

HUS dataset	T1 Baseline	T2 after 3 mouths	T3 after 6 months	T4 after 12 months	T5 after 18 months	T6 after 24 months	T7 after 30 months	T8 after 36 months
Number of Participants	573	410	487	504	451	456	436	469
Breast and treatment data	✓							
Clinical data*	✓			✓				✓
Self – report clinical data**			✓	✓	✓	✓	✓	✓
SocioDemographic	✓		✓	✓	✓	✓	✓	✓
History	✓							
Life Style	✓		✓	✓	✓	✓	✓	✓
Physical performance	✓			✓				✓
Physical activity	✓		✓	✓	✓	✓	✓	✓
Psychosocial self-report questionnaires	✓	✓	✓	✓	✓	✓	✓	✓
***Reported by clinical personnel ** Comorbidities (including psychiatric diseases), health status, disability status, physical pain**								

A1.2 Preparing the data

Preprocessing steps of the retrospective data received by HUS included:

- Translation from Finish to English of approximately 2000 variables in the dataset based on dataset descriptions provided by HUS along with data
- Reduction of data set to the relevant variables
- Reduction of data redundancy
- Re-formatting and re-organization of data for consistency purposes and to facilitate subsequent analysis
- Realization of basic descriptive statistics

Interaction between ICCS and HUS took place to clarify open issues. The interaction was still ongoing at the time of deliverable preparation.

The dataset suffered from a considerable amount of missing data. In order to have a sufficient sample size for accurate estimations, some variables had to be excluded due to (a) too many missing values, (b) all cases falling in only one category and (c) consisting of very few events (<10) in the less frequent category (for bi-categorical variables).

Grouping of categories in variables with detailed coding was considered in certain cases. Continuous variables, such as age, number of positive lymph nodes and tumour size, were also transformed into categorical variables based on recognized cut-off values.

It is noted that one total score for FACIT and BDI questionnaires and the suggested sub-scores for QLQ-C30, QLQ-BR23 and WHQ questions are considered in the subsequent analyses. Alternative approaches will be considered in future work (i.e. Deliverable 4.2 due to M12), e.g. separately analyzing each item of the questionnaires or creating separate groups of items.

A1.3 Patients characteristics

The characteristics of the HUS study group at baseline are presented in Table A2. The sample included only women, who on average had undergone surgery approximately 33 weeks (mean value) prior to participating in the study (Saarto et al. 2012), whereas last chemotherapy cycle and radiotherapy session took place approximately 11.6 and 4 weeks (mean values) respectively, prior study participation (Saarto et al. 2012).

The proportion of missing values varies over time (Table A1). The response rate to the questionnaires (i.e. the percentage of patients have data at a specific time point) at month 3, month 6, month 12, month 18, month 24, month 30, month 36 and follow-up is approximately 72%, 85%, 88%, 79%, 80%, 76%, 82% and 100% respectively. It is noted that even though the overall response rate is high, there are many missing values among responders at a given time point. Characteristically there is no complete case, i.e. a patient with all variables available at all time points. The number of complete cases depends on the selected variables for univariate or multivariate analysis (either statistical or machine-learning).

TABLE A2 Patient clinical and demographic characteristics at baseline

Variables	Counts/ Mean(range)	%/SD	Variables	Counts	%
General and Demographics			*Breast cancer and Treatment data*		
Age	52.5 (35-68)	7.6	Estrogen receptor		
Years of education	13.9 (7-27)	3.4	Positive	443	82.0%
Births	1.8 (0-6)	1	Negative	97	18.0%
Exercise group			Progesterone receptor		
No	271	47.3%	Positive	362	67.0%
Yes	302	52.7%	Negative	178	33.0%
Marital status			pT		
Married or cohabitation	320	66.5%	T1	291	53.9%
Divorced	79	16.4%	T2	208	38.5%
Not married	62	12.9%	T3	32	5.9%
Widow	19	4.0%	T4	7	1.3%
Other	1	0.2%	Tis	1	0.2%
Type of work			Tx	1	0.2%
Agricultural	2	0.4%	pN		
Factory, mine, construction	9	1.9%	N1	205	38.0%
Office, service	322	69.4%	N0	178	33.0%
Study or school	4	0.9%	N2	64	11.9%
Housewife	17	3.7%	N1mi	51	9.4%
Retired	76	16.4%	N3	25	4.6%
Unemployed	12	2.6%	N0i+	17	3.1%
Other	22	4.7%	Grade		
Menopause status before adjuvant therapy			G2	242	44.8%
Postmenopausal	284	52.6%	G3	214	39.6%
Premenopausal	256	47.4%	G1	79	14.6%
			GX	5	0.9%
			Breast surgery, final		
			Mastectomy	278	51.5%
			Breast-conserving	261	48.3%
			Axillary operation, final		
			Dissection	405	75.0%
			Sentinel node biopsy	134	24.8%
			Adjuvant chemo		
			Yes	495	91.7%
			No	45	8.3%
			Radiotherapy		
			Yes	422	78.1%
			No	118	21.9%
			Herceptin		
			No	527	98.9%
			Yes	6	1.1%
			ET		
			Yes	447	82.8%
			No	93	17.2%

A1.4 Case Study: Inter Scale Correlations

Analysis plan

The present study examines the correlations among the various QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scales. It is expected that conceptually related scales (e.g., physical functioning and fatigue) would correlate substantially with one another (correlation coefficient $r > 0.5$). Conversely, those scales with less in common (e.g., role functioning and constipation) are expected to exhibit lower correlations ($r < 0.5$). The correlation was performed using the Pearson method, which measures a linear dependence between two variables. The rcorr( ) function of R in the Hmisc package was applied to produce Pearson correlations. Only complete cases are considered in the above analysis. Only pairwise complete cases were analyzed.

Results

The following figures (A1 – A8) present the correlations among a) the 15 scales of the QLQ-C30 related to functioning (physical, role, cognitive, emotional, social, overall quality of life), symptoms (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea) and financial impact, b) the 8 scales of QLQ-BR23 related to functioning (body image, sexual functioning, sexual enjoyment and future perspective) and symptoms (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss), c) the 9 scales of the WQH related to emotional experience (anxiety and fears, perceived physical attractiveness, depressed mood) and symptoms (memory and concentration, menstrual, somatic, vasomotor, sleep, sexual), d) the BDI score (level of depression) and e) FACIT-F score (level of fatigue) for baseline and months 3, 6, 18, 24, 30, 36 from the study onset.

Of importance is the consistency observed among the correlations at different time points. The correlation 'schema' remains practically the same throughout the 3-year observation window, with a few exceptions. Moderately higher correlations are observed the third year. The meaning and importance of the latter finding needs to be further investigated.

As expected, the strongest correlations at all time points are observed between the scales with similar conceptual meaning i.e. between the fatigue scores of C30 and FACIT-F questionnaires, between the depression scores of WHQ and BDI questionnaires ($|r| > 0.7$) and between the WHQ sleep problems and C30 insomnia scales ($|r| \sim 0.6$). Strong correlations are also observed between C30 sexual enjoyment and C30 sexual functioning scales and WHQ sexual behaviour(M3-M36: $r \sim 0.56$-0.69, Baseline: $r \sim 0.47$-0.6). However, because each scale is assessing different components of the same psychological or functional construct, the correlations are not perfect (i.e. not very close to 1).

Overall, the global quality-of-life scale (C30) correlates strongly with the fatigue scale, both FACIT-F and C30, ($|r| > 0.57$) and substantially with depression, both WHQ ($r \sim 0.5 – 0.58$) and BDI scales ($r \sim$ -0.54- -0.63), and physical, role, and social functioning ($r \sim 0.5$ - 0.6). A low correlation between emotional functioning and quality of life is observed at baseline; however, this becomes stronger in the subsequent months (r up to 0.6). The body image and the systemic therapy side effects scales of the BR23 questionnaire exhibit a moderate correlation with global quality-of-life ($|r|$ between 0.4 and 0.5).

Among C30 functioning scales, a substantial correlation exists at all time points between emotional and cognitive functioning scales ($r \sim 0.53$-0.63) and between social and role functioning scales ($r \sim 0.54$-0.67).

C30 Emotional functioning correlates strongly with depression scales, both WHQ and BDI, WHQ anxiety scale and FACIT-F fatigue scale ($|r| \sim 0.57 – 0.69$).

The C30 Cognitive functioning scale correlates strongly with WHQ memory scale ($r \sim 0.61 – 0.69$), FACIT-F fatigue scale ($r \sim 0.57 – 0.65$) and BDI depression scale ($|r| \sim 0.54 – 0.63$).

The C30 Physical functioning scale has the strongest correlation with both FACIT-F and C30 fatigue scales ($|r| \sim 0.6$).

A strong correlation is noted between C30 role functioning with fatigue scales (FACIT-F and C30) ($|r| \sim 0.57$).

Depression correlates substantially with WHQ anxiety and sleep scales and C30 insomnia ($|r| \sim 0.5 – 0.6$).

Fatigue (FACIT F and to a lesser extend C30) exhibits a substantial correlation with all functioning scales of C30 questionnaire, as well as WHQ somatic and memory scales ($|r| \sim 0.51 – 0.62$).

FACIT-F fatigue score is highly correlated with the BDI depression score ($r < - 0.65$).

A strong correlation is observed between BR23 body image, WHQ attractiveness and depression, (both WHQ and BDI) scales ($|r| \sim 0.54 - 0.6$)

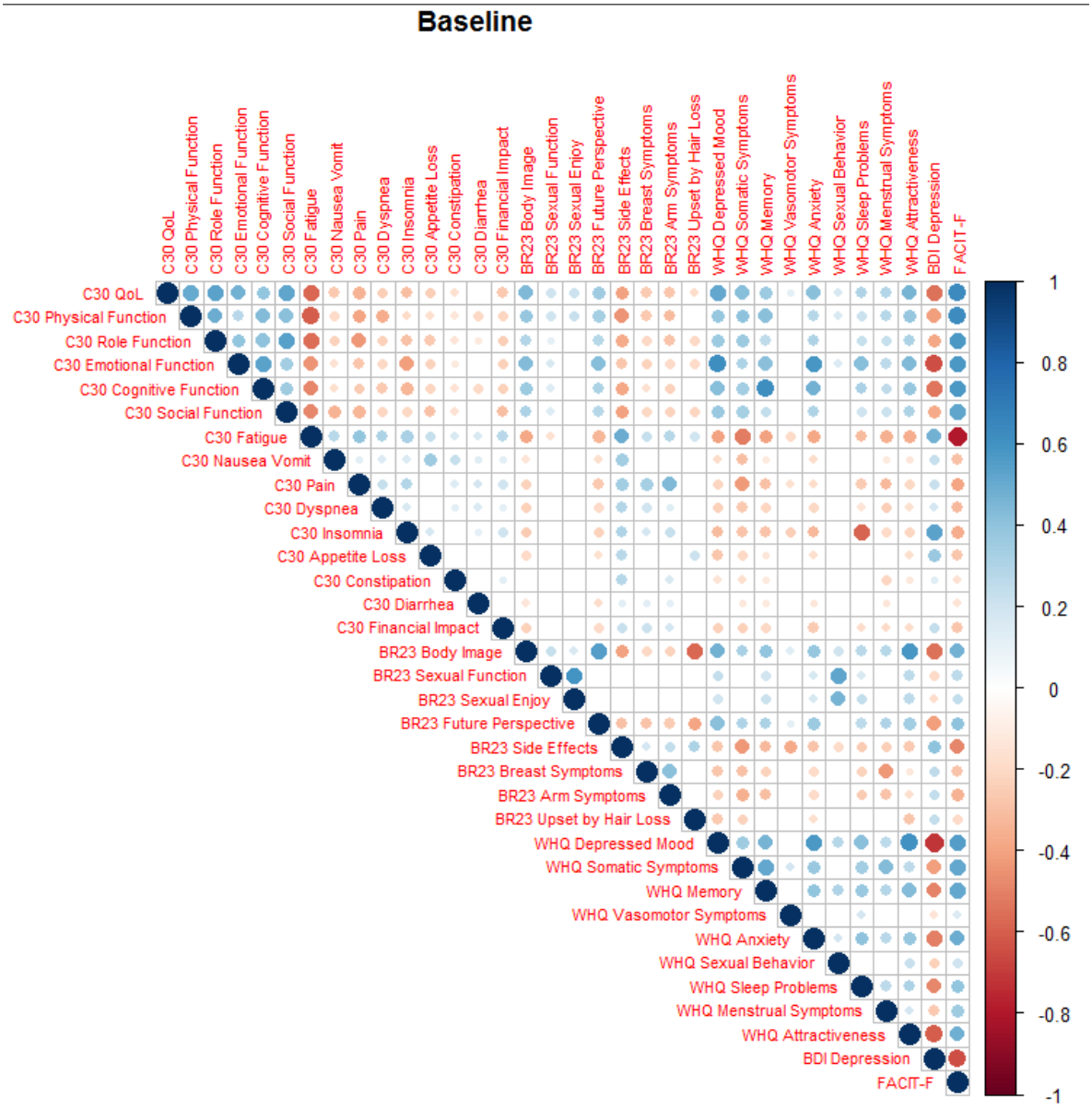


Figure A1 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 upset by hair loss, the B23 sexual enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 200 to 306. In all other variable pairs, the complete cases ranged from 457 to 571.

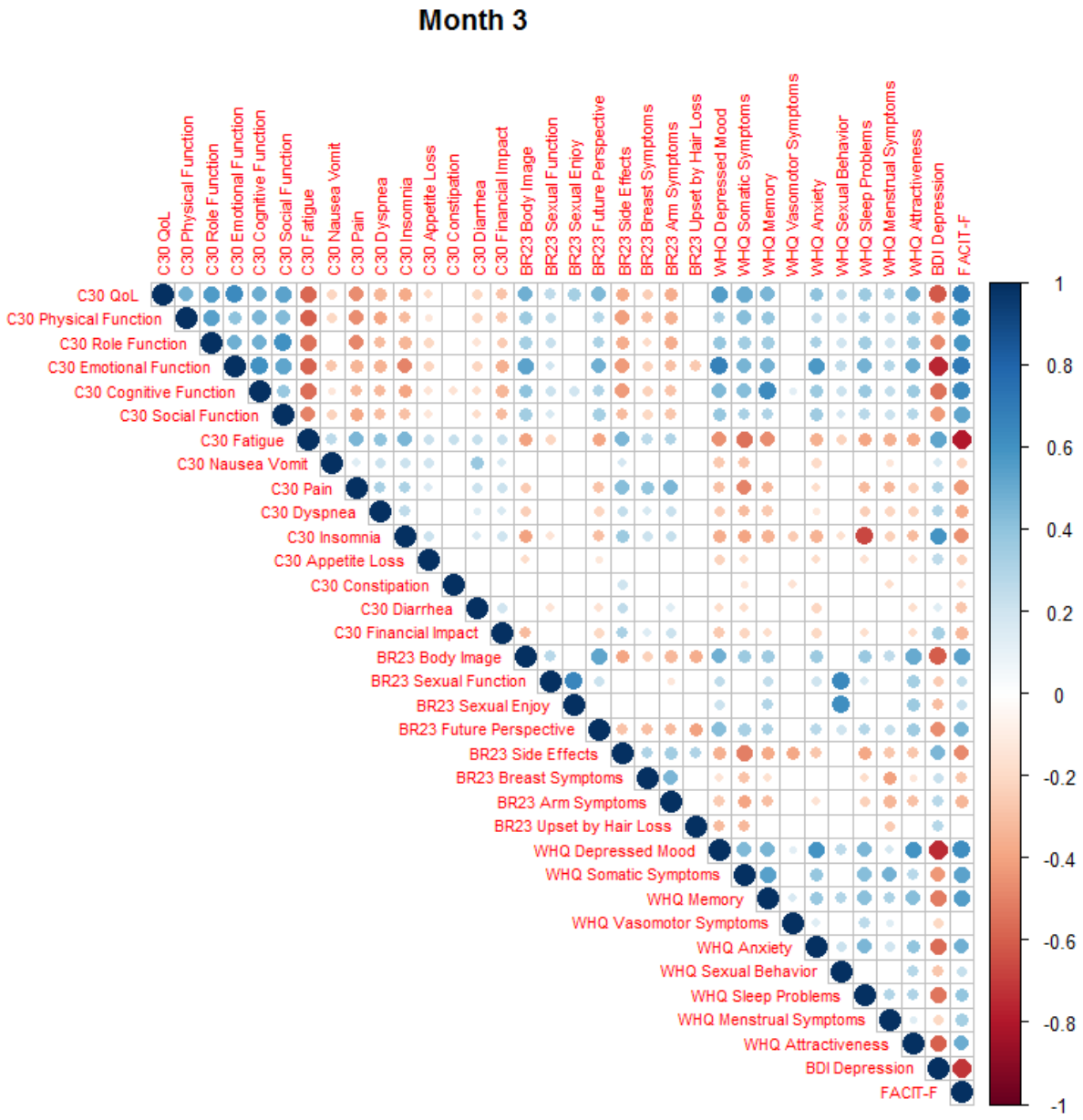


Figure A2 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 3 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 Upset by hair loss, the B23 sexual enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 99 to 241. In all other variable pairs, the complete cases ranged from 339 to 410.

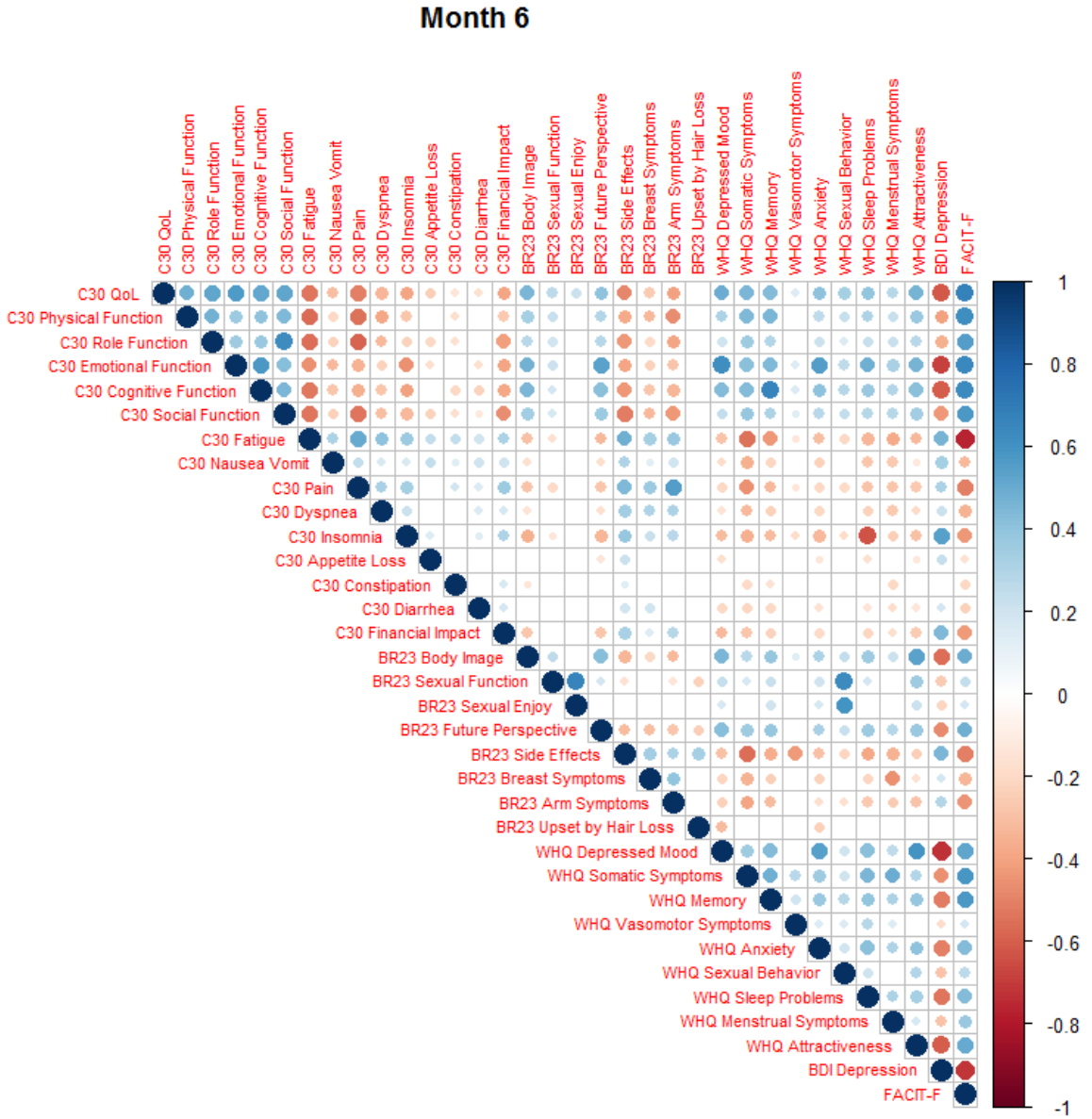


Figure A3 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 6 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 upset by hair loss, the B23 sexual enjoyment and WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 120 to 296. In all other variable pairs, the complete cases ranged from 409 to 486.

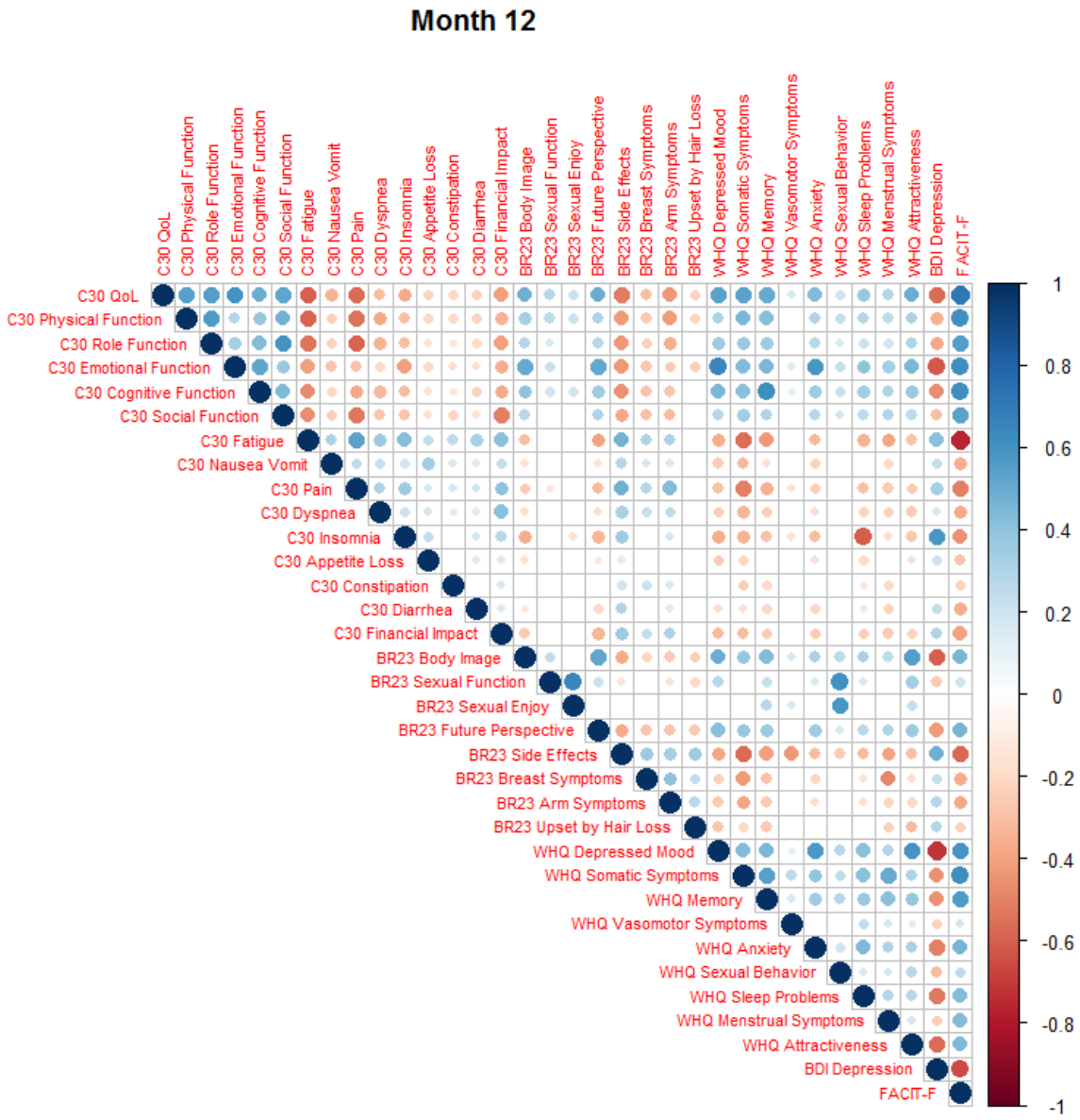


Figure A4 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 12 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 upset by hair loss, the B23 sexual enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 190 to 284. In all other variable pairs, the complete cases ranged from 395 to 468.

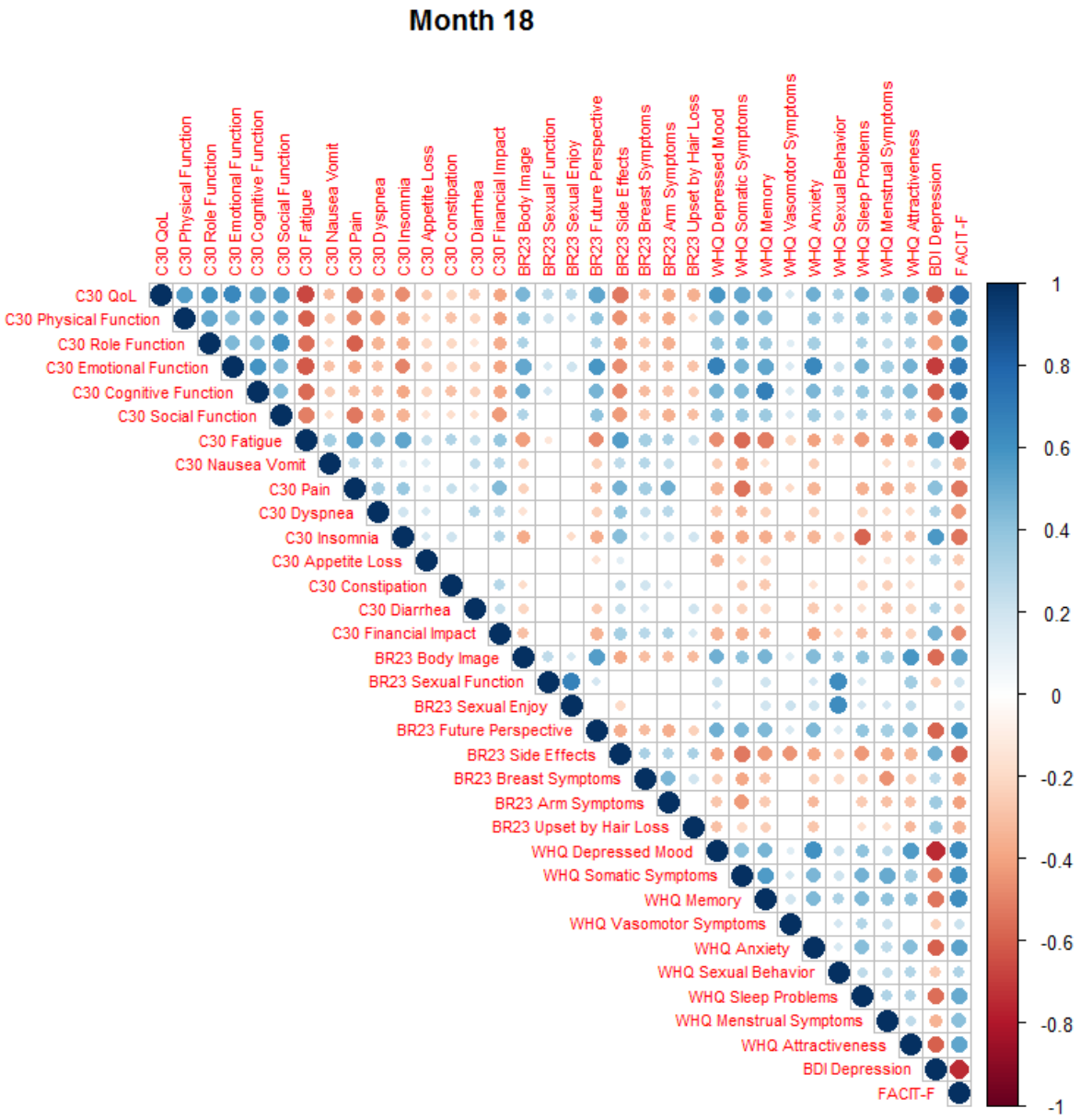


Figure A5 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 18 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 upset by hair loss, the B23 enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 199 to 275. In all other variable pairs, the complete cases ranged from 366 to 434.

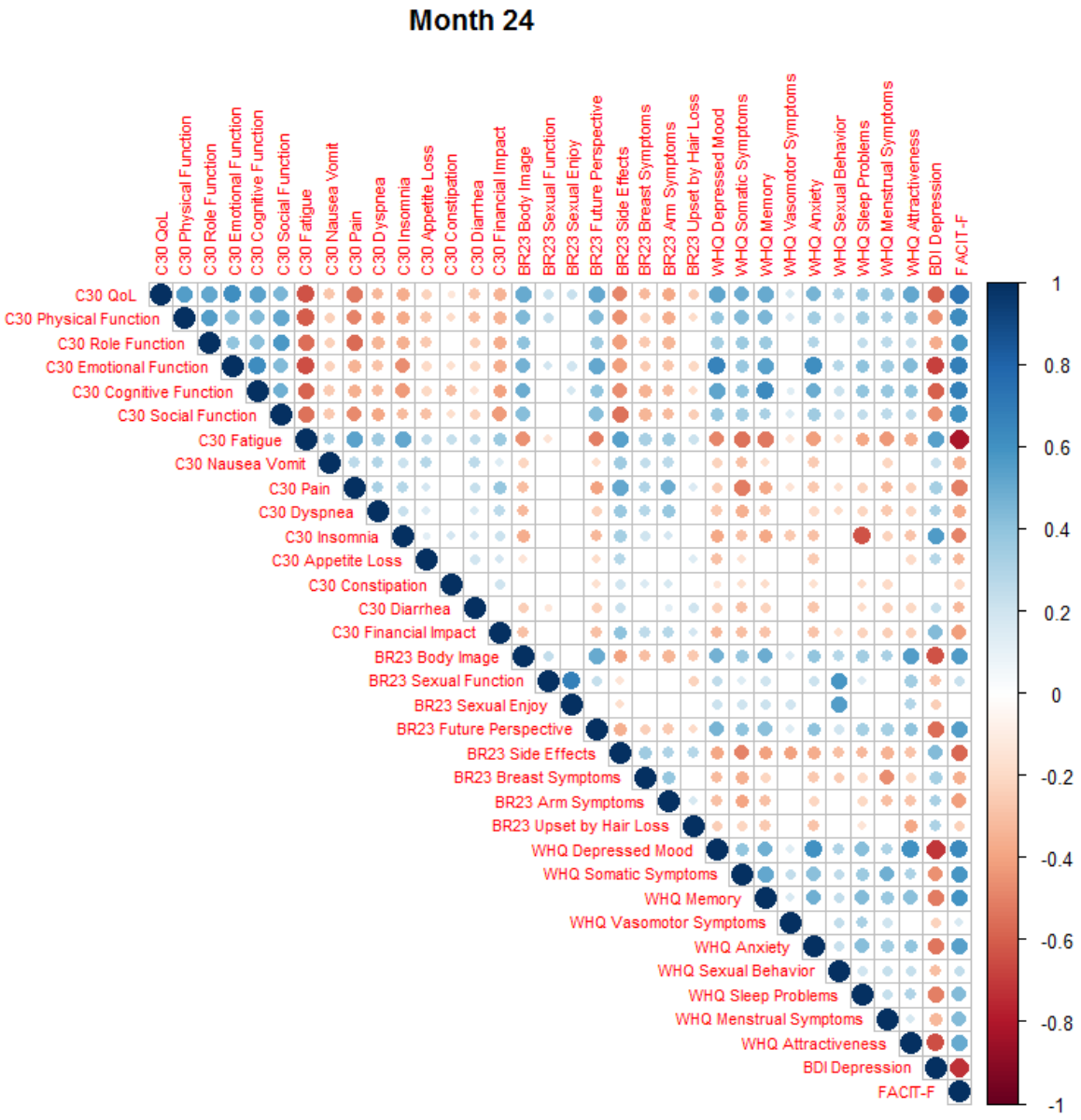


Figure A6 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 24 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 upset by hair loss, the B23 sexual enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 193 to 321. In all other variable pairs, the complete cases ranged from 363 to 433.

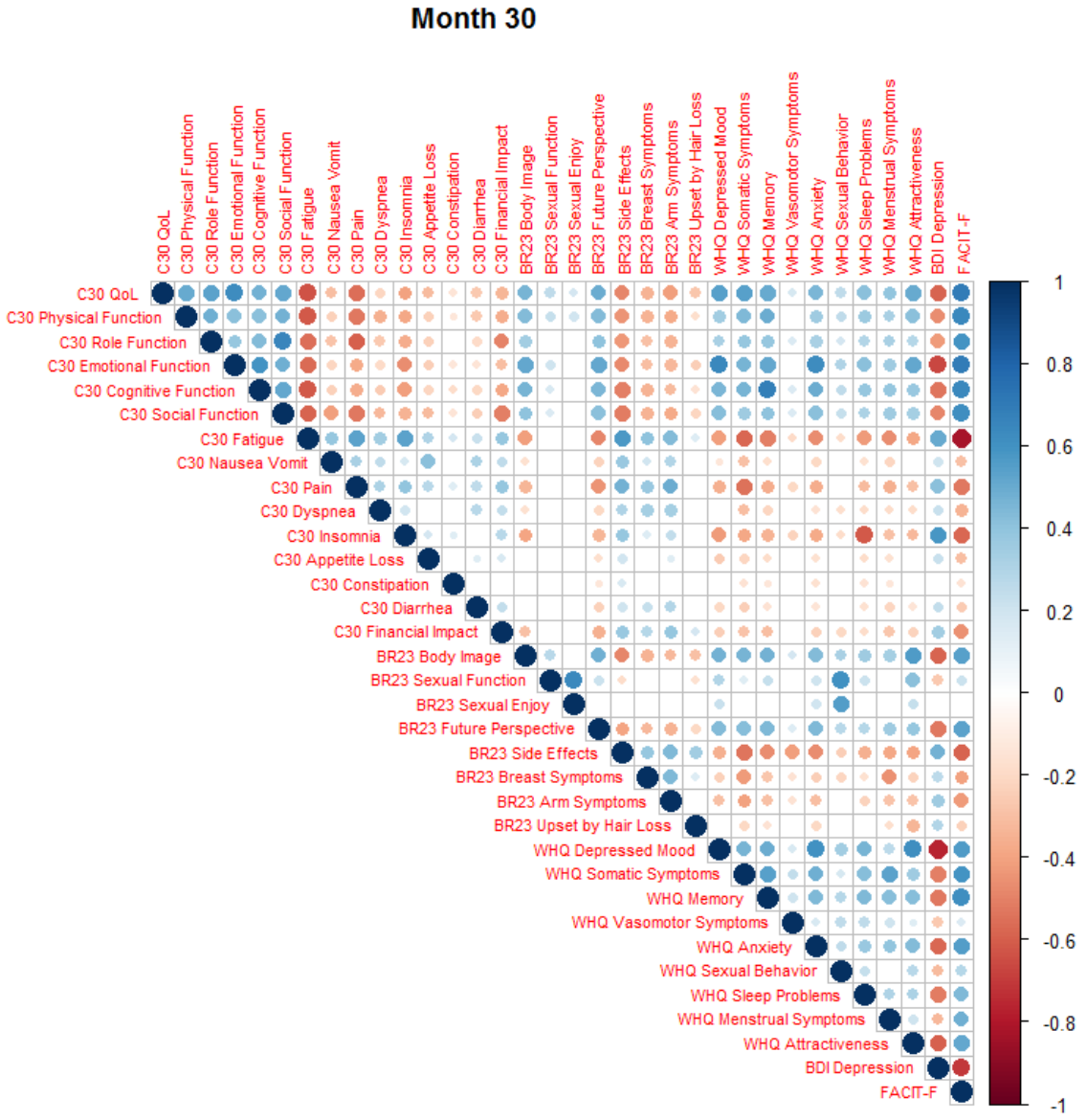


Figure A7 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 30 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were the B23 sexual enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 185 to 232. In all other variable pairs, the complete cases ranged from 305 to 404.

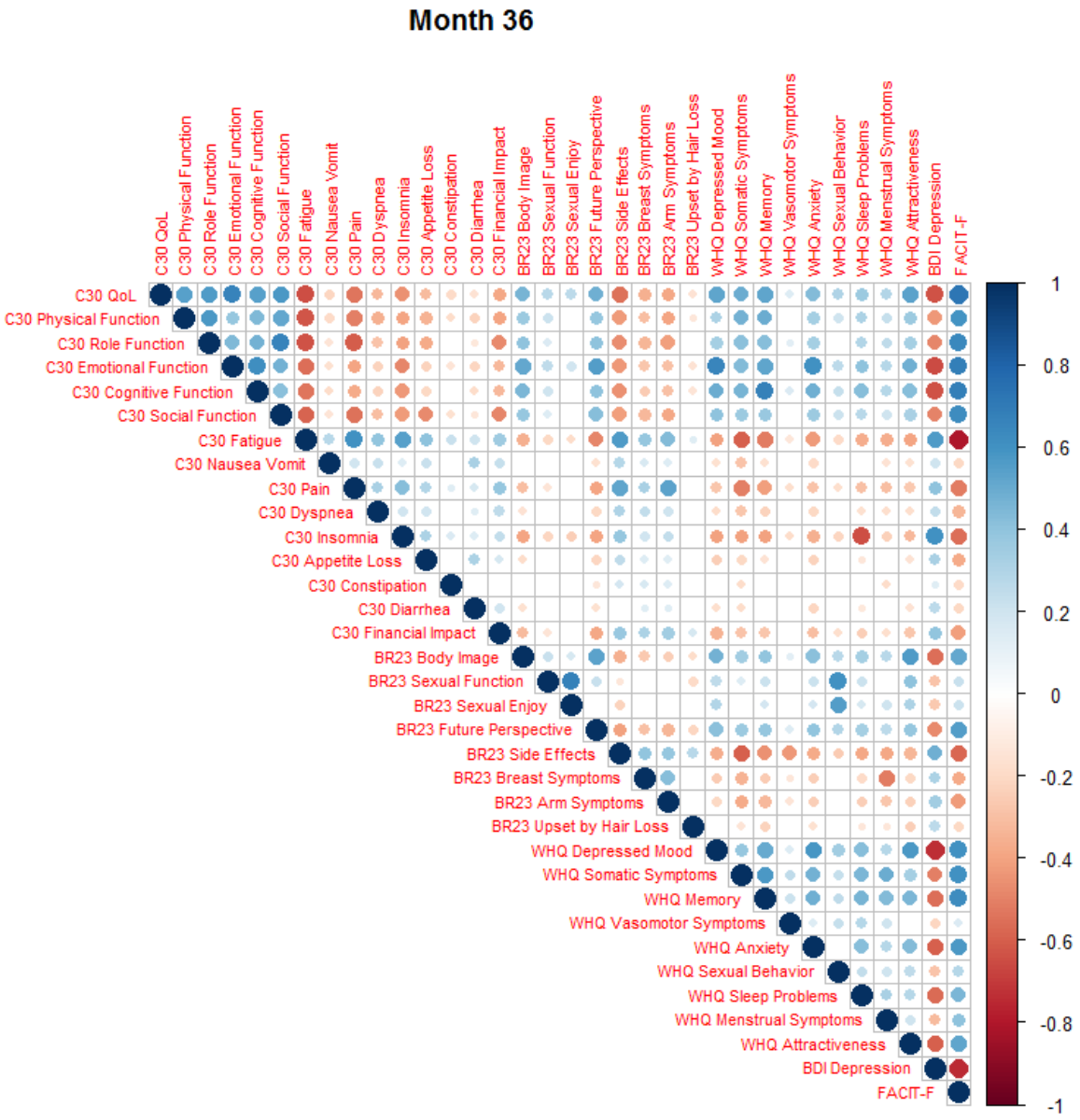


Figure A8 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scores at month 36 from baseline. Positive correlations are displayed in blue and negative correlations in red colour. The colour intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: the pairwise deletion method was applied. The scales with the highest number of missing data were B23 sexual enjoyment and the WQH sexual behaviour. For the correlation analyses between variable pairs including these scales, the number of complete cases ranged from 208 to 240. In all other variable pairs, the complete cases ranged from 388 to 447.

A1.5 Case Study: Assess the Relationship Beween Self-report Questionnaires with Sociodemographic, Medical and Lifestyle Variables at Each Time Point

Analysis Plan

The present study involves an examination of the relationship between the various QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scales with sociodemographic, medical and lifestyle variables at each time point. The purpose is to identify statistically significant differences in psychological scores between two

or more groups of an independent variable e.g. patients having undergone mastectomy or breast conserving surgery. Since the analysis was ongoing at the time of the deliverable preparation, only indicative results are presented here.

One-way ANOVA test (parametric test) and Kruskal-Wallis test (non-parametric alternative, which does not assume that the population distributions follow the normal distribution) were used. The aov() function in R package 'car' was used for ANOVA test and the kruskal.test() function for Kruskal-Wallis test. A "post-hoc" analysis was also performed with Tukey's test using TukeyHSD() function. Post hoc analysis was applied to variables with more than two groups for which a statistically significant result was obtained from the previous analysis. The aim is to identify those groups which are statistically different from each other. Only pairwise complete cases were analyzed.

Because of the sufficient number of patients and the central limit theory, any deviations from normality assumption are not expected to affect the results of anova test. Therefore, no normality checks have been performed for continuous variables.

Results

ANOVA and the Kruskal-Wallis test were consistent for the majority of variables. Only Kruskal test results (p-value) are presented in the following tables (Tables A3) for age, type of breast and axillary surgery, administration of hormone replacement therapy, psychiatric comorbidities, and existence of urinary symptoms.

The age at the initiation of the study is consistently associated throughout the 3-year observation period with C30 physical functioning, BR23 sexual functioning and WHQ vasomotor symptoms. C30 Quality of life is not associated with age.

The type of breast surgery is associated with the BR23 breast symptoms scale and the BR23 menstrual symptoms scale in the first year of the observation period. Women that have undergone mastectomy may report a lower BR23 body image score compared to those that had breast-conserving surgery at all time points; however, differences in the WHQ attractiveness scale are observed mainly in the first months and no difference is evident in the third year.

The type of axillary surgery is associated with arm symptoms at all time points. More specifically, women that have undergone axillary lymph node dissection tend to report a higher BR23 arm symptoms score.

Hormone replacement therapy before breast cancer diagnosis is associated with C30 physical functioning, BR23 sexual functioning and BR23 systemic therapy side effects scales at all time points.

As expected, the presence of psychiatric disease is strongly associated with the global quality of life, the functioning scales (with the exception of sexual functioning and behaviour in the second and the third year), fatigue, depression, anxiety, body image and attractiveness. The association of psychiatric disease with the various symptoms scales is either low or insignificant particularly at baseline and after M24.

Women that experience urinary symptoms tend to report a lower quality of life and functioning and a higher fatigue and depression. The observed associations are less statistically significant at baseline.

Even though smoking seems to be associated with various scales (e.g. anxiety, depression, sleep problems etc.), the associations themselves and their strength, vary considerably between the different time points. Most statistically significant associations are observed at month 18. The fact that the vast majority of participating patients are non-smokers may have influenced the results.

Additional observations based on results not shown here include:

- Perceived overall health status (overall, at work or at leisure time) is negatively associated with the overall QoL score, various domains of functioning (emotional, cognitive, social, role, physical), future perspective, attractiveness and body image.

- Perceived overall health status and disability are associated with symptom severity scales (fatigue, arm symptoms, pain, systemic therapy side effects, somatic symptoms, menstrual symptoms, vasomotor symptoms, sleep problems, dyspnea, breast symptoms)
- All pain scales are negatively associated with the overall QoL score and various domains of functioning (emotional, cognitive, social, role, physical)

- The amount of leisure time exercise is positively associated with QoL and functioning.

- Patients that had doctor appointment(s) or are at sick leave are more prone to report lower QoL.

TABLES A3 Kruskal-Wallis test (p - values) between QLQ-C30, QLQ-BR23, WHQ, DBI, FACIT-F scores and indicative sociodemographic, medical and lifestyle variables at baseline up to M36.

Age	Baseline	M3	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.060	0.530	0.140	0.170	0.817	0.325	0.289	0.042
C30 Physical functioning	0.100	0.000	0.000	0.037	0.002	0.024	0.002	0.000
C30 Role functioning	0.112	0.451	0.300	0.090	0.988	0.045	0.008	0.048
C30 Emotional functioning	0.017	0.435	0.299	0.171	0.640	0.006	0.056	0.533
C30 Cognitive functioning	0.509	0.263	0.303	0.403	0.650	0.302	0.103	0.448
C30 Social functioning	0.132	0.605	0.177	0.878	0.963	0.404	0.058	0.168
C30 Fatigue	0.112	0.567	0.169	0.069	0.796	0.005	0.014	0.053
C30 Nausea and vomiting	0.707	0.368	0.166	0.918	0.050	0.396	0.535	0.288
C30 Pain	0.429	0.489	0.304	0.701	0.803	0.159	0.035	0.140
C30 Dyspnea	0.402	0.239	0.582	0.062	0.613	0.464	0.843	0.085
C30 Insomnia	0.015	0.117	0.432	0.425	0.803	0.322	0.345	0.052
C30 Appetite loss	0.097	0.528	0.278	0.008	0.392	0.240	0.879	0.553
C30 Constipation	0.869	0.322	0.970	0.834	0.144	0.831	0.190	0.573
C30 Diarrhea	0.444	0.358	0.154	0.522	0.211	0.437	0.512	0.157
C30 Financial impact	0.093	0.519	0.998	0.541	0.902	0.743	0.578	0.206
BR23 Body image	0.253	0.282	0.300	0.113	0.773	0.242	0.037	0.353
BR23 Sexual functioning	0.101	0.003	0.021	0.023	0.013	0.000	0.000	0.000
BR23 Sexual enjoyment	0.031	0.000	0.003	0.451	0.244	0.082	0.010	0.218
BR23 Future perspective	0.060	0.612	0.666	0.137	0.914	0.218	0.218	0.097
BR23 Systemic therapy side effects	0.436	0.110	0.000	0.064	0.113	0.041	0.140	0.015
BR23 Breast symptoms	0.695	0.845	0.544	0.419	0.692	0.711	0.924	0.223
BR23 Arm symptoms	0.308	0.322	0.462	0.408	0.495	0.150	0.582	0.228
BR23 Upset by hair loss	0.510	0.499	0.383	0.210	0.263	0.035	0.311	0.096
WHQ Depressed mood	0.554	0.847	0.669	0.803	0.955	0.436	0.354	0.394
WHQ Somatic symptoms	0.471	0.817	0.291	0.483	0.837	0.146	0.065	0.186
WHQ Memory/concentration	0.211	0.208	0.321	0.329	0.718	0.307	0.214	0.719
WHQ Vasomotor Symptoms	0.000	0.000	0.003	0.006	0.006	0.000	0.010	0.015
WHQ Anxiety/fears	0.004	0.927	0.343	0.647	0.464	0.008	0.013	0.029
WHQ Sexual behaviour	0.015	0.056	0.123	0.598	0.426	0.152	0.031	0.223
WHQ Sleep Problems	0.264	0.076	0.337	0.177	0.177	0.014	0.137	0.176
WHQ Menstrual symptoms	0.323	0.151	0.015	0.006	0.003	0.013	0.001	0.030
WHQ Attractiveness	0.475	0.501	0.208	0.133	0.251	0.079	0.187	0.063
BDI Depression	0.036	0.506	0.293	0.108	0.477	0.052	0.167	0.011
FACIT – F score	0.343	0.477	0.498	0.121	0.055	0.061	0.011	0.221

Hormone replacement therapy	Baseline	M3	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.694	0.098	0.197	0.084	0.581	0.341	0.185	0.274
C30 Physical functioning	0.003	0.000	0.000	0.001	0.000	0.003	0.003	0.000
C30 Role functioning	0.511	0.013	0.628	0.169	0.784	0.236	0.734	0.905
C30 Emotional functioning	0.153	0.501	0.517	0.447	0.495	0.173	0.180	0.800
C30 Cognitive functioning	0.137	0.169	0.668	0.958	0.425	0.309	0.273	0.292
C30 Social functioning	0.977	0.173	0.891	0.584	0.697	0.968	0.540	0.566
C30 Fatigue	0.825	0.871	0.706	0.841	0.733	0.150	0.108	0.712
C30 Nausea and vomiting	0.550	0.973	0.905	0.347	0.356	0.808	0.975	0.384
C30 Pain	0.275	0.024	0.108	0.008	0.460	0.992	0.486	0.239
C30 Dyspnea	0.075	0.023	0.040	0.095	0.212	0.777	0.517	0.038
C30 Insomnia	0.774	0.019	0.034	0.031	0.040	0.121	0.791	0.174
C30 Appetite loss	0.067	0.375	0.315	0.000	0.002	0.002	0.354	0.741
C30 Constipation	0.135	0.135	0.951	0.832	0.321	0.612	0.339	0.655
C30 Diarrhea	0.521	0.715	0.831	0.959	0.005	0.532	0.221	0.009
C30 Financial impact	0.034	0.244	0.335	0.319	0.869	0.487	0.211	0.768
BR23 Body image	0.666	0.333	0.674	0.432	0.874	0.275	0.060	0.760
BR23 Sexual functioning	0.061	0.002	0.003	0.001	0.014	0.004	0.012	0.001
BR23 Sexual enjoyment	0.002	0.003	0.001	0.038	0.154	0.003	0.002	0.005
BR23 Future perspective	0.129	0.647	0.323	0.123	0.888	0.339	0.056	0.892
BR23 Systemic therapy side effects	0.000	0.001	0.001	0.002	0.002	0.004	0.032	0.002
BR23 Breast symptoms	0.172	0.524	0.633	0.755	0.232	0.851	0.746	0.594
BR23 Arm symptoms	0.349	0.004	0.057	0.439	0.428	0.233	0.274	0.970
BR23 Upset by hair loss	0.684	0.651	0.025	0.033	0.400	0.406	0.497	0.322
WHQ Depressed mood	0.993	0.845	0.231	0.169	0.567	0.214	0.449	0.008
WHQ Somatic symptoms	0.320	0.089	0.148	0.408	0.782	0.755	0.421	0.245
WHQ Memory/concentration	0.002	0.007	0.014	0.167	0.259	0.195	0.971	0.261
WHQ Vasomotor Symptoms	0.103	0.001	0.000	0.011	0.031	0.002	0.006	0.074
WHQ Anxiety/fears	0.289	0.106	0.581	0.807	0.314	0.214	0.128	0.586
WHQ Sexual behaviour	0.033	0.010	0.035	0.220	0.160	0.177	0.013	0.002
WHQ Sleep Problems	0.086	0.000	0.003	0.101	0.013	0.012	0.167	0.011
WHQ Menstrual symptoms	0.607	0.870	0.396	0.338	0.301	0.393	0.000	0.729
WHQ Attractiveness	0.161	0.379	0.045	0.040	0.688	0.013	0.280	0.059
BDI Depression	0.376	0.382	0.028	0.022	0.094	0.747	0.368	0.278
FACIT – F score	0.497	0.154	0.147	0.657	0.619	0.496	0.376	0.510

Breast surgery	Baseline	M3	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.196	0.509	0.965	0.704	0.615	0.795	0.142	0.513
C30 Physical functioning	0.301	0.994	0.357	0.791	0.603	0.543	0.904	0.752
C30 Role functioning	0.034	0.333	0.235	0.375	0.488	0.001	0.444	0.440
C30 Emotional functioning	0.277	0.339	0.861	0.619	0.109	0.424	0.501	0.466
C30 Cognitive functioning	0.174	0.956	0.480	0.988	0.470	0.398	0.604	0.341
C30 Social functioning	0.099	0.736	0.812	0.425	0.682	0.422	0.252	0.552
C30 Fatigue	0.339	0.532	0.628	0.962	0.605	0.346	0.637	0.387
C30 Nausea and vomiting	0.066	0.628	0.877	0.765	0.731	0.400	0.668	0.177
C30 Pain	0.669	0.756	0.462	0.611	0.911	0.308	0.989	0.750
C30 Dyspnea	0.071	0.611	0.334	0.528	0.542	0.183	0.417	0.214
C30 Insomnia	0.276	0.501	0.590	0.855	0.552	0.887	0.949	0.607
C30 Appetite loss	0.128	0.130	0.303	0.657	0.841	0.636	0.378	0.921
C30 Constipation	0.744	0.076	0.013	0.242	0.926	0.051	0.201	0.495
C30 Diarrhea	0.827	0.374	0.774	0.043	0.590	0.158	0.286	0.335
C30 Financial impact	0.221	0.663	0.753	0.347	0.244	0.890	0.650	0.913
BR23 Body image	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
BR23 Sexual functioning	0.052	0.084	0.288	0.883	0.728	0.616	0.992	0.397
BR23 Sexual enjoyment	0.989	0.627	0.322	0.863	0.126	0.094	0.329	0.035
BR23 Future perspective	0.063	0.064	0.376	0.329	0.031	0.642	0.522	0.333
BR23 Systemic therapy side effects	0.226	0.273	0.198	0.056	0.850	0.851	0.323	0.244
BR23 Breast symptoms	0.003	0.004	0.000	0.004	0.409	0.571	0.943	0.349
BR23 Arm symptoms	0.027	0.153	0.161	0.741	0.155	0.487	0.321	0.185
BR23 Upset by hair loss	0.186	0.680	0.206	0.644	0.518	0.694	0.766	0.975
WHQ Depressed mood	0.304	0.188	0.370	0.258	0.280	0.321	0.854	0.966
WHQ Somatic symptoms	0.762	0.748	0.549	0.671	0.857	0.857	0.636	0.950
WHQ Memory/concentration	0.085	0.581	0.655	0.783	0.452	0.891	0.789	0.945
WHQ Vasomotor Symptoms	0.244	0.009	0.150	0.046	0.433	0.309	0.036	0.124
WHQ Anxiety/fears	0.038	0.042	0.207	0.788	0.053	0.275	0.973	0.104
WHQ Sexual behaviour	0.833	0.781	0.784	0.342	0.751	0.004	0.719	0.183
WHQ Sleep Problems	0.100	0.463	0.830	0.591	0.531	0.357	0.774	0.305
WHQ Menstrual symptoms	0.017	0.003	0.000	0.004	0.465	0.134	0.113	0.038
WHQ Attractiveness	0.000	0.001	0.053	0.072	0.005	0.024	0.221	0.195
BDI Depression	0.154	0.037	0.461	0.818	0.219	0.966	0.903	0.865
FACIT – F score	0.677	0.457	0.150	0.589		0.388	0.307	0.590

Axillary surgery	Baseline	M3	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.903	0.239	0.791	0.293	0.990	0.182	0.828	0.581
C30 Physical functioning	0.736	0.059	0.428	0.905	0.738	0.511	0.598	0.579
C30 Role functioning	0.612	0.175	0.577	0.750	0.689	0.445	0.407	0.425
C30 Emotional functioning	0.813	0.143	0.369	0.974	0.454	0.442	0.879	0.973
C30 Cognitive functioning	0.352	0.030	0.492	0.429	0.873	0.322	0.580	0.640
C30 Social functioning	0.747	0.505	0.676	0.482	0.593	0.898	0.869	0.083
C30 Fatigue	0.446	0.556	0.891	0.906	0.961	0.983	0.994	0.873
C30 Nausea and vomiting	0.723	0.519	0.814	0.945	0.806	0.927	0.698	0.305
C30 Pain	0.569	0.015	0.550	0.585	0.420	0.396	0.970	0.590
C30 Dyspnea	0.892	0.052	0.068	0.606	0.904	0.879	0.726	0.869
C30 Insomnia	0.514	0.721	0.841	0.608	0.373	0.589	0.796	0.527
C30 Appetite loss	0.385	0.884	0.813	0.706	0.857	0.758	0.354	0.944
C30 Constipation	0.575	0.709	0.554	0.369	0.506	0.738	0.833	0.431
C30 Diarrhea	0.080	0.414	0.642	0.162	0.768	0.904	0.065	0.822
C30 Financial impact	0.309	0.820	0.267	0.580	0.790	0.786	0.911	0.010
BR23 Body image	0.256	0.022	0.055	0.027	0.025	0.003	0.251	0.171
BR23 Sexual functioning	0.941	0.654	0.911	0.711	0.384	0.802	0.203	0.844
BR23 Sexual enjoyment	0.022	0.135	0.325	0.381	0.448	0.158	0.403	0.140
BR23 Future perspective	0.128	0.066	0.995	0.108	0.600	0.559	0.667	0.324
BR23 Systemic therapy side effects	0.345	0.812	0.810	0.640	0.533	0.250	0.592	0.535
BR23 Breast symptoms	0.416	0.066	0.496	0.058	0.154	0.062	0.106	0.690
BR23 Arm symptoms	0.000	0.000	0.000	0.000	0.000	0.025	0.002	0.075
BR23 Upset by hair loss	0.358	0.680	0.897	0.862	0.751	0.933	0.950	0.049
WHQ Depressed mood	0.590	0.512	0.399	0.655	0.474	0.369	0.633	0.358
WHQ Somatic symptoms	0.396	0.425	0.340	0.529	0.513	0.987	0.969	0.551
WHQ Memory/concentration	0.924	0.096	0.604	0.276	0.660	0.457	0.913	0.896
WHQ Vasomotor Symptoms	0.555	0.724	0.218	0.740	0.160	0.106	0.414	0.414
WHQ Anxiety/fears	0.776	0.455	0.326	0.817	0.679	0.663	0.729	0.740
WHQ Sexual behaviour	0.587	0.392	0.484	0.179	0.012	0.405	0.537	0.129
WHQ Sleep Problems	0.486	0.099	0.457	0.110	0.935	0.232	0.748	0.464
WHQ Menstrual symptoms	0.465	0.451	0.541	0.681	0.570	0.257	0.335	0.522
WHQ Attractiveness	0.377	0.026	0.680	0.653	0.184	0.064	0.720	0.588
BDI Depression	0.702	0.278	0.734	0.619	0.971	0.498	0.490	0.500
FACIT – F score	0.595	0.428	0.523	0.796	0.852	0.445	0.369	0.783

Psychatric disease	Baseline	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.000	0.000	0.000	0.000	0.000	0.002	0.000
C30 Physical functioning	0.004	0.070	0.000	0.002	0.000	0.020	0.000
C30 Role functioning	0.000	0.000	0.000	0.000	0.000	0.220	0.001
C30 Emotional functioning	0.000	0.000	0.000	0.000	0.000	0.000	0.000
C30 Cognitive functioning	0.000	0.000	0.000	0.000	0.000	0.003	0.000
C30 Social functioning	0.000	0.000	0.000	0.000	0.000	0.014	0.000
C30 Fatigue	0.000	0.000	0.000	0.000	0.000	0.002	0.000
C30 Nausea and vomiting	0.048	0.067	0.001	0.000	0.253	0.031	0.136
C30 Pain	0.057	0.002	0.002	0.000	0.001	0.009	0.000
C30 Dyspnea	0.045	0.235	0.047	0.001	0.000	0.012	0.050
C30 Insomnia	0.028	0.002	0.001	0.000	0.007	0.030	0.019
C30 Appetite loss	0.006	0.100	0.002	0.000	0.038	0.037	0.218
C30 Constipation	0.006	0.001	0.154	0.152	0.001	0.233	0.193
C30 Diarrhea	0.695	0.035	0.000	0.000	0.041	0.029	0.140
C30 Financial impact	0.000	0.000	0.000	0.000	0.000	0.983	0.000
BR23 Body image	0.010	0.000	0.000	0.000	0.001	0.002	0.002
BR23 Sexual functioning	0.007	0.006	0.039	0.143	0.050	0.037	0.064
BR23 Sexual enjoyment	0.736	0.065	0.295	0.364	0.455	0.255	0.830
BR23 Future perspective	0.013	0.000	0.000	0.000	0.152	0.001	0.000
BR23 Systemic therapy side effects	0.002	0.000	0.000	0.000	0.000	0.000	0.008
BR23 Breast symptoms	0.080	0.216	0.029	0.038	0.038	0.154	0.005
BR23 Arm symptoms	0.033	0.000	0.000	0.011	0.005	0.020	0.000
BR23 Upset by hair loss	0.282	0.037	0.303	0.003	0.237	0.356	0.869
WHQ Depressed mood	0.000	0.000	0.000	0.000	0.000	0.000	0.000
WHQ Somatic symptoms	0.000	0.023	0.000	0.000	0.001	0.001	0.001
WHQ Memory/concentration	0.000	0.000	0.000	0.000	0.000	0.000	0.000
WHQ Vasomotor Symptoms	0.809	0.688	0.047	0.457	0.334	0.262	0.222
WHQ Anxiety/fears	0.000	0.000	0.000	0.000	0.000	0.000	0.000
WHQ Sexual behaviour	0.012	0.007	0.039	0.528	0.468	0.092	0.539
WHQ Sleep Problems	0.000	0.000	0.000	0.000	0.000	0.015	0.001
WHQ Menstrual symptoms	0.002	0.108	0.000	0.005	0.235	0.002	0.201
WHQ Attractiveness	0.000	0.000	0.000	0.000	0.004	0.000	0.006
BDI Depression	0.000	0.000	0.000	0.000	0.000	0.006	0.000
FACIT – F score	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Urinary symptoms	Baseline	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.041	0.009	0.000	0.002	0.000	0.000	0.000
C30 Physical functioning	0.003	0.013	0.000	0.005	0.000	0.000	0.000
C30 Role functioning	0.021	0.008	0.003	0.000	0.001	0.001	0.000
C30 Emotional functioning	0.441	0.001	0.001	0.001	0.001	0.000	0.006
C30 Cognitive functioning	0.005	0.000	0.000	0.000	0.000	0.000	0.000
C30 Social functioning	0.035	0.001	0.000	0.013	0.000	0.000	0.009
C30 Fatigue	0.095	0.000	0.000	0.000	0.000	0.000	0.000
C30 Nausea and vomiting	0.585	0.008	0.005	0.357	0.078	0.291	0.009
C30 Pain	0.007	0.010	0.000	0.000	0.000	0.003	0.000
C30 Dyspnea	0.009	0.051	0.002	0.004	0.002	0.125	0.158
C30 Insomnia	0.617	0.008	0.065	0.001	0.000	0.012	0.038
C30 Appetite loss	0.048	0.299	0.821	0.017	0.050	0.968	0.189
C30 Constipation	0.536	0.030	0.103	0.866	0.044	0.683	0.044
C30 Diarrhea	0.828	0.006	0.394	0.661	0.007	0.003	0.000
C30 Financial impact	0.304	0.001	0.028	0.000	0.000	0.000	0.002
BR23 Body image	0.318	0.082	0.004	0.002	0.001	0.000	0.033
BR23 Sexual functioning	0.532	0.496	0.817	0.544	0.139	0.076	0.178
BR23 Sexual enjoyment	0.038	0.494	0.018	0.255	0.849	0.122	0.646
BR23 Future perspective	0.524	0.001	0.012	0.003	0.008	0.001	0.007
BR23 Systemic therapy side effects	0.000	0.003	0.000	0.008	0.000	0.001	0.000
BR23 Breast symptoms	0.001	0.017	0.000	0.103	0.000	0.000	0.001
BR23 Arm symptoms	0.242	0.008	0.022	0.006	0.001	0.000	0.001
BR23 Upset by hair loss	0.798	0.349	0.038	0.350	0.286	0.518	0.236
WHQ Depressed mood	0.228	0.000	0.002	0.494	0.001	0.000	0.064
WHQ Somatic symptoms	0.000	0.000	0.000	0.000	0.000	0.000	0.000
WHQ Memory/concentration	0.001	0.000	0.000	0.000	0.000	0.000	0.000
WHQ Vasomotor Symptoms	0.754	0.135	0.317	0.032	0.059	0.012	0.037
WHQ Anxiety/fears	0.308	0.000	0.011	0.232	0.010	0.000	0.052
WHQ Sexual behaviour	0.105	0.376	0.104	0.016	0.003	0.004	0.043
WHQ Sleep Problems	0.434	0.003	0.028	0.003	0.034	0.043	0.014
WHQ Menstrual symptoms	0.085	0.000	0.045	0.001	0.000	0.000	0.052
WHQ Attractiveness	0.304	0.093	0.032	0.088	0.002	0.004	0.020
BDI Depression	0.040	0.000	0.000	0.000	0.000	0.000	0.000
FACIT – F score	0.052	0.000	0.000	0.000	0.000	0.000	0.000

Present smoking	Baseline	M6	M12	M18	M24	M30	M36
C30 Global QoL	0.064	0.002	0.003	0.000	0.108	0.005	0.005
C30 Physical functioning	0.078	0.006	0.001	0.000	0.010	0.305	0.002
C30 Role functioning	0.749	0.343	0.006	0.001	0.442	0.219	0.008
C30 Emotional functioning	0.022	0.006	0.050	0.017	0.196	0.219	0.003
C30 Cognitive functioning	0.543	0.118	0.087	0.004	0.345	0.337	0.023
C30 Social functioning	0.102	0.108	0.242	0.025	0.428	0.211	0.505
C30 Fatigue	0.378	0.044	0.040	0.005	0.003	0.094	0.036
C30 Nausea and vomiting	0.000	0.028	0.016	0.000	0.022	0.042	0.475
C30 Pain	0.224	0.011	0.035	0.000	0.331	0.103	0.016
C30 Dyspnea	0.828	0.192	0.081	0.000	0.012	0.448	0.056
C30 Insomnia	0.000	0.007	0.056	0.104	0.007	0.055	0.015
C30 Appetite loss	0.005	0.106	0.178	0.037	0.286	0.063	0.002
C30 Constipation	0.226	0.624	0.238	0.406	0.068	0.302	0.215
C30 Diarrhea	0.020	0.034	0.011	0.000	0.005	0.093	0.002
C30 Financial impact	0.000	0.014	0.014	0.005	0.094	0.291	0.049
BR23 Body image	0.009	0.024	0.101	0.000	0.019	0.003	0.001
BR23 Sexual functioning	0.451	0.869	0.116	0.013	0.002	0.001	0.005
BR23 Sexual enjoyment	0.151	0.002	0.004	0.027	0.077	0.755	0.410
BR23 Future perspective	0.028	0.915	0.229	0.001	0.175	0.550	0.263
BR23 Systemic therapy side effects	0.009	0.000	0.000	0.000	0.003	0.035	0.004
BR23 Breast symptoms	0.002	0.004	0.014	0.237	0.185	0.397	0.127
BR23 Arm symptoms	0.421	0.136	0.090	0.022	0.071	0.074	0.601
BR23 Upset by hair loss	0.692	0.766	0.266	0.254	0.004	0.020	0.468
WHQ Depressed mood	0.000	0.004	0.014	0.001	0.137	0.102	0.240
WHQ Somatic symptoms	0.005	0.009	0.001	0.000	0.016	0.024	0.011
WHQ Memory/concentration	0.193	0.332	0.143	0.004	0.720	0.513	0.211
WHQ Vasomotor Symptoms	0.508	0.233	0.194	0.436	0.294	0.421	0.094
WHQ Anxiety/fears	0.000	0.052	0.002	0.000	0.163	0.254	0.007
WHQ Sexual behaviour	0.669	0.732	0.843	0.936	0.056	0.934	0.427
WHQ Sleep Problems	0.000	0.005	0.029	0.002	0.009	0.090	0.016
WHQ Menstrual symptoms	0.072	0.151	0.048	0.055	0.007	0.960	0.589
WHQ Attractiveness	0.012	0.096	0.006	0.001	0.107	0.001	0.000
BDI Depression	0.001	0.001	0.003	0.000	0.000	0.030	0.000
FACIT – F score	0.195	0.006	0.001	0.004	0.004	0.055	0.015

A1.6 Case Study: Temporal Changes in Scales

Analysis Plan

Repeated-measures ANOVA was performed to the total patient sample to detect any statistically significant changes in the QLQ-C30, QLQ-BR23, WHQ, FACIT and BDI scales during the 3-year observation window (Table A4). A conventional analysis was performed using the aov() function of R and a mixed-effects analysis using lme() function from nlme package and anova() function of R.

If the repeated measures ANOVA with mixed effects model is statistically significant, we run multiple comparisons on the mixed effects model in order to identify where these differences occur. We have used the glht() function from the package multcomp. Only complete cases were analyzed.

Results

The results of the two methods are consistent with the exception of WQH attractiveness and C30 Role functioning.

Statistically significant differences over time were observed for eleven of the QLQ-C30 scales: global quality of life, physical functioning, social functioning, fatigue and financial impact ($p < 0.0001$), insomnia and appetite loss ($p < 0.001$), nausea/vomiting, role functioning, emotional functioning and pain ($p < 0.05$).

Statistically significant differences over time at significance level $p < 0.0001$ were observed for almost all of the QLQ-BR23 scales as well as BDI Depression and FACIT – F score.

Regarding the WHQ scales, statistically significant differences over time were observed for: vasomotor symptoms and menstrual symptoms ($p < 0.0001$), memory/concentration ($p < 0.01$), anxiety/fears, sleep problems and attractiveness ($p < 0.05$).

Multiple comparisons revealed that for the C30 functional and fatigue scales and the BDI depression scale and the FACIT scale the differences in means are mainly observed between the baseline and the subsequent time points. Such observations may imply that changes are manifested early, within the three-six first months of the observation period. Future perspective shows a gradual improvement throughout the whole three-year period. A gradual change in BR23 body image and symptom scales is also observed.

Repeated-measures ANOVA has failed to detect any statistically significant changes from baseline to month 36 in the scores of C30 cognitive functioning, C30 dyspnea C30 constipation, C30 diarrhea, BR23 sexual enjoyment, WHQ depressed mood, WHQ somatic symptoms and WHQ sexual behaviour.

It is noted that there has been a considerable number of missing values for BR23 sexual enjoyment, the majority of which stemming from patients reporting no or low sexual functioning.

It is noted that the scores and the score trajectories over time are characterized by considerable inter-patient heterogeneity. Only mean behaviours have been examined here.

TABLE A4 Repeated-measures ANOVA results (p-values). The colour density is proportional to the significance levels 0, 0.001, 0.01 and 0.05.

Scale	Mixed-effects analysis	Conventional analysis
C30 Global QoL	0.0000	0.0000
C30 Physical functioning	0.0000	0.0000
C30 Role functioning	0.0192	0.1060
C30 Emotional functioning	0.0152	0.0284
C30 Cognitive functioning	0.7812	0.8000
C30 Social functioning	0.0000	0.0000
C30 Fatigue	0.0000	0.0000
C30 Nausea and vomiting	0.0114	0.0220
C30 Pain	0.0414	0.0181
C30 Dyspnea	0.8269	0.8990
C30 Insomnia	0.0001	0.0003
C30 Appetite loss	0.0003	0.0008
C30 Constipation	0.5867	0.5890
C30 Diarrhea	0.3943	0.3770
C30 Financial impact	0.0000	0.0000
BR23 Body image	0.0000	0.0000
BR23 Sexual functioning	0.0000	0.0000
BR23 Sexual enjoyment	0.1255	0.0881
BR23 Future perspective	0.0000	0.0000
BR23 Systemic therapy side effects	0.0000	0.0000
BR23 Breast symptoms	0.0000	0.0000
BR23 Arm symptoms	0.0000	0.0000
BR23 Upset by hair loss	0.0000	0.0000
WHQ Depressed mood	0.4540	0.5300
WHQ Somatic symptoms	0.2344	0.2710
WHQ Memory/concentration	0.0011	0.0020
WHQ Vasomotor Symptoms	0.0000	0.0000
WHQ Anxiety/fears	0.0478	0.0332
WHQ Sexual behaviour	0.5268	0.3340
WHQ Sleep Problems	0.0161	0.0199
WHQ Menstrual symptoms	0.0000	0.0000
WHQ Attractiveness	0.0481	0.0940
BDI Depression	0.0000	0.0000
FACIT – F score	0.0000	0.0000

A2. Preliminary Correlation Analysis with Retrospective data: The HUJI Dataset

A2.1 Dataset Description

The data, following anonymization, has been provided by Prof. Ruth Pat-Horenczyk, THE HEBREW UNIVERSITY OF JERUSALE, Israel, within the framework of the BOUNCE EU funded project. The study details and outcome have been previously described [Hamama-Raz et al. 2012, 2016, Pat-Horenczyk et al 2015, 2016]. A short summary is provided here.

Researchers Involved in Data Collection: Ruth Pat-Horenczyk PhD, Shlomit Perry PhD, Yaira Hamama-Raz, PhD, Levi Solomyak BA Shira Goldenberg MA, Chariklia Tziraki MD & Salomon Stemmer MD

Purpose: The purpose of the study was to evaluate the long-term effect of group intervention in female patients with early-stage breast cancer. The group intervention was intended to enhance emotion regulation and build resilience. The intervention and comparison group were self-selected based on participants' willingness to take part in the intervention program (Horenczyk et al 2016).

Sample Origin: The data has been based on a sample of N=201 women after breast cancer. It has been collected at the Davidoff Center, Rabin Medical Center.

Inclusion criteria for the study were: (1) patients with a diagnosis of breast cancer who had completed adjuvant therapy (chemotherapy, radiotherapy) at least three months previously, (2) age 25–75 years, (3) Hebrew speaking, (4) first-time diagnosis of breast cancer, (5) stage 1–3 breast cancer and (6) absence of other chronic illness.

Measures: Six waves of measurements (within-subjects) starting in 2011, with a follow-up study after 3-6 years (about 10% of the patients died), was conducted. In particular, all patients were asked to complete several self-rating scales at five time points: baseline, 6, 12 and 24 months later and at follow-up. Moreover, the patients who participated in the intervention workshop were asked to complete the questionnaires at the end of the intervention workshop (month 3 from baseline).

The HUJI retrospective data include:

Background data at baseline (T1):

- **Demographics** information (Age, country of birth, marital status, number of children, education, work status, occupation, place of residence, etc)
- **Illness parameters (**Stage of breast cancer, types of treatment (chemotherapy or/and radiotherapy, hormonal therapy), treatment protocol (doxorubicin based, trastuzumab), etc.)
- **Physiological data** (sleep problems, obesity, etc)

Psychosocial self-report questionnaires at six time points (T1-T6):
Note that some of the measures used in T6 were different than in the previous waves.

Posttraumatic stress symptoms. The Posttraumatic Stress Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997) was used to assess the severity of posttraumatic distress. The PDS is a commonly used measure of PTSD that assesses the frequency of 17 symptoms and symptom severity.

Functional impairment. It was measured by asking respondents to rate their level of impairment in nine domains, including work, relationships with friends or family, or general satisfaction with life, using a scale from 0 (no impairment) to 5 (severe impairment).

Depression. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a well-validated 20-item measure based on ratings in four primary symptom areas: (a) depressed affect; (b) lack of positive affect; (c) somatic symptoms; and (d) interpersonal difficulties.

Cognitive and emotion regulation. The Cognitive Emotion Regulation Questionnaire (CERQ) is a multidimensional, 18-item scale that identifies coping strategies used by respondents following stressful or negative life events (Garnefski & Kraaij, 2006). Responses are organized into nine subscales, divided into *positive*: acceptance, positive refocusing, refocus on planning, positive reappraisal, putting into perspective and *negative:* self-blame, rumination, catastrophizing, and blaming others.

Coping flexibility. The Perceived Ability to Cope with Trauma (PACT) scale (Bonanno, Pat-Horenczyk, & Noll, 2011). The PACT is a 20 item-scale that assess ability to cope with potentially traumatic event. The PACT is divided into two subscales: (a) forward focus, comprised of 12 items, and (b) trauma focus, comprised of eight items.

Posttraumatic growth. The Posttraumatic Growth Inventory (PTGI; Tedeschi & Calhoun, 1996) consists of 21 items designed to measure five interrelated subscales that reflect perceived positive outcomes reported after a traumatic event. These include: (a) realization of new possibilities ; (b) an increased sense of personal strength; (c) a greater appreciation of life) ;d) an increased sense of closeness with others ; and (e) spiritual growth.

Ego Resilience. Fourteen items measuring the general construct of ego resilience (Block & Kremen, 1996).

Feeling Today. SressTod, ResTod, HopeTod. Three items: overall assessment of distress level, level of perceived resilience, and amount of hope for the future – designed for this study.

Distress. Distress1-Distress6. The Kessler psychological distress scale K6 (Kessler et al, 2002).
PCL-5. PTSD assessment checklist according to DSM-V criteria (Weathers et al, 2013) with 20 items.

TABLE A5 Number of participants and data availability per time point for HUJI retrospective data.

HUJI dataset	T1 Baseline	T2 after 3 mouths	T3 after 6 months	T4 after 12 months	T5 after 24 months	T6 Follow up 3-6 years
Number of Participants	**199**	**48**	**110**	**86**	**52**	**138**
Demographics	✓					
Clinical and treatment data	✓					
Reported symptoms (sleep problems, obesity etc)	✓					
Psychosocial self-report questionnaires	✓	✓	✓	✓	✓	✓*

* Different set of questionnaires than previous time points

A2.2 Preparing the data

A data cleaning of the HUJI retrospective dataset is being performed in the framework of WP4. The data cleaning steps performed so far include:

- For every variable, comparison of all values to what is listed in the code/explanation manual provided along with the data. In the case of standardized questionnaires, values were compared against questionnaires' scales and derived overall scores were recalculated.

- Consistency checks between variables to identify erroneous inliers. For example, variables of the similar meaning are compared, e.g. Child vs Children, WorkStat vs RNotWork, Heat vs HeatH etc (see P.Appendix 2B for variable name explanation).

- Realization of basic descriptive statistics for every variable of the dataset as well as joint statistics between variables. Descriptive statistics also help identify outliers, inconsistencies, strange patterns in (joint) distributions and erroneous inliers (when viewed in relation to other variables).

- Re-organization of data in long or wide format to facilitate subsequent analysis. Duplicate patients were removed.

- Continuous variable age was also transformed into categorical variable based on typical cut-off values.

It is noted that the above work is still in progress. ICCS is working in close interaction HUJI to resolve inconsistencies found during the screening/diagnostic phase of the data analysis and has requested additional clarifications and descriptions whenever needed.

The pattern of missing values has not been studied yet. A partial imputation of missing data took place in the case of reported symptoms at baseline (heat waves, mood swings, sleep problems, obesity, decrease in comfort with the body, disruption in sexuality and interference with a sense of femininity). The following rules were applied:

- If the patient reports that she does not experience a specific symptom and the severity level of this symptom is a missing value (e.g variable Heat=0 (no) and variable HeatH is a missing value), then the severity level is imputed with the value 0.

- If the severity level for a specific symptom is between 1 and 4 and the symptom is a missing value (e.g variable Heat is a missing value and variable HeatH=3), then the symptom is imputed with the value 1 (=yes).

- If the severity level for a specific symptom is 0 and the symptom is a missing value (e.g. variable Heat is a missing value and variable HeatH=0), then the symptom is imputed with the value 0 (=no).

A2.3 Patients characteristics

The characteristics of the study group at baseline are presented in Table A6. The sample included only women, who on average had been diagnosed with breast-cancer 15.51 months (SD=3.67) prior to participating in the study (Pat-Horenczyk et al 2016). The patients had completed adjuvant therapy at least 3 months prior to study inclusion (Pat-Horenczyk et al 2016).The provided cohort includes records from 201 Jewish female women after breast cancer between the ages of 26-72 (Mean= 50.45, SD=10.85), out of which 143 were born in Israel. Stages of breast cancer: Stage I (24%) Stage II (56%),

Stage III (N= 19%). Most of the patients received both chemotherapy and radiation treatment whereas the others received exclusively chemotherapy.

TABLE A6 Patient clinical and demographic characteristics at baseline

Variables	Count/ Mean(range)	%/SD	Variables	Count	%
General and Demographics			*Breast cancer and Treatment data*		
Age	50.5 (26-72)	10.9	Disease stage		
Births	2.7 (0-10)	1.4	1	47	24.6%
Workshop participation			2	107	56.0%
No	106	53.5%	3	37	19.4%
Yes	92	46.5%	Treatment type		
Married			Chemo only	20	10.2%
No	32	16.2%	Chemo + Radio	177	89.8%
Yes	166	83.8%	Herceptin		
Children			No	137	69.2%
No	12	6.1%	Yes	61	30.8%
Yes	187	93.9%	Hormonal		
Work status			No	50	26.3%
Not employed	78	41.3%	Yes	140	73.7%
Part time	30	15.9%	Family history		
Full time	81	42.9%	No	121	64.0%
Born in Israel			Yes	68	36.0%
No	55	27.8%			
Yes	143	72.2%			
Urban residence					
No	44	22.2%			
Yes	154	77.8%			
Religious					
Religious	27	13.7%			
Traditional	49	24.9%			
Secular	121	61.4%			

The proportion of missing values varies significantly over time (Table A5). Only 20 patients have records at least some records all time points. The response rate to the questionnaires at baseline, month 3, month 6, month 12, month 24 and follow-up were approximately 99%, 24%, 55%, 43%, 26% and 69% respectively. It is noted that at month 3 the vast majority of the records comes from patients that participated in the intervention workshop (45 out of the 48 patients with records at T2).

A2.4 Case Study: Inter and Intra scale correlations

Analysis plan

The present study involves an examination of the correlations among the PTSD (Posttraumatic stress symptoms), Functional impairment, CES-D (Depression), CER (Cognitive and emotion regulation), PACT (Coping flexibility), PTGI (Posttraumatic growth), EGO (Ego Resilience), PCL (Posttraumatic

stress symptoms) and KESSLER (Distress) scales as well as the user perceived levels of distress, resilience and hope. Only overall scores derived from the above questionnaire are considered. Analysis of each item of the questionnaires will be implemented in future work. The correlation was performed using Pearson method, which measures a linear dependence between two variables. The rcorr( ) function of R in the Hmisc *package* was applied to produce pearson *correlations*.

Results

Figures A9 – A13 present the correlations at time points M0, M3, M6, M12 and M24 among a) the positive cognitive emotion regulation; the negative cognitive emotion regulation and the overall cognitive emotion regulation of the CERQ questionnaire, b) the overall functional impairment, c) the overall CES-D Depression scale, d) the overall PACT coping flexibility scale, e) the PTSD posttraumatic stress diagnostic scale, e) the EGO Resilience scale, f) the overall PTGI posttraumatic growth scale and g) the overall patient assessment of distress, resilience and future hope. Indicative results are described below.

Among the CERQ scales, strong correlations are observed between the overall scale and the positive and negative cognitive emotional regulation scales. This is to be expected since overall score is derived based on the items of positive and negative scales. On the other hand, an insignificant correlation exists between the positive and negative regulation scales.

Overall the strongest inter scale correlations are observed between the PTSD posttraumatic stress symptoms, the CES-D depression and the functional impairment scales (r~ 0.64 - 0.84).

Overall, PTGI Posttraumatic growth exhibits insignificant to low correlations with most scales at all time points. Moderate correlations (r~0.54-0.64) are observed between PTGI Posttraumatic growth and EGO Resilience at months 3-24. The highest correlation between these two scales is observed at month 24

A moderate correlation (r~0.52) between EGO Resilience and user perceived resilience levels is observed at months 6, 12 and 24. A moderate correlation (r~0.55-0.68) between PDS Posttraumatic stress scale and user perceived distress levels is noted at all time points except M3.

Figure A14 presents the correlations at follow up between a) the positive cognitive emotion regulation; the negative cognitive emotion regulation and the overall cognitive emotion regulation of the CERQ questionnaire, b) the overall PACT coping flexibility scale, c) the overall PTGI posttraumatic growth scale, d) the PCL posttraumatic stress diagnostic scale and e) the Kessler Psychological Distress Scale.

Correlations are overall insignificant. Moderate correlations are observed between PCL and Distress scales (r~ 0.47), between PCL and PACT scales (r~ - 0.42) and between Distress and CERQ negative scales (r~ 0.47).

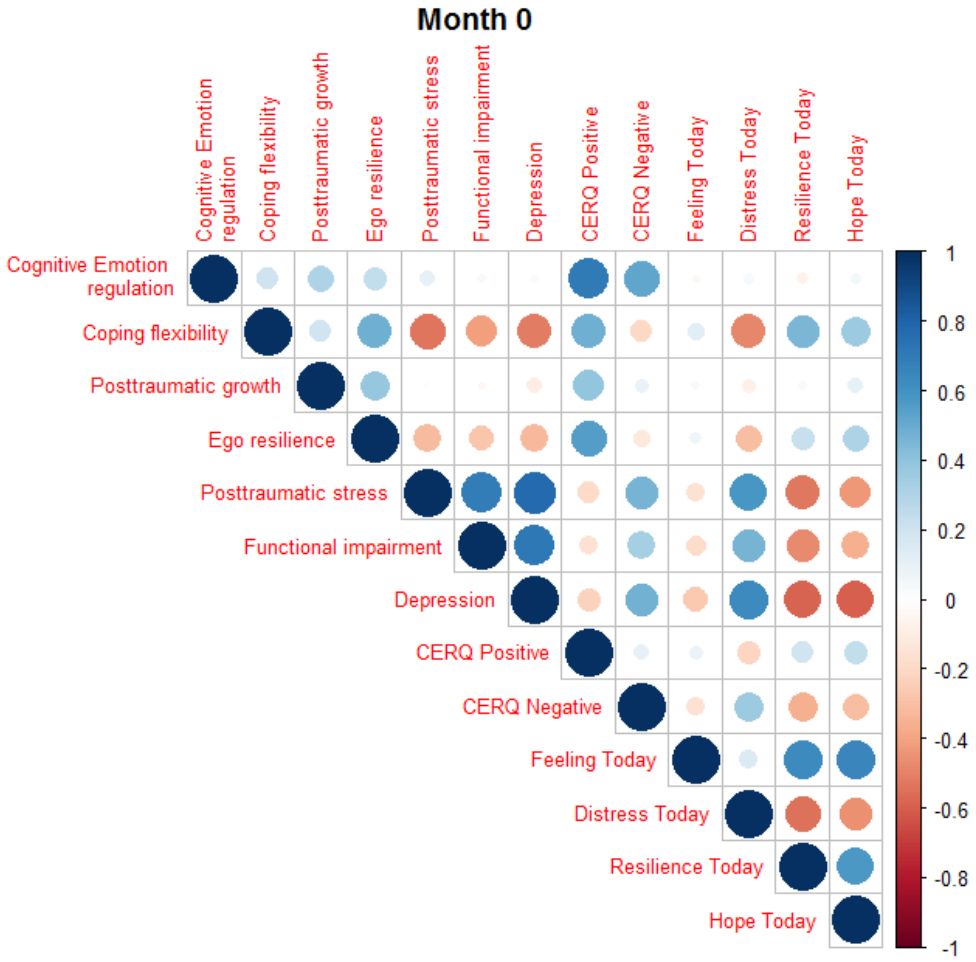


Figure A9 Graphical representation of the correlation matrix between the various scales at baseline. Positive correlations are displayed in blue and negative correlations in red color. The color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: Pair wise deletion method was applied.

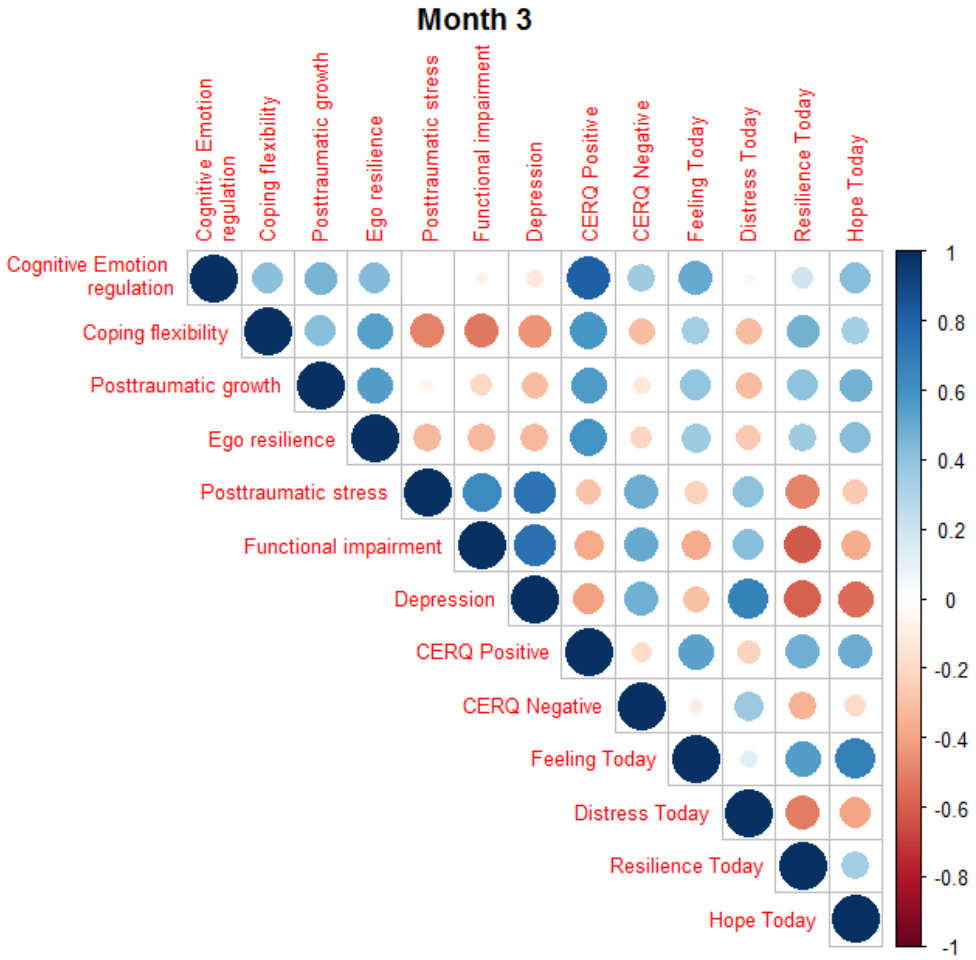


Figure A10 Graphical representation of the correlation matrix between the various scales at month 3 from baseline. Positive correlations are displayed in blue and negative correlations in red color. The color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: Pair wise deletion method was applied.

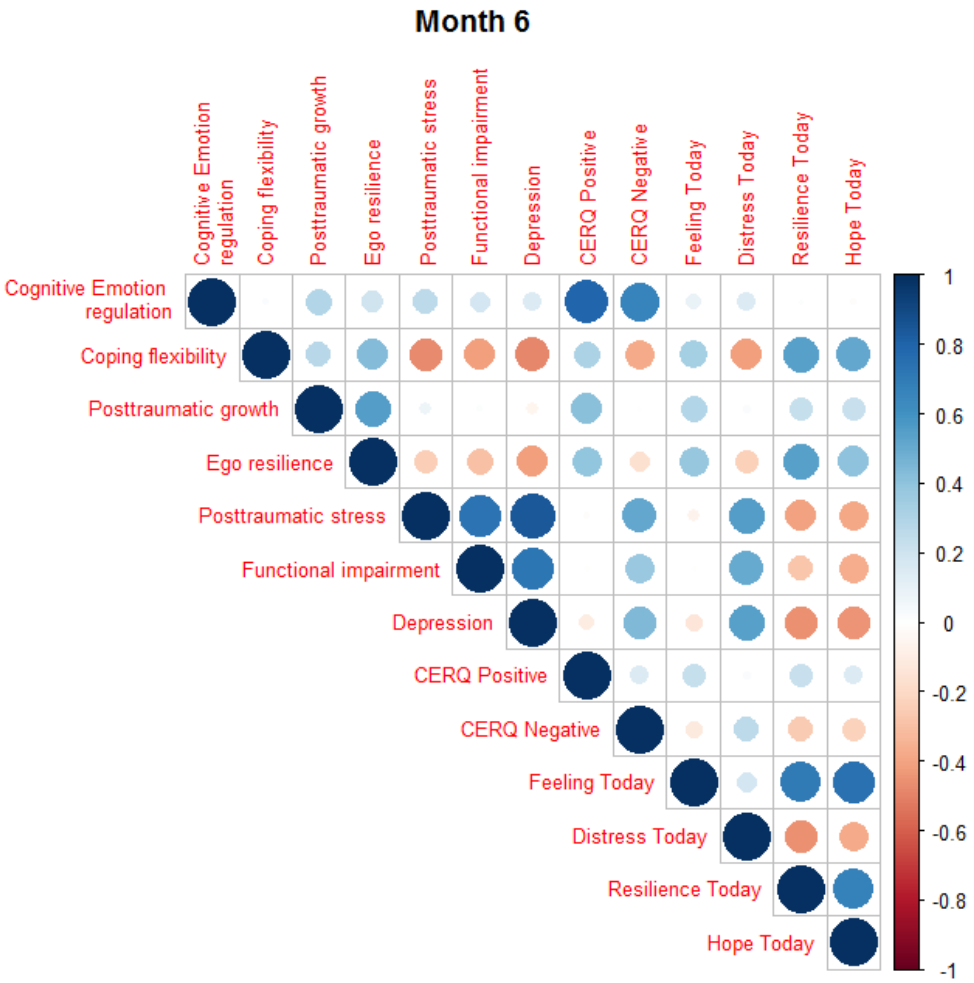


Figure A11 Graphical representation of the correlation matrix between the various scales at month 6 from baseline. Positive correlations are displayed in blue and negative correlations in red color. The color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: Pair wise deletion method was applied.

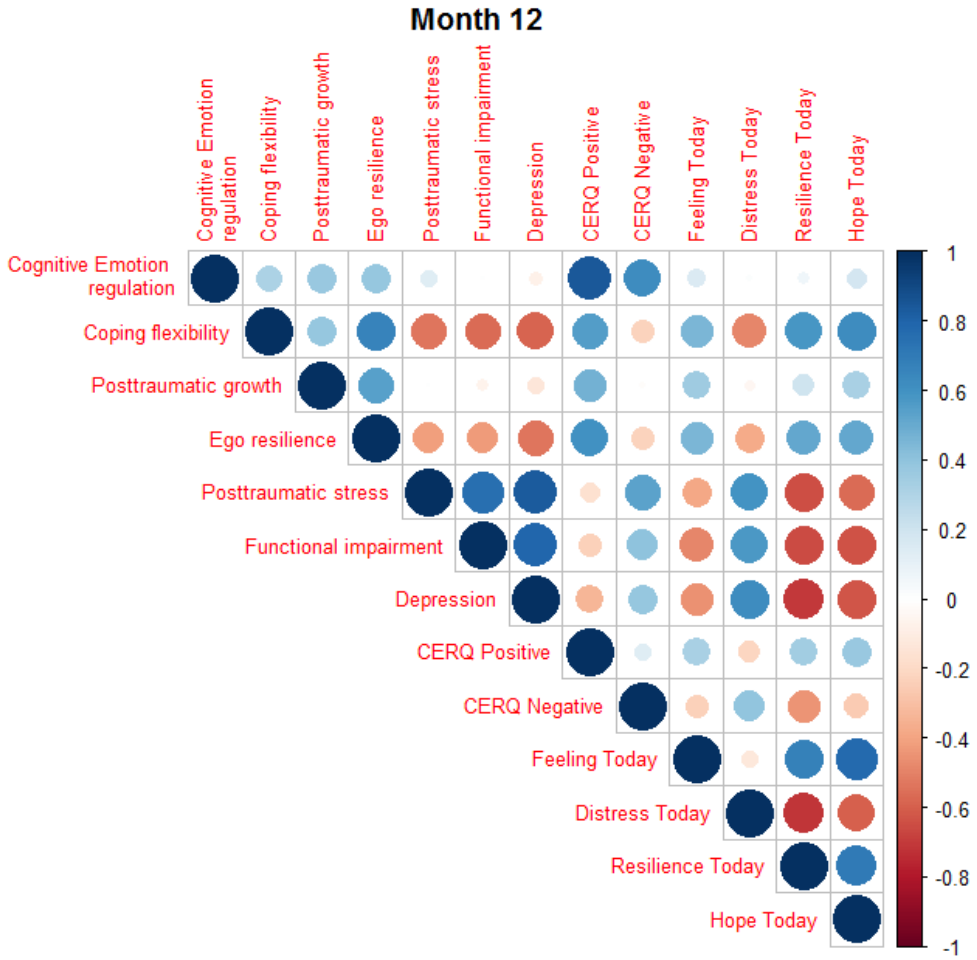


Figure 12 Graphical representation of the correlation matrix between the various scales at month 12 from baseline. Positive correlations are displayed in blue and negative correlations in red color. The color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: Pair wise deletion method was applied.

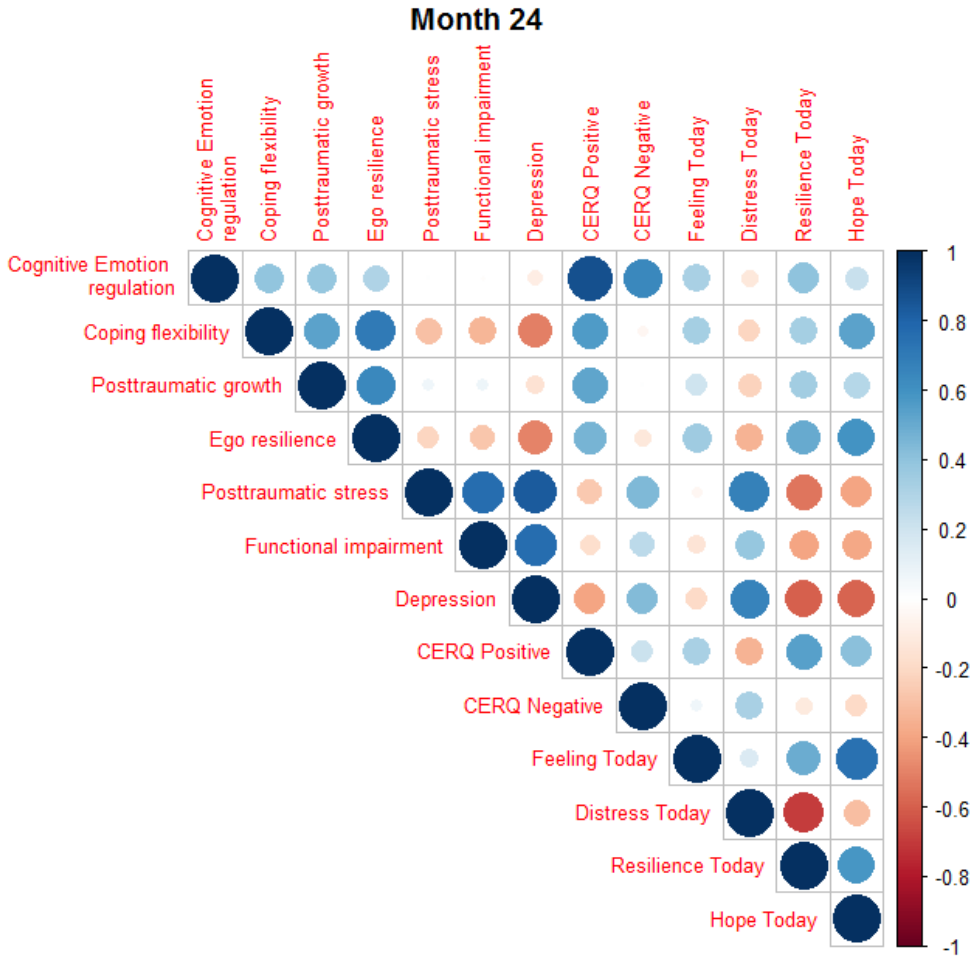


Figure 13 Graphical representation of the correlation matrix between the various scales at month 24 from baseline. Positive correlations are displayed in blue and negative correlations in red color. The color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are leaved blank. Handling of missing data: Pair wise deletion method was applied.

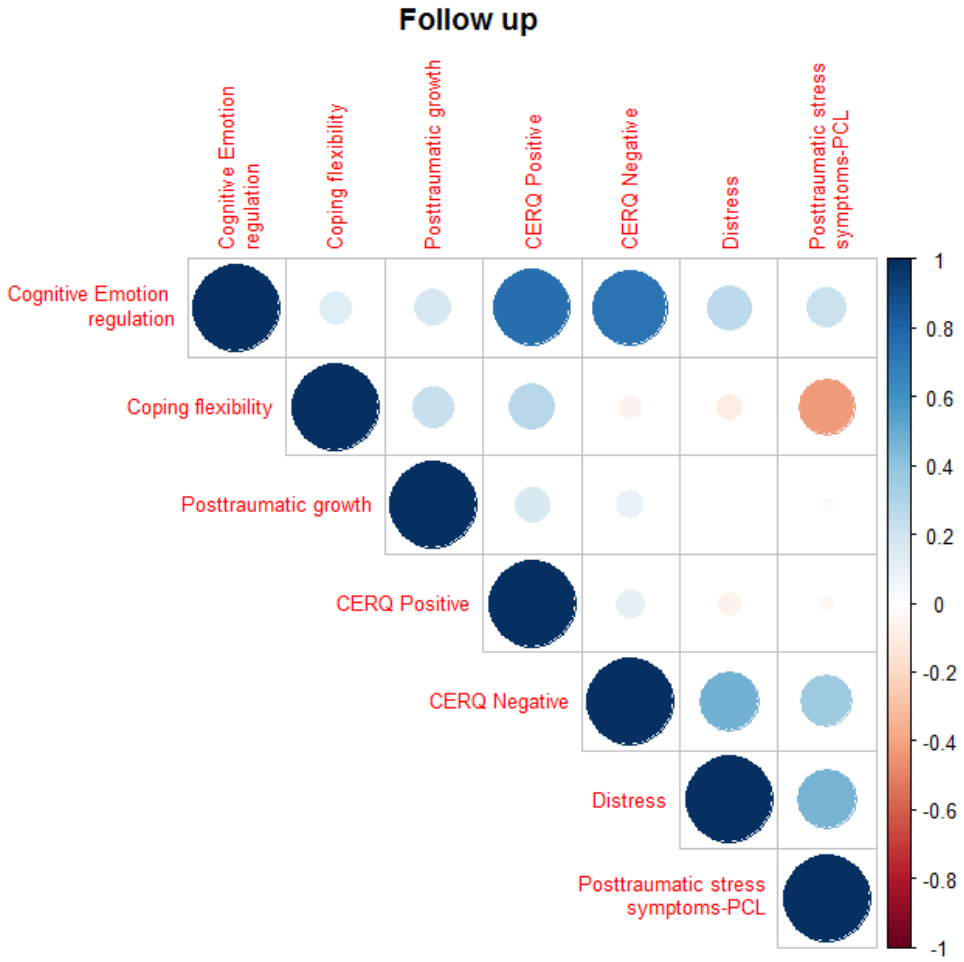


Figure A14 Graphical representation of the correlation matrix between the various scales at follow. Positive correlations are displayed in blue and negative correlations in red color. The color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are left blank. Handling of missing data: Pair wise deletion method was applied.

A2.5 Case Study: Assess the relationship between self-report questionnaires with sociodemographic and medical variables at baseline

Analysis plan

The present study involves an examination of the relationship between the various PTSD (Posttraumatic stress), Functional impairment, CES-D (Depression), CERQ (Cognitive and emotion regulation), FLEX (Coping flexibility), PTGI (Posttraumatic growth), EGO (Ego Resilience), PCL (Posttraumatic stress symptoms) and KESSLER (Distress) scales as well as the user perceived levels of distress, resilience and hope with sociodemographic, medical variables and reported symptoms at baseline. No lifestyle variables are included in the HUJI dataset. The purpose is to identify statistically significant differences in psychological scores between two or more groups of an independent variable e.g. patients having participated in intervention workshop or not.

We utilized one-way ANOVA test or Kruskal-Wallis test when the assumptions of the former were violated. Kruskal-Wallis test is a non-parametric alternative to ANOVA test, which does not assume that the population distributions follow the normal distribution. The aov() function of 'R' package was used for the ANOVA test and the kruskal.test() function for the Kruskal-Wallis test. Anova assumptions were tested using Shapiro-Wilk test (that checks the normality assumption) and Levene's test (that checks the homogeneity of variance assumption). "Post-hoc" analyses were subsequently

performed with Tukey's test (parametric) using TukeyHSD() function and Dunn's test (non parametric) using dunnTest() function. The aforementioned post hoc analyses were applied to variables with more than two groups for which a statistical significant result was obtained from the Anova test or the Kruskal-Wallis test, respectively. The aim is to explore which groups are statistically different from each other. A statistical significance level of 5% was considered for all studies.

The effect size of differences was assessed using eta squared (etasq() function of R package) and epsilon squared (epsilonSquared() function of R package) measures.

Chi-square and fisher tests were performed to explore the dependencies among sociodemographic variables, medical variables and reported symptoms at baseline.

Results

The analysis refers to a subgroup of 198 patients that have the majority of clinical and psychological data at baseline available. In particular, two patients in the dataset had no clinical data or psychological measures at baseline and one patient had most clinical data missing (including participation in the intervention). These patients were excluded from the analysis.

Even though the Normality assumption was violated for almost all the independent variables (p-value of Shapiro-Wilk test was less than 0.05), Anova and Kruskal-Wallis test were consistent in most of the cases. Only Kruskal test results (p-value) are presented in the following tables (Tables A7, A8).

Part A: Sociodemographic and medical variables (Tables A7)

At baseline, the patients that agreed to participate in the Intervention (n=92) reported significantly higher levels of stress today, posttraumatic stress, functional impairment, depression,and negative cognitive emotion regulation and lower levels of resilience, flexibility and positive cognitive emotion regulation. The results are in agreement with the Hamama-Raz et al. (2012). It is noted, that the patient sample analyzed in Hamama-Raz et al. (2012) is a subset of the one provided for the needs of BOUNCE and is analyzed here. The mean and median of stress today, posttraumatic stress symptoms, functional impairment and depression remains higher in the group of participants throughout the 24 months observation period however the differences in most cases are not statistical significant at an alpha level of 0.05. The differences observed between participants and non-participants for coping flexibility, negative and positive CER and resilience today are not statistically significant throughout the 2-year observation period. CER positive is slightly higher for participants the first year but not at the end of the second year; however, these differences are not significant. A non-significantly higher level of negative CER for non participants is observed for at the end of second year. PCL is significantly higher for patients that participated in the group intervention. Kessler distress level is also higher for participants but the difference is statistical significant at an alpha level of 0.1. It is noted that the frequency of participants was significantly higher among patients that reported disruption in sexuality, interference with a sense of femininity and heat waves.

Posttraumatic growth tends to decrease with age for all time points. Contrary to kruskal test, we get no significant pairwise difference with post hoc analysis. Furthermore, younger ages tend to have a higher positive CER. Significant pairwise differences are detected at baseline and month 12.

Married women are characterized by less hope today. The difference is statistical significant at baseline and month 3.

Unemployed patients tend to experience greater depression. The differences are statistical significant at baseline and month 12.

Women that have been treated with chemo only report significantly higher posttraumatic stress symptoms at follow up. Posttraumatic stress symptoms are higher throughout the two year observation period, with the exception of baseline, but the differences are not statistical significant.

Patients receiving hormonal therapy have a higher coping flexibility. The difference is statistical significant at follow up (and month3; however, at month 3 the number of patients not receiving hormonal therapy is low).

Patients receiving disability pension have a significantly higher depression throughout the 2 year observation period. They are characterized by higher functional impairment, which is significant the first year of the observation period. Furthermore, posttraumatic stress symptoms and distress levels are significantly higher at follow up for this subgroup of patients. Posttraumatic stress symptoms are also higher throughout the observation period, but the differences are not statistically significant. Significantly higher stress today and significantly lower hope today are sporadically observed.

Native Israelis tend to maintain a better psychology throughout the observation period. Significant differences for the majority of the psychological scales are observed at month 12.

Whether finished the workshop, having children, living in the city, stage and being a carrier does not seem to have an effect on the specific psychological measures.

Overall, the effect size for all of the statistically significant differences previously reported are small. Because the sample size is very small in some time points, especially in month 3 and month 5, non-significant findings could be due to inadequate sample size. Furthermore, the smaller the sample size is, the more deviations are expected from the true population effects.

TABLES A7 Kruskal-Wallis test (p values) between CES-D, PTSD, CERQ, PACT, PTGI, EGO, PCL, KESSLER, functional impairment, stress today, resilience today and hope today scales and sociodemographic and medical variables at baseline up to follow up. The colour density is proportional to the significance levels 0.0001, 0.001, 0.01 and 0.05.

Participation in the intervention	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.0002	0.2586	0.3446	0.0730	0.1560	NA
Resilience today	0.0051	0.1854	0.5359	0.2453	0.5792	NA
Hope today	0.1690	0.2845	0.7567	0.1550	0.5403	NA
PACT Coping flexibility	0.0012	0.8982	0.7054	0.1040	0.7209	0.2246
PTGI Posttraumatic growth	0.1566	0.1220	0.4069	0.2938	0.0893	0.5984
EGO Resilience	0.1277	0.3478	0.1686	0.5091	0.1805	NA
PTSD Posttraumatic stress symptoms	0.0010	0.4554	0.4277	0.0613	0.0830	NA
Functional impairment	0.0413	0.3572	0.0205	0.0620	0.0770	NA
CES-D Depression	0.0038	0.0839	0.5475	0.0276	0.3584	NA
CERQ Positive cognitive emotion regulation	0.0012	0.1949	0.4921	0.9330	0.5904	0.5739
CERQ Negative cognitive emotion regulation	0.0345	0.8466	0.9477	0.9859	0.4549	0.2406
K6 Distress level	NA	NA	NA	NA	NA	0.0751
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0060
Whether finished intervention	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.8716	0.1161	0.7247	0.4677	0.2754	NA
Resilience today	0.9846	0.9339	0.8839	0.2825	0.7250	NA
Hope today	0.4251	0.8246	0.6091	0.7256	0.7098	NA
PACT Coping flexibility	0.9022	0.1949	0.7414	0.4978	0.2466	0.2644
PTGI Posttraumatic growth	0.4779	0.9775	0.9518	0.3200	0.3155	0.0617
EGO Resilience	0.1160	0.8685	0.4349	0.0774	0.0689	NA
PTSD Posttraumatic stress symptoms	0.1581	0.0471	0.9024	0.4024	0.6157	NA
Functional impairment	0.2364	0.0862	0.8756	0.8556	0.5008	NA
CES-D Depression	0.4693	0.0978	0.9644	0.0546	0.4172	NA
CERQ Positive cognitive emotion regulation	0.5526	0.9310	0.4282	0.6024	0.8470	0.4884
CERQ Negative cognitive emotion regulation	0.1070	0.4013	0.4425	0.2123	0.8465	0.6332
K6 Distress level	NA	NA	NA	NA	NA	0.5513
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.1074
Age	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.7524	0.5178	0.4813	0.9240	0.4349	NA
Resilience today	0.9987	0.4296	0.5140	0.8366	0.7005	NA
Hope today	0.8340	0.3265	0.5712	0.4202	0.9380	NA
PACT Coping flexibility	0.8494	0.7962	0.2395	0.6915	0.3592	0.6631
PTGI Posttraumatic growth	0.0439	0.0265	0.0343	0.0166	0.2337	0.1373
EGO Resilience	0.6728	0.6065	0.7764	0.2030	0.7871	NA
PTSD Posttraumatic stress symptoms	0.8033	0.8269	0.6902	0.8436	0.1218	NA
Functional impairment	0.3706	0.6459	0.2156	0.8035	0.5306	NA
CES-D Depression	0.9592	0.7604	0.0502	0.9238	0.8244	NA
CERQ Positive cognitive emotion regulation	0.0059	0.0995	0.3007	0.0270	0.1036	0.4249
CERQ Negative cognitive emotion regulation	0.0614	0.7851	0.6895	0.7359	0.7106	0.7380
K6 Distress level	NA	NA	NA	NA	NA	0.4780
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.8562
Stage	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.4205	0.5033	0.8377	0.3366	0.1424	NA
Resilience today	0.6410	0.8813	0.7816	0.6253	0.3957	NA
Hope today	0.1808	0.9074	0.8931	0.9791	0.9736	NA
PACT Coping flexibility	0.8074	0.3900	0.1121	0.7593	0.7282	0.0343
PTGI Posttraumatic growth	0.6997	0.5582	0.4201	0.1402	0.5721	0.0882
EGO Resilience	0.8256	0.9002	0.9132	0.5759	0.4709	NA
PTSD Posttraumatic stress symptoms	0.8595	0.4739	0.5748	0.4193	0.2452	NA
Functional impairment	0.5179	0.7036	0.3506	0.6115	0.4952	NA
CES-D Depression	0.6670	0.7313	0.6227	0.7380	0.2407	NA
CERQ Positive cognitive emotion regulation	0.6988	0.8738	0.2716	0.8445	0.6759	0.4202
CERQ Negative cognitive emotion regulation	0.2253	0.7010	0.7427	0.8868	0.3415	0.5775
K6 Distress level	NA	NA	NA	NA	NA	0.8930
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.9404

Protocol	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.6905	0.7985	0.9865	0.5613	0.1660	0.1821
Resilience today	0.8424	0.2299	0.0727	0.5284	0.2925	0.4075
Hope today	0.4908	0.0271	0.1791	0.6805	0.1956	0.2008
PACT Coping flexibility	0.9964	0.4273	0.5219	0.5181	0.9567	0.0187
PTGI Posttraumatic growth	0.4109	0.4750	0.4021	0.6684	0.7885	0.7761
EGO Resilience	0.0396	0.7458	0.0391	0.3382	0.2239	NA
PTSD Posttraumatic stress symptoms	0.8908	0.9031	0.5907	0.2239	0.0253	NA
Functional impairment	0.1043	0.1876	0.1517	0.5621	0.3504	NA
CES-D Depression	0.4648	0.4383	0.5210	0.4749	0.1854	NA
CERQ Positive cognitive emotion regulation	0.4902	0.3150	0.4408	0.6808	0.5550	0.8463
CERQ Negative cognitive emotion regulation	0.8913	0.1203	0.3402	0.8992	0.1364	0.7138
K6 Distress level	NA	NA	NA	NA	NA	0.4285
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.2017
Treatment type	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.4709	0.0478	0.1041	0.3826	0.4766	0.8529
Resilience today	0.6504	0.8224	0.5666	0.8141	0.3254	0.1997
Hope today	0.8902	1.0000	0.7682	0.4904	0.0869	0.3205
PACT Coping flexibility	0.9705	0.0521	0.1593	0.8189	0.7033	0.5221
PTGI Posttraumatic growth	0.2801	0.8189	0.1508	0.6867	0.0893	0.1810
EGO Resilience	0.3636	0.7507	0.1499	0.4919	0.2065	NA
PTSD Posttraumatic stress symptoms	0.7498	0.0760	0.0909	0.1638	0.2835	NA
Functional impairment	0.1882	0.0211	0.3225	0.4517	0.1062	NA
CES-D Depression	0.3601	0.0616	0.1139	0.6225	0.2521	NA
CERQ Positive cognitive emotion regulation	0.0452	0.8888	0.1688	0.7990	0.9419	0.5699
CERQ Negative cognitive emotion regulation	0.1186	0.2709	0.5273	0.6464	1.0000	0.2879
K6 Distress level	NA	NA	NA	NA	NA	0.5956
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0096
Herceptin	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.2270	0.7051	0.8154	0.3259	0.6405	0.7033
Resilience today	0.5443	0.2035	0.9569	0.1660	0.4870	0.2759
Hope today	0.7680	0.1229	0.2875	0.1526	0.2864	0.9299
PACT Coping flexibility	0.8270	0.7637	0.1816	0.1908	0.1663	0.4269
PTGI Posttraumatic growth	0.3981	0.5843	0.3493	0.2095	0.9259	0.4623
EGO Resilience	0.0328	0.5109	0.8649	0.7359	0.3468	NA
PTSD Posttraumatic stress symptoms	0.2477	0.6084	0.9432	0.8192	0.3520	NA
Functional impairment	0.5000	0.9376	0.9425	0.0571	0.6146	NA
CES-D Depression	0.5162	0.6477	0.9216	0.4547	0.3064	NA
CERQ Positive cognitive emotion regulation	0.0876	0.4671	0.2115	0.5296	0.5348	0.1392
CERQ Negative cognitive emotion regulation	0.1241	0.7725	0.7491	0.9127	0.0444	0.7879
K6 Distress level	NA	NA	NA	NA	NA	0.3851
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.7646
Hormonal	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.1568	0.0117	0.2140	0.5356	0.3366	0.5074
Resilience today	0.5651	0.0535	0.0938	0.5688	0.5737	0.3592
Hope today	0.8169	0.9535	0.0045	0.3896	0.6440	0.2866
PACT Coping flexibility	0.1456	0.0290	0.1657	0.1797	0.2821	0.0096
PTGI Posttraumatic growth	0.4116	0.5497	0.2922	0.9634	0.7558	0.5546
EGO Resilience	0.6346	0.0113	0.3192	0.5472	0.6714	NA
PTSD Posttraumatic stress symptoms	0.5750	0.0022	0.5727	0.9565	0.0727	NA
Functional impairment	0.4746	0.0474	0.7396	0.3822	0.0270	NA
CES-D Depression	0.6486	0.0249	0.8027	0.3912	0.1445	NA
CERQ Positive cognitive emotion regulation	0.9591	0.4256	0.9911	0.3912	0.9734	0.3221
CERQ Negative cognitive emotion regulation	0.2796	0.1253	0.7733	0.9565	0.8325	0.2655
K6 Distress level	NA	NA	NA	NA	NA	0.1004
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0791

Urban residence	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.9396	0.5797	0.8006	0.2447	0.9896	0.7184
Resilience today	0.7253	0.2917	0.2898	0.1601	0.8707	0.7558
Hope today	0.8182	0.6167	0.7765	0.4861	0.1817	0.2292
PACT Coping flexibility	0.4334	0.4380	0.8985	0.3026	0.8163	0.5326
PTGI Posttraumatic growth	0.9299	0.6503	0.9971	0.1247	0.5933	0.9223
EGO Resilience	0.7557	0.3677	0.7984	0.3981	0.9629	NA
PTSD Posttraumatic stress symptoms	0.2765	0.0137	0.7588	0.0738	0.5149	NA
Functional impairment	0.0865	0.8239	0.5343	0.7946	0.3752	NA
CES-D Depression	0.5715	0.3978	0.6477	0.1890	0.7357	NA
CERQ Positive cognitive emotion regulation	0.1550	0.0538	0.0852	0.0697	0.2747	0.3419
CERQ Negative cognitive emotion regulation	0.4266	0.9374	0.1524	0.3424	0.4610	0.0664
K6 Distress level	NA	NA	NA	NA	NA	0.8827
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.2063
Married	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.5611	0.6202	0.8872	0.7563	0.0915	0.8034
Resilience today	0.0799	0.5412	0.3256	0.9019	0.3446	0.5293
Hope today	0.0146	0.0376	0.1519	0.2597	0.6338	0.9481
PACT Coping flexibility	0.6864	0.4688	0.2098	0.9336	0.1850	0.5390
PTGI Posttraumatic growth	0.3855	0.2557	0.9375	0.4226	0.4772	0.4318
EGO Resilience	0.0228	0.8988	0.2993	0.2932	0.9220	NA
PTSD Posttraumatic stress symptoms	0.7965	0.9696	0.7091	0.9917	0.2273	NA
Functional impairment	0.8646	0.9288	0.8052	0.8776	0.3689	NA
CES-D Depression	0.8967	0.8189	0.9061	0.3045	0.2267	NA
CERQ Positive cognitive emotion regulation	0.2011	0.9773	0.9062	0.9626	0.0718	0.2926
CERQ Negative cognitive emotion regulation	0.1230	0.7218	0.5373	0.9709	0.7134	0.6271
K6 Distress level	NA	NA	NA	NA	NA	0.5925
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.4937
Israeli	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.1299	0.7297	0.4973	0.0716	0.0035	0.9729
Resilience today	0.0728	0.9050	0.1398	0.0049	0.1498	0.1331
Hope today	0.6965	0.6929	0.2206	0.0007	0.0215	0.1390
PACT Coping flexibility	0.3650	0.9620	0.2266	0.3355	0.9307	0.6321
PTGI Posttraumatic growth	0.6309	0.9513	0.4447	0.0911	0.8726	0.6562
EGO Resilience	0.9012	0.4742	0.0963	0.0445	0.3169	NA
PTSD Posttraumatic stress symptoms	0.4747	0.0817	0.0015	0.0051	0.1511	NA
Functional impairment	0.0471	0.7556	0.0117	0.0138	0.0840	NA
CES-D Depression	0.0626	0.2883	0.0006	0.0010	0.0475	NA
CERQ Positive cognitive emotion regulation	0.9500	0.7675	0.3468	0.1288	0.3533	0.6970
CERQ Negative cognitive emotion regulation	0.3535	0.7280	0.0442	0.1561	0.9268	0.0018
K6 Distress level	NA	NA	NA	NA	NA	0.0133
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0528
Have children	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.5098	0.6421	0.5216	0.8628	0.6444	0.5263
Resilience today	0.7972	0.6601	0.5758	0.7187	0.7455	0.5461
Hope today	0.7143	0.4215	0.1420	0.2664	0.1703	0.4013
PACT Coping flexibility	0.8009	0.2151	0.2247	0.6846	0.7684	0.7728
PTGI Posttraumatic growth	0.3668	0.6924	0.1114	0.5815	0.2537	0.1085
EGO Resilience	0.6101	0.5696	0.9357	0.6876	0.4317	NA
PTSD Posttraumatic stress symptoms	0.2604	0.5018	0.9895	0.4108	0.7681	NA
Functional impairment	0.8526	0.9793	0.4756	0.8139	0.6321	NA
CES-D Depression	0.6084	0.9794	0.6166	0.5298	0.7679	NA
CERQ Positive cognitive emotion regulation	0.2578	0.8469	0.8336	0.5419	1.0000	0.2215
CERQ Negative cognitive emotion regulation	0.6338	0.4389	0.1814	0.9926	0.2286	0.6134
K6 Distress level	NA	NA	NA	NA	NA	0.5881
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.8567

Carrier	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.0533	0.0882	0.4437	0.7814	0.5533	0.7767
Resilience today	0.9706	0.8144	0.6108	0.9783	0.2524	0.1044
Hope today	0.6435	0.3284	0.3514	0.8782	0.7145	0.4244
PACT Coping flexibility	0.1934	0.2991	0.6116	0.2850	0.6505	1.0000
PTGI Posttraumatic growth	0.3985	0.4029	0.9581	0.5248	0.8209	0.0793
EGO Resilience	0.6777	0.8670	0.7628	0.6450	0.6735	NA
PTSD Posttraumatic stress symptoms	0.9830	0.8144	0.2525	0.4981	0.5818	NA
Functional impairment	0.5117	0.0854	0.5479	0.3947	0.7586	NA
CES-D Depression	0.2590	0.1080	0.4356	0.1097	0.4755	NA
CERQ Positive cognitive emotion regulation	0.0695	0.7290	0.0111	0.8495	0.3004	0.8677
CERQ Negative cognitive emotion regulation	0.2512	0.0828	0.2969	0.9567	0.4170	0.5577
K6 Distress level	NA	NA	NA	NA	NA	0.6764
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.2222
Family histrory	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.6149	0.5047	0.2413	0.3055	0.6161	0.1115
Resilience today	0.0677	0.3048	0.2712	0.1967	0.7318	0.6570
Hope today	0.1278	0.6942	0.6907	0.3891	0.2990	0.1508
PACT Coping flexibility	0.3241	0.5268	0.9251	0.2087	0.7659	0.1498
PTGI Posttraumatic growth	0.3468	0.5267	0.6014	0.8580	0.1910	0.0137
EGO Resilience	0.2777	0.7912	0.3124	0.2099	0.8131	NA
PTSD Posttraumatic stress symptoms	0.5291	0.5650	0.5711	0.1470	0.8372	NA
Functional impairment	0.1968	0.4592	0.0310	0.0724	0.2290	NA
CES-D Depression	0.0265	0.2493	0.3680	0.1352	0.1682	NA
CERQ Positive cognitive emotion regulation	0.5648	0.2169	0.4543	0.4162	0.1112	0.4675
CERQ Negative cognitive emotion regulation	0.3918	0.6461	0.2423	0.0116	0.1390	0.2481
K6 Distress level	NA	NA	NA	NA	NA	0.4840
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.8043
Religious	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.5458	0.8330	0.7899	0.5989	0.1718	0.0427
Resilience today	0.2731	0.2710	0.8458	0.8191	0.1729	0.5522
Hope today	0.9024	0.8869	0.5937	0.8095	0.6481	0.7738
PACT Coping flexibility	0.6488	0.1524	0.7484	0.9207	0.9961	0.8978
PTGI Posttraumatic growth	0.0129	0.8085	0.3321	0.1010	0.2241	0.2118
EGO Resilience	0.8027	0.3388	0.4897	0.2052	0.6608	NA
PTSD Posttraumatic stress symptoms	0.1595	0.1704	0.0178	0.1441	0.3087	NA
Functional impairment	0.2045	0.2120	0.2957	0.1584	0.0574	NA
CES-D Depression	0.0814	0.3772	0.0628	0.1628	0.0280	NA
CERQ Positive cognitive emotion regulation	0.2393	0.2566	0.1892	0.0866	0.2440	0.5592
CERQ Negative cognitive emotion regulation	0.2191	0.5769	0.8770	0.7282	0.5653	0.0495
K6 Distress level	NA	NA	NA	NA	NA	0.3575
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.3261
Work status	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.1342	0.4197	0.6954	0.0257	0.6137	0.2367
Resilience today	0.7886	0.4470	0.5971	0.3452	0.9909	0.1116
Hope today	0.2614	0.1706	0.4643	0.3017	0.8360	0.2356
PACT Coping flexibility	0.3937	0.4464	0.3888	0.6639	0.8300	0.1495
PTGI Posttraumatic growth	0.2083	0.1935	0.3803	0.3294	0.4912	0.9318
EGO Resilience	0.7615	0.7369	0.5331	0.1749	0.3162	NA
PTSD Posttraumatic stress symptoms	0.1542	0.0984	0.1664	0.2972	0.3194	NA
Functional impairment	0.2587	0.6978	0.0419	0.2619	0.4562	NA
CES-D Depression	0.0160	0.0644	0.0743	0.0147	0.2333	NA
CERQ Positive cognitive emotion regulation	0.2603	0.7824	0.8712	0.3042	0.4433	0.1206
CERQ Negative cognitive emotion regulation	0.1695	0.5586	0.2329	0.0322	0.6158	0.4393
K6 Distress level	NA	NA	NA	NA	NA	0.6421
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.5925

Income from work	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.2469	0.4799	0.7247	0.0813	0.9014	0.3665
Resilience today	0.5367	0.1412	0.5507	0.3036	0.8256	0.2114
Hope today	0.4246	0.0158	0.4743	0.1522	0.4409	0.2651
PACT Coping flexibility	0.2937	0.9296	0.8346	0.4074	0.6701	0.3540
PTGI Posttraumatic growth	0.0944	0.1256	0.1566	0.0476	0.9427	0.8416
EGO Resilience	0.8684	0.3949	0.2928	0.1028	0.9763	NA
PTSD Posttraumatic stress symptoms	0.2732	0.1925	0.0997	0.2579	0.9289	NA
Functional impairment	0.4881	0.3022	0.0679	0.2036	0.4949	NA
CES-D Depression	0.0580	0.0531	0.0673	0.0132	0.2453	NA
CERQ Positive cognitive emotion regulation	0.3201	0.4002	0.6405	0.0660	0.0498	0.6364
CERQ Negative cognitive emotion regulation	0.3130	0.6162	0.1932	0.1130	0.5576	0.6613
K6 Distress level	NA	NA	NA	NA	NA	0.6759
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.5994
Income from disability pension	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.0357	0.1513	0.2464	0.0134	0.2665	0.2381
Resilience today	0.2935	0.0551	0.0936	0.2062	0.4015	0.7935
Hope today	0.4676	0.0258	0.6036	0.0287	0.7057	0.4379
PACT Coping flexibility	0.1839	0.4058	0.1627	0.2476	0.3302	0.6708
PTGI Posttraumatic growth	0.2676	0.0308	0.1844	0.1054	0.4019	0.7969
EGO Resilience	0.7033	0.1104	0.0871	0.0609	0.4991	NA
PTSD Posttraumatic stress symptoms	0.2749	0.2892	0.0526	0.0935	0.2539	NA
Functional impairment	0.0236	0.2768	0.0192	0.0040	0.1188	NA
CES-D Depression	0.0086	0.0329	0.0039	0.0062	0.0237	NA
CERQ Positive cognitive emotion regulation	0.1889	0.0141	0.9556	0.0151	0.0513	0.2741
CERQ Negative cognitive emotion regulation	0.3431	0.4567	0.4442	0.3036	0.9909	0.0541
K6 Distress level	NA	NA	NA	NA	NA	0.0117
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0063
Income from pension	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.1697	0.2112	0.5770	0.6558	0.2100	0.9542
Resilience today	0.5830	0.9897	0.2044	0.3162	0.3889	0.6226
Hope today	0.5683	0.1060	0.5607	0.9587	0.4431	0.5625
PACT Coping flexibility	0.9530	0.7279	0.0245	0.4285	0.9547	0.2833
PTGI Posttraumatic growth	0.0419	0.3600	0.4647	0.9563	0.2261	0.3923
EGO Resilience	0.3388	0.9794	0.1188	0.2193	0.2107	NA
PTSD Posttraumatic stress symptoms	0.6183	0.6704	0.2778	0.3916	0.4949	NA
Functional impairment	0.1533	0.8459	0.9327	0.5733	0.7633	NA
CES-D Depression	0.9129	0.0934	0.5420	0.7295	0.8198	NA
CERQ Positive cognitive emotion regulation	0.2537	0.7082	0.3655	0.3409	0.3024	0.9313
CERQ Negative cognitive emotion regulation	0.5743	0.0626	0.1462	0.3221	0.3550	0.2109
K6 Distress level	NA	NA	NA	NA	NA	0.2243
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.1173

Part B: Patient reported symptoms (Tables A8)

Patients were asked to report the existence and severity of the following symptoms only at baseline. No relevant record exists for the subsequent time points.

Heat waves: Heat waves are mostly related with age (more frequent in younger patients (<50), and Herceptin (more frequent in patients not receiving Herceptin) as well as stage (more frequent in stage 2 than 1). Most patients experiencing heat waves also experience sleep problems and/or mood swings, contrary to patients that did not report heat waves at baseline (the latter have a more balanced distribution among the other symptoms).

Patients that have reported heat waves (Before Imputation: No:43, Yes:138. After Imputation: No: 47, Yes:146) are also reporting statistically significant higher posttraumatic stress symptoms, higher functional impairment and lower resilience at baseline. With respect to PTSD subscales, the main differences are observed for 'physical reactions when reminded of the trauma', 'difficulty in sleeping' and 'irritability'. Functional impairment and post-traumatic stress symptoms remain higher throughout the two-year observation period (with the exception of M3). However, the differences are statistical significant at 0.05 level only for PTSD values the second year of observation. Post-traumatic stress symptoms remains higher at follow up for the patients that reported heat waves at baseline but the differences are not statistical significant. The effect size of all differences as assessed by *epsilon squared* are small.

When we take into consideration the severity of heat waves, the patients reporting the higher level of the specific symptom (level four) at baseline have significantly lower (from 2) EGO resilience at baseline, month 6 and month 12. It is noted, that overall, an increase in severity level is not accompanied by a decrease in EGO resilience. PTSD and functional impairment for patients reporting higher symptom severity are higher throughout the 2-year period, but differences are statistically significant only at baseline. At follow up, post-traumatic stress symptoms (PCL) for patients that have reported 3 or 4 severity level of their symptom 'heat waves' is significantly higher than those reporting no or a low (level one) level of heat waves.

Mood swings: Married women experience significantly more mood swings. Furthermore, the proportion of patients of traditional faith level that experience mood swings is higher than those of secular faith. The frequency of the symptoms Interference with a sense of femininity, disruption in sexuality, discomfort with body, sleep problems and heat waves is higher among patients experiencing mood swings than those that do not.

At baseline, negative CER, stress today and posttraumatic growth are significantly higher, whereas resilience today, hope today and coping flexibility are significantly lower for patients reporting mood swings (Before Imputation: No:48, Yes: 132. After Imputation: No:52, Yes:140). Posttraumatic stress symptoms, depression and functional impairment remain significantly higher throughout the 2-year observation period for patients experiencing mood swings at baseline. Negative CER, stress today and post-traumatic growth remain higher during the 2-year period but the differences are not statistically significant at all time points. At follow up, negative CER, distress levels and PCL posttraumatic stress symptoms are significantly higher. The effect size of the differences are medium as assessed based on *epsilon squared*.

At baseline, posttraumatic stress symptoms, depression, functional impairment, stress today and negative CER gradually increases, whereas hope and resilience today gradually decreases with increased level of symptom severity. Overall the effect size is high. With the exception of patients that have reported the higher level of symptom severity (it is noted that patients reporting severity "4" vary between 2-7 for M3-M24), functional impairment, posttraumatic stress symptoms and depression gradually increases with increased level of severity for time points M6, M12 and M24. Even though Kruskal test detects statistically significant differences, post-hoc analysis (dunn-test with p adjustment)

may fail in some cases (M12, M24). The effect size is high at baseline and medium at the other time points. In most cases, post hoc analysis reveals that these differences are statistical significant between the lower and higher levels of severity.

Sleep problems: The frequency of sleep problems does not seem to be related to any sociodemographic or clinical parameter. The frequency of the symptoms heat waves, mood swings and interference with a sense of femininity is higher among patients experiencing sleep problems than those that do not.

Patients that have reported sleep problems (Before Imputation: No:58, Yes:123. After Imputation: No:59, Yes:133) are reporting significantly higher post-traumatic stress symptoms (especially pds 13:difficulty in sleeping , relieving trauma, concentration), depression (especially restless sleep and difficulty concentrating), functional impairment (especially work and leisure activities) and higher posttraumatic growth at baseline. Functional impairment, posttraumatic stress symptoms, depression and post traumatic growth remains higher remain higher throughout the 2 year observation period (with the exception of functional impairment at M3), but the differences are statistically significant at M6 (and M12 for PTG). At follow up, both negative and positive CER are higher for patients reporting sleep problems at baseline. Overall, the effect size of the differences is small.

When we take into consideration the severity level of sleep problems, patients reporting higher levels of severity (three or four) report significantly higher depression, functional impairment and posttraumatic stress symptoms and significantly lower hope today, EGO resilience and resilience today at baseline, than those reporting no or low levels of symptom severity. The effect size of differences is medium. Posttraumatic stress symptoms and depression remain significantly higher throughout the first year after baseline. The effect size is medium.

Obesity: Obesity problems are less frequent in women above 63 years of age. The frequency of the symptoms *discomfort with their body* and *disruption in sexuality*, is higher among patients experiencing obesity problems than those that do not.

Overall, experiencing problems with obesity (Before Imputation: No:90, Yes:89. After Imputation: No:97, Yes:95) does not have a statistically significant effect on psychological scales at baseline, throughout the 2-year observation period or at follow up. Analyzing the severity of obesity problems, statistical significant differences are observed between no or low levels and the highest level of obesity problems, at baseline for stress today, posttraumatic stress symptoms, functional impairment, depression and negative CER and at follow up for negative CER, posttraumatic stress symptoms and distress level. The highest level of symptom severity is associated with worse psychology in all cases, but the effect size of the differences are small or small to medium.

Discomfort with their body: Almost all patients that had received chemotherapy reported discomfort with their body in contrast with patients that had received both chemotherapy and radiotherapy. This may be related to the type of surgery that these group of patients have undergone (however, there is no knowledge if there were different surgery types). The frequency of the symptoms interference with a sense of femininity, disruption in sexuality, mood swings and obesity problems is higher among patients reporting discomfort with their body than those that do not.

At baseline, negative CER, stress today, post-traumatic stress symptoms, depression and functional impairment are significantly higher, whereas resilience today, hope today and coping flexibility are significantly lower for patients reporting discomfort with their body (Before Imputation: No:55, Yes:121. After Imputation: No:63, Yes: 125). The effect size of the differences are small to medium. For this subgroup of patients posttraumatic stress symptoms, stress today, depression and functional impairment remains higher, whereas resilience today, hope today and coping flexibility remains lower throughout the 2-year observation period. The effect size of the differences are small in most cases and not statistical significant for all time points. At follow up, negative CER, posttraumatic stress symptoms (PCL) and distress level are still higher for patients experiencing decrease in comfort with their body at

baseline and the differences are statistical significant. The effect size is medium for negative CER and PCL and small for distress level.

Analyzing the effect of symptom severity, posttraumatic stress symptoms and functional impairment gets worse with the increase of severity level and the differences are statistical significant the first year (except month 3) in most cases between no symptom and the rest levels of severity. Differences in depression are statistical significant at baseline and month 6 between levels 0 or 1 and the highest level of severity. At follow up, pairwise comparisons reveal statistical significant differences between no symptom and all levels of symptom severity for posttraumatic stress sympotms, and negative CER and between no symptom and the higher levels of severity for distress levels.

Disruption in sexuality: The frequency of this symptom declines with age. The frequency of the symptoms interference with a sense of femininity, body discomfort, mood swings and obesity problems is higher among patients reporting disruption in sexuality than those that do not.

Patients experiencing disruption in sexuality (Before Imputation: No:58, Yes:117. After Imputation: No:64 Yes: 124) are reporting significantly higher stress symptoms, depression and CERQ negative, post traumatic growth and significantly lower resilience today and coping flexibility, but the effect size is small. A medium effect size is observed for post-traumatic stress symptoms, and functional impairment (especially relations with family members and sexual family and relations), with a higher level characterized the patients reporting sexual distruption at baseline. During the 2 year observation period significantly higher values for patients with sexual disruption at baseline are observed for stress today post traumatic stress symptoms, functional impairment. The effect size is in most cases small. At follow up, CERQ negative, post traumatic growth and distress level are significantly higher for patients reporting disruption in sexuality at baseline, but the effect size is small. Taking into consideration the severity of sexual disruption statistical differences of medium effect size are observed at baseline for stress today , resilience today, coping flexibility, post traumatic stress sympotms depression, functional impairment and CERQ negative, as well as distress level, post traumatic stress sympotms and CERQ negative at follow up. The statistically significant differences are observed between patients reporting no or low levels of severity and high level, with the latter experiencing a worse psychology.

Interference with a sense of femininity: Almost all patients that had received chemotherapy reported discomfort with their body in contrast with patients that had received both chemotherapy and radiotherapy. This may be related to the type of surgery that these group of patients have undergone (however, there is no knowledge if there were different surgery types). The frequency of the symptoms interference with a sense of disruption in sexuality, mood swings and discomfort with their body is higher among patients reporting *Interference with a sense of femininity* than those that do not.

Patients reporting interference with a sense of femininity (Before Imputation: No:90, Yes:87. After Imputation: No: 95, Yes: 95) have significantly higher (of medium effect size) stress symptoms, depression and CERQ negative, post traumatic growth and significantly lower resilience today and coping flexibility, but the effect size is small.

Analyzing the effect of symptom severity throughout the 2-year observation period, significant differences are observed for posttraumatic stress symptoms, functional impairment and depression between the highest level of symptom severity and level zero or the lower levels. Stress today is significantly higher, and resilience today and hope today are significantly lower between level 0 and levels 3 and/or 4 at baseline. Statistical differences are observed for negative CER, at baseline, between the higher and lower levels of severity. Overall, coping flexibility decreases with the increase of severity level the first six months. At follow up, distress level and negative CER are significantly higher, for the higher levels of severity, whereas posttraumatic stress symptoms are significantly lower for level 0. The effect size of the differences range from medium to high.

It is noted that, because the sample size is very small in some time points, especially in month 3 and month 5, non-significant findings could be due to inadequate sample size. Furthermore, the smaller the sample size is, the more deviations are expected from the true population effects.

TABLES A8 Kruskal-Wallis test (p - values) between CES-D, PTSD, CERQ, PACT, PTGI, EGO, PCL, KESSLER, functional impairment, stress today, resilience today and hope today scales and reported symptoms at baseline up to follow up. The colour density is proportional to the significance levels 0.0001, 0.001, 0.01 and 0.05.

Heat Waves	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.1658	0.7290	0.1561	0.2473	0.5744	NA
Resilience today	0.0346	0.7707	0.4758	0.3800	0.8571	NA
Hope today	0.8050	0.5871	0.8200	0.2789	0.8533	NA
PACT Coping flexibility	0.5176	0.8679	0.3378	0.2144	0.9158	0.9865
PTGI Posttraumatic growth	0.3597	0.1323	0.5544	0.2903	0.7223	0.2945
EGO Resilience	0.5209	0.2854	0.5735	0.1571	0.4460	NA
PTSD Posttraumatic stress symptoms	0.0199	0.9447	0.0800	0.0249	0.0229	NA
Functional impairment	0.0094	0.2841	0.4251	0.1197	0.1192	NA
CES-D Depression	0.1357	0.5323	0.2441	0.3538	0.5672	NA
CERQ Positive cognitive emotion regulation	0.7797	0.2170	0.6459	0.9594	0.6407	0.1836
CERQ Negative cognitive emotion regulation	0.1350	0.3315	0.0470	0.7442	0.6165	0.1255
K6 Distress level	NA	NA	NA	NA	NA	0.1982
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0431
Mood Swings	**Baseline**	**M3**	**M6**	**M12**	**M24**	**Follow up**
Stress today	0.0000	0.1183	0.2008	0.0018	0.0789	NA
Resilience today	0.0000	0.0286	0.5420	0.0842	0.5063	NA
Hope today	0.0034	0.3324	0.1479	0.0532	0.7646	NA
PACT Coping flexibility	0.0002	0.0240	0.1178	0.3451	0.7300	0.9583
PTGI Posttraumatic growth	0.0017	0.8312	0.0415	0.2070	0.0950	0.0797
EGO Resilience	0.2303	0.3060	0.2635	0.7025	0.3433	NA
PTSD Posttraumatic stress symptoms	0.0000	0.0134	0.0000	0.0002	0.0052	NA
Functional impairment	0.0000	0.0099	0.0003	0.0076	0.0114	NA
CES-D Depression	0.0000	0.0464	0.0146	0.0033	0.0289	NA
CERQ Positive cognitive emotion regulation	0.0733	0.5637	0.7291	0.7649	0.5053	0.1035
CERQ Negative cognitive emotion regulation	0.0000	0.2962	0.0489	0.1660	0.5046	0.0000
K6 Distress level	NA	NA	NA	NA	NA	0.0000
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0001
Sleep Problems	**Baseline**	**M3**	**M6**	**M12**	**M24**	**Follow up**
Stress today	0.1566	0.9439	0.5117	0.6734	0.6613	NA
Resilience today	0.0920	0.2696	0.7934	0.8818	0.2867	NA
Hope today	0.3068	0.5797	0.4198	0.7949	0.3755	NA
PACT Coping flexibility	0.0864	0.8973	0.8364	0.8254	0.7511	0.3347
PTGI Posttraumatic growth	0.0076	0.2377	0.0038	0.0361	0.0758	0.2741
EGO Resilience	0.3382	0.9813	0.2133	0.0792	0.0408	NA
PTSD Posttraumatic stress symptoms	0.0001	0.9906	0.0356	0.1928	0.1145	NA
Functional impairment	0.0271	0.5250	0.0412	0.0880	0.1753	NA
CES-D Depression	0.0121	0.8694	0.0197	0.3339	0.8737	NA
CERQ Positive cognitive emotion regulation	0.1110	0.5505	0.2139	0.5683	0.6089	0.0075
CERQ Negative cognitive emotion regulation	0.3513	0.0986	0.8852	0.7683	0.4111	0.0017
K6 Distress level	NA	NA	NA	NA	NA	0.2066
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0940
Obesity	**Baseline**	**M3**	**M6**	**M12**	**M24**	**Follow up**
Stress today	0.4193	0.6117	0.1104	0.7904	0.6785	NA
Resilience today	0.7733	0.8857	0.2421	0.2946	0.6506	NA
Hope today	0.4199	0.9205	0.7784	0.8051	0.2381	NA
PACT Coping flexibility	0.7660	0.6910	0.4557	0.2720	0.4722	0.6102
PTGI Posttraumatic growth	0.9100	0.9365	0.7423	0.1810	0.9091	0.6566
EGO Resilience	0.5873	0.4659	0.9394	0.6091	0.3857	NA
PTSD Posttraumatic stress symptoms	0.1053	0.9121	0.5446	0.6846	0.5065	NA
Functional impairment	0.3355	0.9118	0.7252	0.9665	0.6460	NA
CES-D Depression	0.1892	0.9383	0.6336	0.9745	0.4942	NA
CERQ Positive cognitive emotion regulation	0.4280	0.8453	0.8793	0.7702	0.2655	0.9272
CERQ Negative cognitive emotion regulation	0.2894	0.8069	0.6600	0.4349	0.2944	0.2476
K6 Distress level	NA	NA	NA	NA	NA	0.0994
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0529

Decrease in comfort with the body	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.0006	0.1202	0.0359	0.0255	0.0076	NA
Resilience today	0.0061	0.8813	0.1287	0.0819	0.2969	NA
Hope today	0.0032	0.6175	0.0554	0.0118	0.3008	NA
PACT Coping flexibility	0.0000	0.1034	0.0113	0.0929	0.2778	0.1206
PTGI Posttraumatic growth	0.4865	0.7196	0.7686	0.8486	0.6566	0.4525
EGO Resilience	0.1586	0.8227	0.9888	0.2222	0.9922	NA
PTSD Posttraumatic stress symptoms	0.0001	0.4705	0.0058	0.0494	0.0054	NA
Functional impairment	0.0000	0.4175	0.0008	0.0049	0.1031	NA
CES-D Depression	0.0000	0.3569	0.0457	0.0212	0.1214	NA
CERQ Positive cognitive emotion regulation	0.2173	0.3659	0.3258	0.1076	0.2885	0.3358
CERQ Negative cognitive emotion regulation	0.0142	0.2166	0.0301	0.1536	0.8873	0.0000
K6 Distress level	NA	NA	NA	NA	NA	0.0248
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0000
Disruption in Sexuality	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.0451	0.5546	0.0119	0.3823	0.0300	NA
Resilience today	0.0477	0.4254	0.7351	0.7922	0.4807	NA
Hope today	0.1657	0.6611	0.8176	0.7649	0.9474	NA
PACT Coping flexibility	0.0060	0.4333	0.8383	0.8001	0.8493	0.6150
PTGI Posttraumatic growth	0.0293	0.3288	0.1051	0.0835	0.3779	0.0214
EGO Resilience	0.5132	0.4328	0.1656	0.4710	0.8727	NA
PTSD Posttraumatic stress symptoms	0.0000	0.2032	0.0177	0.1562	0.0138	NA
Functional impairment	0.0000	0.0693	0.0011	0.6910	0.0176	NA
CES-D Depression	0.0036	0.3476	0.4015	0.5416	0.1488	NA
CERQ Positive cognitive emotion regulation	0.5662	0.6256	0.0421	0.1247	0.1581	0.4759
CERQ Negative cognitive emotion regulation	0.0129	0.1163	0.2582	0.3772	0.5604	0.0101
K6 Distress level	NA	NA	NA	NA	NA	0.0250
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0014
Interference with a sense of femininity	Baseline	M3	M6	M12	M24	Follow up
Stress today	0.0003	0.8287	0.0035	0.1566	0.0182	NA
Resilience today	0.0006	0.1939	0.2664	0.1759	0.0348	NA
Hope today	0.0051	0.0907	0.1504	0.0576	0.4418	NA
PACT Coping flexibility	0.0001	0.0080	0.1442	0.4162	0.2387	0.9097
PTGI Posttraumatic growth	0.0832	0.9436	0.1488	0.1970	0.0644	0.0780
EGO Resilience	0.3802	0.2141	0.7276	0.9345	0.9673	NA
PTSD Posttraumatic stress symptoms	0.0000	0.0940	0.0000	0.0142	0.0000	NA
Functional impairment	0.0000	0.0245	0.0001	0.0006	0.0000	NA
CES-D Depression	0.0000	0.2589	0.0154	0.0510	0.0005	NA
CERQ Positive cognitive emotion regulation	0.0829	0.2781	0.4023	0.7318	0.1751	0.3246
CERQ Negative cognitive emotion regulation	0.0093	0.5358	0.4399	0.1716	0.5275	0.0024
K6 Distress level	NA	NA	NA	NA	NA	0.0005
PCL-5 Posttraumatic stress symptoms	NA	NA	NA	NA	NA	0.0000

A2.5 Case Study: Temporal changes in scales

Analysis plan

Repeated-measures ANOVA was performed to the total patient sample to detect any statistically significant changes in the CERQ, PACT, *PTGI*, EGO, CES-D, PDS and Functional scales and the levels of distress, hope and resilience during the 2-year observation window and at follow-up (whenever applicable). A conventional analysis was performed using the aov() function of R and a mixed-effects analysis using lme() function from nlme package and anova() function of R.

If the repeated measures ANOVA with mixed effects model is statistically significant, multiple comparisons on the mixed effects model are realized in order to explore where these differences occur. Glht() function from package multcomp was used.

Results

Repeated Anova results are reported in Table A9. Boxplots and the time course of mean values for the total scores of the various psychological scales are depicted in Figures 15-16.

Statistically significant differences over time at significant level <0.001 were observed for CERQ positive cognitive regulation (Table A9). Overall CERQ positive seems to improve over time (Figure A16). However, multiple comparisons revealed that differences are statistical significant between baseline and follow up, as well as between month 6 and follow up.

Statistically significant differences over time at significant level <0.05 were observed for stress today, EGO resilience, PDS posttraumatic stress symptoms and CERQ negative cognitive regulation. An improvement over time is observed for stress today. Differences are statistical significant between baseline and M12. Similarly, posttraumatic stress symptoms seem to decline over time, but the improvement is statistical significant only between baseline and month 24. For EGO resilience, a statistically significant improvement is observed between baseline and month 24. Finally, CERQ negative cognitive regulation seems to decrease the second year and at follow up. The improvement is statistical significant between baseline and follow up. Improvements over time observed for functional impairment and depression are not statistical significant.

TABLE A9 Repeated-measures Anova results (p-values)**.** Color density is proportional to significant levels 0.001, 0.01 and 0.05.

	Repeated Anova	
	Conventional analysis	**Mixed-effects analysis**
Stress today	0.1401	0.0271
Resilience today	0.4279	0.2531
Hope today	0.6025	0.7537
PACT Coping flexibility	0.2343	0.3003
PTGI Posttraumatic growth	0.2338	0.2036
EGO Resilience	0.0169	0.0217
PTSD Posttraumatic stress symptoms	0.0835	0.0322
Functional impairment	0.3865	0.1753
CES-D Depression	0.2895	0.1855
CERQ Positive cognitive emotion regulation	0.0004	0.0001
CERQ Negative cognitive emotion regulation	0.0484	0.0269

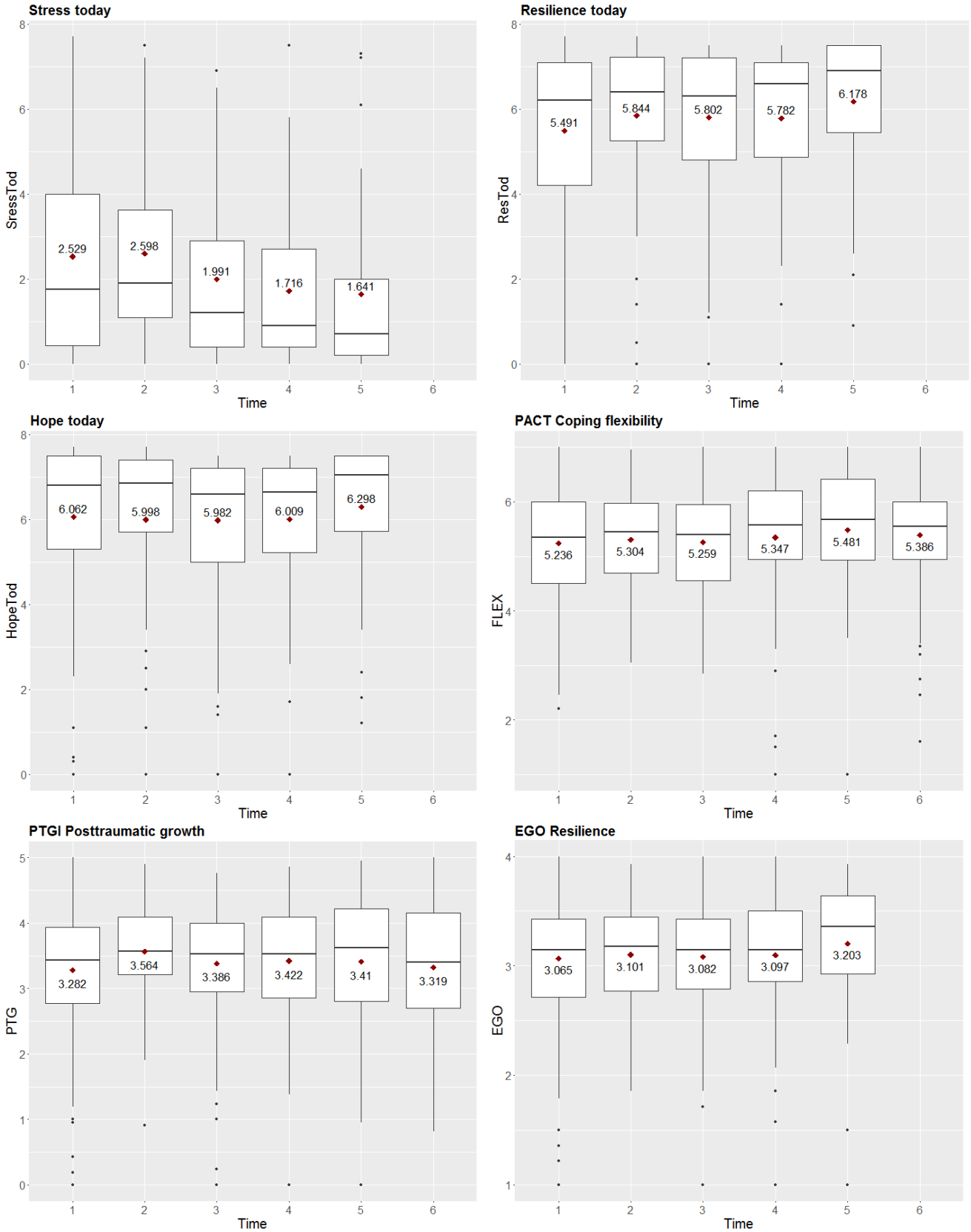


Figure A15 Boxplots for various psychological variables. The mean value for each time point is noted. Time "1"=Baseline, Time "2"=Month 3, Time "3"=Month 6, Time "4"=Month 12, Time "5"=Month 24, Time "6"=Follow up

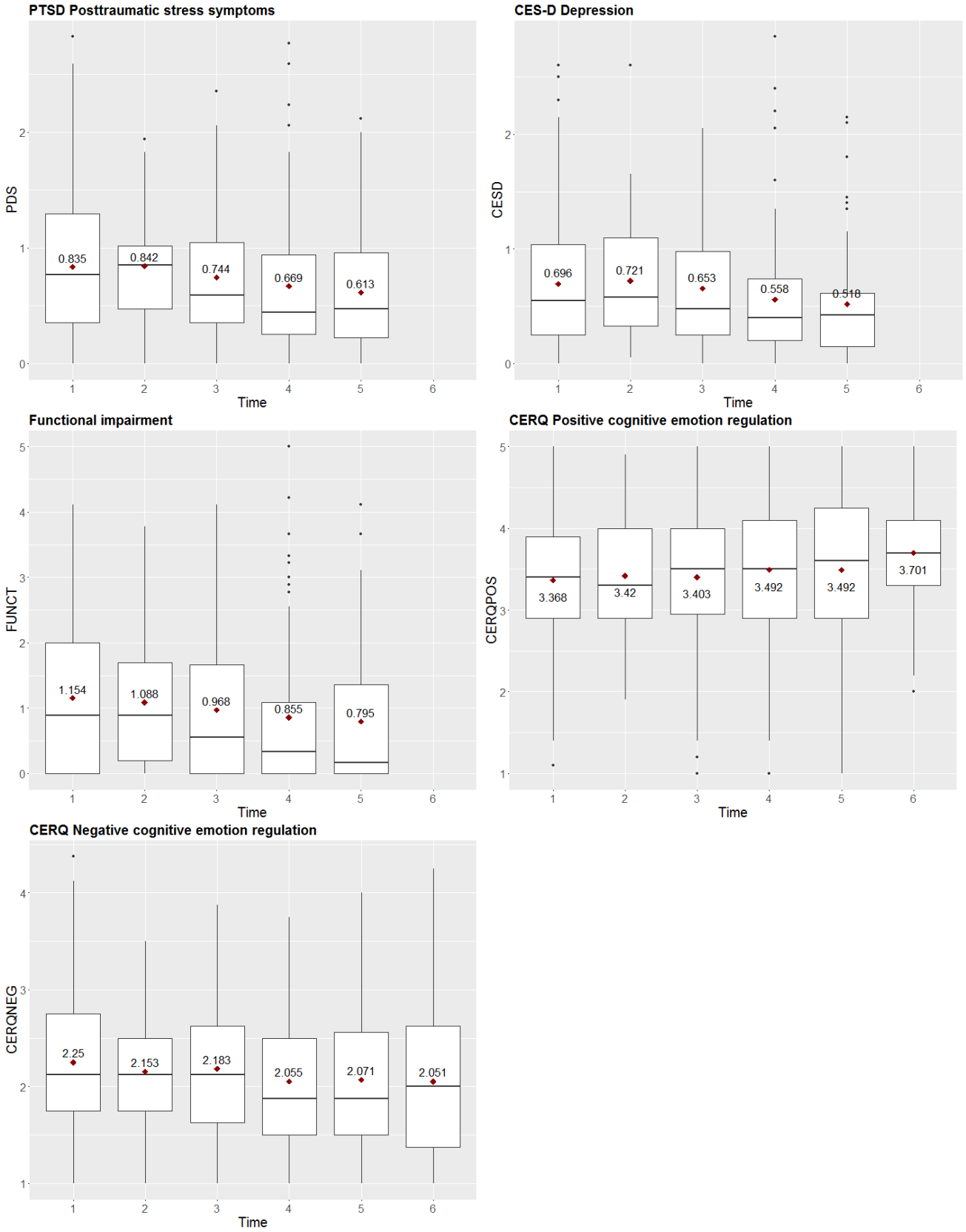


Figure A16 Boxplots for various psychological variables. The mean value for each time point is noted. Time "1"=Baseline, Time "2"=Month 3, Time "3"=Month 6, Time "4"=Month 12, Time "5"=Month 24, Time "6"=Follow up

A3. Preliminary correlation analysis with retrospective data: The CHAMP dataset

A3.1 Dataset description

The data following anonymization has been provided by Dr. Berta Sousa, Champalimaud Breast Unit, Lisbon, Portugal within the framework of the BOUNCE EU funded project. A short summary is provided here.

Researchers for data collection: Susan Valerio, Fátima Cardoso, Albino Oliveira-Maia, Berta Sousa, Raquel Lemos, Luzia Travado, Nikolaos Papanikolaou

Aim: This study has an observational retrospective design: it looks backwards to medical, functional, demographic, and psychometric data collected in CR/CCC databases and examines the correlation between biological and psychological factors. The collection of the data will regard all the breast cancer patients treated with curative intent until 2017. The dataset represents a very heterogenous population where data was retrospectively collected to be integrated in a larger dataset.

Patients: The collection of the data will regard all the breast cancer patients treated with curative intent until 2017 at the Breast Unit of CR/CCC. These are patients referred by the oncologists to a neuropsychiatry appointment which already represents a selected population in our clinic. This means breast cancer patients with psychological problems not able to manage by oncologists/nurses at the clinic; patients with enough economic resources to have personalised psychological support and treatment and mainly patients living in Lisbon.

Inclusion criteria: To be eligible for inclusion in the study, each patient must fulfill the criteria (1) Female 40-65years of age at the time of diagnosis; (2) Histologically confirmed invasive early or locally advanced operable breast cancer; (3) TNM tumour stage I, II or III.

Exclusion criteria included: (1) Presence of distant metastases; (2) History of another malignancy or contralateral invasive breast cancer within the last five years of breast cancer diagnosis, except the curable basal cell carcinoma of skin or carcinoma in situ of the uterine cervix; (3) History of early onset (i.e., before 40 years of age) mental disorder (i.e., schizophrenia, psychosis, bipolar disorder, major depression) or severe neurologic disorder (i.e., neurodegenerative disorder, dementia); (4) Uncontrolled concomitant diseases such as clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease or cardiac arrhythmia not well controlled with medication); (5) Treatment for any major illness in the last half year of breast cancer diagnosis,

Sample: Data for 111 patients are provided. Psychological assessment took place once. The CHAMP retrospective data include:

- **SocioDemographics:** date of birth, marital status, education level
- **Genetic risk factors:** Family history, Genetic test
- **Breast data at diagnosis:** dates (biopsy, image acquisition), histologic type, grade, Ki-67, type of imaging, Tumor Size (cT), Lymph node involvement (cN), Multifocality / Multicentrality, Distant metastases (cM)receptor status (estrogen, progesterone), Her2 expression, Ki-67,
- **Pathology data (post-surgery):** pT, pN, Histological type, Grade, Estrogen Receptor, Progesteron Receptor, HER 2 Receptor, Ki67, Margins, Lymphovascular invasion, Genomic test, Molecular classification, Staging results

- **Treatment data:** date of surgery, type of breast surgery, type of axillary operation, radiation therapy (type, dates, dose, fractions, boost), systemic treatment (chemo, biological, hormone, endocrine treatment)
- **Follow up data:** Relapse, Date of relapse, Current disease status, Date of last follow up
- **Psychosocial self-report questionnaires and questionnaires for cognitive function:**
  - ***The Distress Thermometer:*** A single 0-10 scale item developed to assess the distress levels of cancer patients.
  - ***Hospital Anxiety and Depression scale (HADs):*** It is a 14 item scale, seven of the items relate to anxiety and seven relate to depression. The anxiety and depressive subscales are also valid measures of severity of the emotional disorder. The sum of total scores for depression and anxiety is provided.
  - ***Mini Mental Status- Examination (MMSE***): It is a screening tool used to assess objective cognitive function. It consists of a set of questions, grouped in seven categories: orientation to time, orientation to place, registration of three words, attention and calculation, recall of three words, language and visual construction. The total score is provided.
  - ***Addenbrookes Cognitive Examination Revised (ACE-R):*** Is a cognitive screening tool to address the lack of MMSE sensitivity in the diagnosis of dementia. The overall result of ACE-R includes an amount equal to the result of the MMSE, and further allows the assessment of multiple domains. The Portuguese experimental version was developed in community and clinical samples geriatric (Gonçalves et al. 2015).
  - ***Wechsler Adult Intelligence Scale subtests (WAIS III):***
    - ***Digit Span subtest:*** It comprises two modalities. Forward - repeat number sequences with increasing length, in the same order as presented aurally to access immediate memory; and backward – repeat digit sequences in reverse order, to achieve working memory.
    - **Symbol Search subtest**: Working within a specific time limit, the examinee scans a search group and indicates whether one of the symbols in the target group matches. This subtest measures processing speed, short-term visual memory, visual-motor coordination, cognitive flexibility, visual discrimination, psychomotor speed, and speed of mental operation.
  - ***Trail Making Test A and B:*** The ***Trail Making Test* (TMT)** consists of two parts. TMT-A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-B except the person must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). The TMT provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. The TMT-A & TMT-B were validated for the Portuguese population with an adult sample by Cavaco et al (2013).
  - ***Stroop test:*** Assessment tool for executive functions, response inhibition and selective attention, originally developed by Stroop (Stroup, 1935) and revised by Golden & Freshwater (2002), in an American adult population. The validation for the Portuguese population includes a sample of participants from 15 to 100 years was published by Fernandes (2013).
  - ***Beck Depression Inventory (BDI-II):*** The BDI-II is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression among the following domains: mood, pessimism, sense of failure, pleasure, guilt, punishment feelings, self-dislike, suicide, crying, indecisiveness, concentration fatigue, appetite, loss of interest, irritability, sleep, loss of energy, worthlessness, agitation, loss interest in sex. The total score is provided.

- ***State-trait Anxiety Inventory:*** The STAI is a commonly used measure of trait and state anxiety [16]. It can be used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes. Form Y, its most popular version, has 20 items for assessing trait anxiety and 20 for state anxiety. It was adapted for the Portuguse population by Santos & Silva (1997).
- ***EORTC QLC 30:*** It has been widely used in clinical practice and clinical trials for measuring quality of life (QoL) in patients with cancer. Includes 30 items for 15 dimensions/scales: five functional scales (physical, role, cognitive, social, and emotional functioning), three symptom scales (fatigue, nausea/vomiting, and pain), five single-item symptom scales (dyspnea, sleep disturbances, appetite loss, constipation, and diarrhea), single-item scale for financial impact, and a global health status.

A detailed listing of the data that were disseminated by CHAMP to BOUNCE partners is attached in P.APPENDIX 2D.

A3.2 Preparing the data

A data cleaning of the CHAMP retrospective dataset is being performed in the framework of WP4. The data cleaning steps performed so far include:

- For every variable, comparison of all values to what is listed in the code/explanation manual provided along with the data. In the case of standardized questionnaires, values were compared against questionnaires' scales.
- Consistency checks between variables to identify erroneous inliers. For example, dates were checked against a reasonable chronological order (e.g. surgery not taking place prior to biopsy) or whether staging was consistent with pTpN classification etc.
- Realization of basic descriptive statistics for every variable of the dataset as well as joint statistics between variables. Descriptive statistics also help identify outliers, inconsistencies, strange patterns in (joint) distributions and erroneous inliers (when viewed in relation to other variables).
- Continuous variable age and education level was also transformed into categorical variable based on typical cut-off values.
- Based on dates patients receiving adjuvant or neoadjuvant treatment were determined.

It is noted that the above work is still in progress. ICCS is working in close interaction with Champalimaud to resolve inconsistencies found during the screening/diagnostic phase of the data analysis and has requested additional clarifications and descriptions whenever needed.

Regarding psychological measures, the dataset suffered from a considerable amount of missing data.

A3.3 Patients characteristics

The characteristics of the study group at baseline are presented in Table 10. The provided cohort includes records of women diagnosed with breast cancer between the ages of 28-75 (mean= 51). Stages of breast cancer: Stage I (33.3%) Stage II (51.4%), Stage III (N= 15.3%). 77% of patients had conservative breast cancer surgery, which has a positive impact in QoL, but, on the other hand, the majority have received chemotherapy (64%), which has a negative impact in QoL. Chemotherapy was mostly administered in the neoadjuvant setting (41.67%). The majority of women received radiotherapy (84.39%). Psychological assessment took place on average 16.44 months (range: 7 days- 61 months, SD=15.96 months) after diagnosis.

TABLE 10 Patient clinical and demographic characteristics at baseline

Variables	Mean(range)/ Counts	SD / %	Variables	Counts	%
General and Demographics			*Breast cancer and Treatment data*		
Age	51.0 (28-75)	10.6	Grade		
Years of education	15.5 (4-24)	3.3	Grade 1	16	14.41%
Marital status			Grade 2	54	48.65%
Married	73	68.22%	Grade 3	15	13.51%
Single	10	9.35%	Undetermined	26	23.42%
Common-law partner	5	4.67%	Breast surgery		
Divorced	14	13.08%	Lumpectomy	86	77.48%
Widow	5	4.67%	Mastectomy	25	22.52%
Family history			Axillary management		
None	49	44.14%	SLNB	69	62.16%
Breast and/or ovarian cancer	43	38.74%	ALND	35	31.53%
Other than breast & ovarian	19	17.12%	ALND after SLNB	7	6.31%
			Chemotherapy		
Breast cancer and Treatment data			Adjuvant	24	22.22%
Estrogen receptor			Neoadjuvant	45	41.67%
Negative	14	12.61%	None	39	36.11%
Positive	74	66.67%	Radiotherapy		
Undetermined	23	20.72%	None	17	15.32%
Progesterone receptor			Local	53	47.45%
Negative	19	17.12%	Local-regional	41	36.94%
Positive	69	62.16%	Systemic treatment		
Undetermined	23	20.72%	Chemo only	15	13.51%
HER- 2 receptor			Chemo plus biologicals	8	7.21%
Negative	74	66.67%	Chemo plus biologicals & ET	17	15.32%
Positive	14	12.61%	Chemo plus ET	32	28.83%
Undetermined	23	20.72%	ET only	38	34.23%
Staging results - AJCC 7th Ed.			Biologicals only	1	0.90%
Ia	35	31.53%			
Ib	2	1.80%			
IIa	34	30.63%			
IIb	23	20.72%			
IIIa	9	8.11%			
IIIb	4	3.60%			
IIIc	4	3.60%			

ET:endocrine therapy, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection

A3.4 Case Study: Inter and Intra scale correlations

Analysis plan

The present study involves an examination of the correlations among the various Distress Thermometer, HADS, MMSE ACE-R, WAISS III, TMT, Stroop, STAI, BDI and QLQ-C30 scales. The correlation was performed using Pearson method, which measures a linear dependence between two

variables. The rcorr( ) function of R in the Hmisc *package* was applied to produce pearson *correlations*. Pairwise complete cases were analyzed. A significance level of 1% (p-value=0.01) is considered in the analysis.

Results

The following figure presents the correlations among a) the Distress Thermometer, b) the HADS total score related to anxiety and depression, c) the BDI score (level of depression), d) the trait and state anxiety as measured by the STAI scale, e) the summary score of QLQ-C30 related to quality of life and aspects of cognitive function as assessed by f) the MMSE and ACE-R tests, g) the subtests of WAISS, Digit Span (working memory) and Symbol Search (processing speed), h) TMT Part A and Part B (flexibility of thinking on a visual-motor sequencing task) and i) the Stroop tests Word, Color and Word & Color (selective attention and cognitive flexibility). Regarding psychological questionnaires related to anxiety and depression, patients have completed either HADS scale and Distress Thermometer or BDI and STAI scales.

The number of complete cases for most scale pairs is low (3 - 22), resulting in an insufficient sample size to reach statistical significance at 1% level for low to moderate correlation coefficients. This is why the majority of the correlations in Figure 17 are statistical insignificant (p-value >0.01). Furthermore, for some pairs no complete case exists, i.e. no patient answered both questionnaires. These pairs are denoted as "NA" in Figure 17.

The strongest intra correlations are observed between the Trait and State subscales of STAI questionnaire (r ~0.84) and the Color and Word & Color parts of STROOP test (r ~0.8). A very strong correlation also exists between the Word and Color subscales of STROOP test (r ~0.77). Furthermore, substantial correlations are observed between the parts A and B of TMT test (r ~0.62) and Word and Word & Color subscales of STROOP test (r ~0.54). No statistical significant correlation exists between the Digit Span and Symbol Search of WAISS test.

With reference to the psychological questionnaires, the BDI depression scale correlates strongly with both Trait and State anxiety scales (STAI), especially the former one (r ~0.79 and 0.71 respectively). The Distress Thermometer exhibits a moderate correlation with HADS overall score (r ~0.55). No statistical significant correlation exists between C30 total score and any other scale.

Cognitive function as assessed by ACE-R test correlates strongly with Trail Making part A test (r ~0.78), as well as MMSE test (r ~0.65). It is noted, the MMSE test is part of the ACE-R test.
The Symbol Search of the WAISS test is substantially correlated with the Part B of Trail Making Test (r ~0.68) and the Colour and Colour&Word subtests of Stroop Test (r ~0.58 and 0.54 respectively).

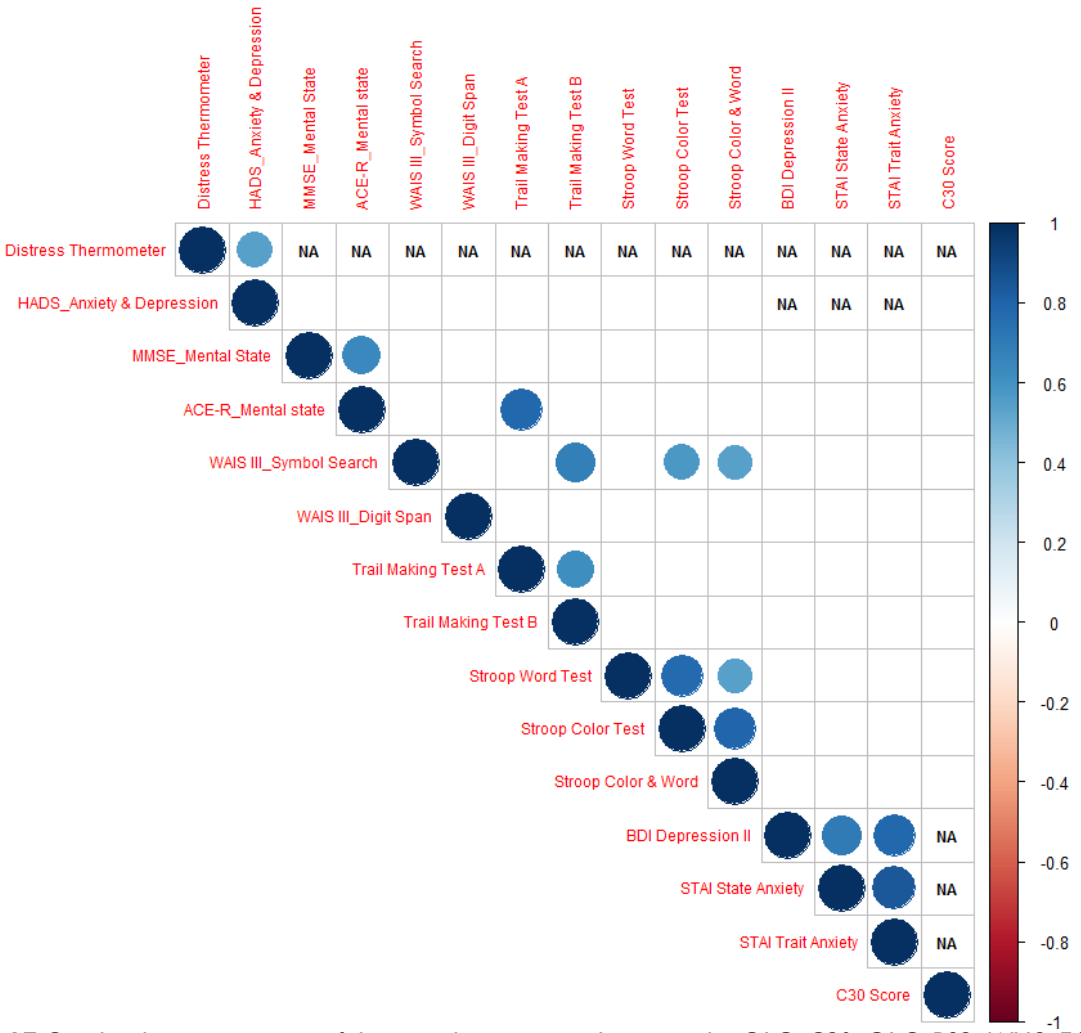


Figure 17 Graphical representation of the correlation matrix between the QLQ-C30, QLQ-B23, *WHQ*, FACIT and BDI scores at baseline. Positive correlations are displayed in blue and negative correlations in red color. Color intensity and the size of the circle are proportional to the correlation coefficients. Not significant correlations (p-value < 0.01) are leaved blank. Missing correlations (i.e. when the pairs of scales have no complete cases to analyse) are displayed as NA.

A3.5 Case Study: Assess the relationship between self-report questionnaires with sociodemographic and medical variables at baseline

Analysis plan

The present study involves an examination of the relationship between the various QLQ-C30, BDI, HADS, STAI, Distress Thermometer, MMSE, ACE-R, WAISS, TMT and STROOP scales with sociodemographic and medical variables at baseline. No lifestyle variables are included in the CHAMP dataset. The purpose is to identify statistically significant differences in psychological scores and cognitive functioning between two or more groups of an independent variable e.g. patients having undergone mastectomy or lumpectomy.

We utilized one-way ANOVA test or Kruskal-Wallis test when the assumptions of the former were violated. Kruskal-Wallis test is a non-parametric alternative to ANOVA test, which does not assume that the population distributions follow the normal distribution. The aov() function of 'R' package was used for the ANOVA test and the kruskal.test() function for the Kruskal-Wallis test. Anova assumptions were tested using Shapiro-Wilk test (that checks the normality assumption) and Levene's

test (that checks the homogeneity of variance assumption). "Post-hoc" analyses were subsequently performed with Tukey's test (parametric) using TukeyHSD() function and Dunn's test (non parametric) using dunnTest() function. The aforementioned post hoc analyses were applied to variables with more than two groups for which a statistical significant result was obtained from the Anova test or the Kruskal-Wallis test, respectively. The aim is to explore which groups are statistically different from each other. A statistical significance level of 5% was considered for all studies.

Chi square tests were performed among sociodemographic and medical variables for each subgroup of patients that has performed each cognitive test or filled each psychological questionnaire.

Results

Due to the small size of the complete cases and the fact that fact that the normality assumption is violated for some of the variables (e.g. MMSE and ACE-R), Anova and Kuskal results are not consistent in several cases. In Tables 11-12 the results of Anova test are depicted for variables that do not significantly deviate from the normality assumption, whereas in Table 13 the results of Kruskal test are presented for the variables that significantly deviate from the normality assumption. Only differences that are statistical significant at 0.05 level are presented.

We observe that many variables have a very low sample size (below 10) in some of their categories. Because of the limited sample size, the rest of the medical and sociodemographic categories are not equally represented. Therefore, it is possible that many of the observed effects do not correspond to true population effects but are present only in our sample. Below we report some indicative results.

- State anxiety is higher in patients with negative estrogen receptor (ER-). Patients not receiving hormone therapy have also a significantly higher STAI trait and state anxiety score. It is noted that, negative estrogen receptor is considered a negative prognostic factor in combination with other characteristics. Moreover, the majority of patients not receiving hormone therapy are either triple negative (ER-, progesterone negative (PR-) and HER2 -), which is associated with poor prognosis.
- Hospital anxiety and depression decreases with the increase of time between diagnosis and assessment date, after the first year from diagnosis, but the differences are not statistical significant.
- MMSE performance decreases with age. However, not all differences between age groups are statistical significant. Overall, MMSE scores indicate no cognitive impairment (scores 26-30) with the exception of one patient.

TABLE A11 ANOVA test: QLQ-C30, BDI, HADS, STAI and Distress Thermometer scores versus sociodemographic characteristics and medical profile of the patients at baseline. Only statistically significant results are reported (p-value<0.05). For variables with more than two groups, groups are separated by letters. Groups sharing the same letter are not significantly different based on post-hoc test. SD: Standard deviation, F: F-value of Anova test, P: p-value of Anova test, S:p-value of Shapiro-Wilk test, L: p-value of Levene's test.

	State Anxiety (STAI)
Estrogen Receptor Biopsy	***Mean ± SD***
Negative (n=14)	55.4 ± 9.4
Positive (n=40)	47.9 ± 12.7
F	4.084
P	**0.048**
S	0.178
L	0.162

	EORTC- QLC-30
Radiotherapy	***Mean ± SD***
Yes *(n=6)*	51.9 ± 16.2
No (n=2)	83.3 ± 11.8
F	6.155
P	**0.048**
S	0.758
L	0.835

	State Anxiety (STAI)
Hormone Therapy	***Mean ± SD***
No (n=15)	55.2 ± 9.1
Yes (n=40)	47.9 ± 12.6
F	4.228
P	**0.045**
S	0.191
L	0.097

	Hospital Anxiety and Depression (HADS)	
Family history	***Mean ± SD***	
None *(n=16)*	21.5 ± 9.5	a
Breast/Ovarian (n=25)	14.95 ± 7.1	b
Other (n=8)	20.8 ± 6.1	a b
F	4.571	
P	**0.015**	
S	0.106	
L	0.226	

TABLE A12 ANOVA test: STROOP and WAIS scores versus sociodemographic characteristics and medical profile of the patients at baseline. Only statistically significant results are reported (p-value<0.05). For variables with more than two groups, groups are separated by letters. Groups sharing the same letter are not significantly different based on post-hoc test. SD: Standard deviation, F: F-value of Anova test, P: p-value of Anova test, S:p-value of Shapiro-Wilk test, L: p-value of Levene's test.

	Stroop Word Test	
Family history	***Mean ± SD***	
None (n=10)	56.1 ± 7.4	a
Breast/Ovarian (n=9)	45.7 ± 7.2	b
Other (n=3)	57.7 ± 4.7	a b
F	6.192	
P	**0.009**	
S	0.967	
L	0.615	

	Stroop Color Test
Lymph node involvement (cN)	***Mean ± SD***
N0 (n=16)	93.1 ± 12.3
N1 (n=6)	46.8 ± 28.8
N3 (n=0)	
F	4.656
P	**0.043**
S	0.352
L	0.174

	Stroop Color Test	
Family history	***Mean ± SD***	
None (n=10)	56.8 ± 12.9	a b
Breast/Ovarian (n=9)	45.9 ± 8.8	a
Other (n=3)	68.7 ± 14.2	b
F	4.998	
P	**0.018**	
S	0.174	
L	0.610	

	Digit Span (WAIS III)
HER 2 Receptor Biopsy	***Mean ± SD***
Negative (n=17)	12.6 ± 1.6
Positive (n=4)	9.8 ± 1.3
Not applicable/ Undetermined (n=0)	
F	11.046
P	**0.004**
S	0.471
L	0.513

	Symbol Search (WAIS III)	
Family history	***Mean ± SD***	
None (n=10)	14.1 ± 2.0	a
Breast/Ovarian (n=9)	13.6 ± 1.9	a
Other (n=3)	17.7 ± 2.3	b
F	4.926	
P	**0.019**	
S	0.091	
L	0.818	

TABLE A13 Kruskal test: MMSE, ACE-R and TMT scores versus sociodemographic characteristics and medical profile of the patients at baseline. Only statistically significant results are reported (p-value<0.05). For variables with more than two groups, groups are separated by letters. Groups sharing the same letter are not significantly different based on post-hoc test. SD: Standard deviation, K: p-value of Kruskal test, S:p-value of Shapiro-Wilk test.

	Mini Mental State (MMSE)		
Type of radiotherapy	***Mean ± SD***	***Median***	
Local-regional (n=17)	27.6 ± 1.5	27	a
Local (n=19)	27.7 ± 2.6	28	ab
None (n=5)	29.4 ± 0.9	30	b
K	**0.041**		
S	0.000		

	Trail Making Test B	
Lymph node involvement (cN)	***Mean ± SD***	***Median***
N0 (n=16)	93.1 ± 12.3	97.5
N1 (n=6)	46.8 ± 28.8	40
N3 (n=0)		
Nx (n=0)		
K	**0.009**	
S	0.000	

	Mini Mental State (MMSE)	
Breast surgery	***Mean ± SD***	***Median***
Lumpectomy (n=31)	27.5 ± 2.2	27
Mastectomy (n=10)	29.2 ± 1.0	29.5
K	**0.005**	
S	0.000	

	Trail Making Test A		
Progesteron Receptor Post surgery	***Mean ± SD***	***Median***	
Negative (n=6)	86.8 ± 17.0	94.5	ab
Positive (n=11)	76.3 ± 27.1	77	a
Not applicable Undetermined (n=5)	99.0 ± 0.0	99	b
K	**0.045**		
S	0.013		

	Mini Mental State (MMSE)		
Age	***Mean ± SD***	***Median***	
<40 (n=7)	28.9 ± 1.2	30	ab
40 - 49 (n=15)	27.9 ± 1.6	29.5	ab
50 - 59 (n=12)	28.6 ± 1.1	29.25	b
60 - 69 (n=3)	27.0 ± 0.0	27	ab
70-75 (n=3)	23.7 ± 4.9	26.5	a
K	**0.020**		
S	0.024		

	Trail Making Test A		
Type of chemo	***Mean ± SD***	***Median***	
Adjuvant (n=8)	76.6 ± 17.4	77	a
Neoadjuvant (n=8)	98.9 ± 0.4	99	b
None (n=6)	75.2 ± 34.1	93	ab
K	**0.021**		
S	0.005		

	Trait Anxiety (STAI)	
Hormone Therapy	***Mean ± SD***	***Median***
No (n=14)	56.8 ± 9.7	54
Yes (n=41)	47.2 ± 13.0	50
K	**0.028**	
S	0.033	

A3.6 Case Study: Analysis of disease-free survival

One of the objectives of BOUNCE is to develop algorithms for predicting long term clinical relapse and survival by taking into account current/past biological, sociodemographic, psychosocial, personal, clinical and life-style patient characteristics. In the present section we perform a univariate analysis to test the effect of clinical characteristics, cognitive function and subjective well-being on disease-free survival. It is noted that CHAMP dataset (and BOUNCE project) does not include metastatic cases. In CHAMP dataset 6 out of 108 patients (5.6%) experienced local/regional relapse and 5 out of 108 patients (4.6%) experienced distant relapse. All patients survived during the observation period. The reference time point for relapse is the date of diagnosis/biopsy. In our analysis patients experiencing either local/regional or distant relapse are considered one category.

Analysis plan

For categorical variables, overall relapse-free survival curves (one for each category) were produced by the Kaplan-Meier method, and were compared using the log-rank test. For continuous variables univariate Cox regression was applied. The survdiff() and the coxph() functions of R in the 'Survival' *package* were applied for log-rank test and Cox regression analysis respectively.

Results

Resulting statistically significant variables for disease-free survival are presented in Tables 14-15.

Statistically significant clinical variables in CHAMP dataset for disease-free survival, based on log rank and cox regression, include pT classification, hormone treatment and age at 0.05 significance level and estrogen receptor and type of chemotherapy (adjuvant, neoadjuvant, none) at 0.1 significance level. In particular, relapse among patients of older age and patients with positive estrogen receptor is less frequent. Furthermore, in CHAMP dataset, patients not receiving hormone treatment and patient receiving neoadjuvant chemotherapy have a higher frequency of relapse. Because treatment plan (hormone treatment, chemotherapy) is associated with tumor clinical characteristics (e.g. estrogen and progesterone receptor etc), the observed prognostic significance of treatment choices needs to be further investigated.

Psychological assessment was realized after relapse in 4/11 cases (specifically 6, 8, 23 and 28 months). Analysis failed to identify any correlation of quality of life, depression, anxiety and cognitive function scales with disease-free survival.

TABLE A14 P-values of the log rank test for the most statistically significant variables at p=0.1 level

Variable	*P-value*
Disease-free survival	
pT	0.0004
Type of Hormone Therapy	0.0333
Estrogen Receptor Post surgery	0.0604
Hormone Therapy (yes/no)	0.0635
Chemotherapy	0.0906
Estrogen Receptor biopsy	0.0952

TABLE A15 P-values of the Cox regression analysis for the most statistically significant variables at p=0.1 level

Variable	Likelihood ratio test *P-value*	Wald test *P-value*	Log rank test *P-value*
Disease-free survival			
Age	0.0195	0.0291	0.0246

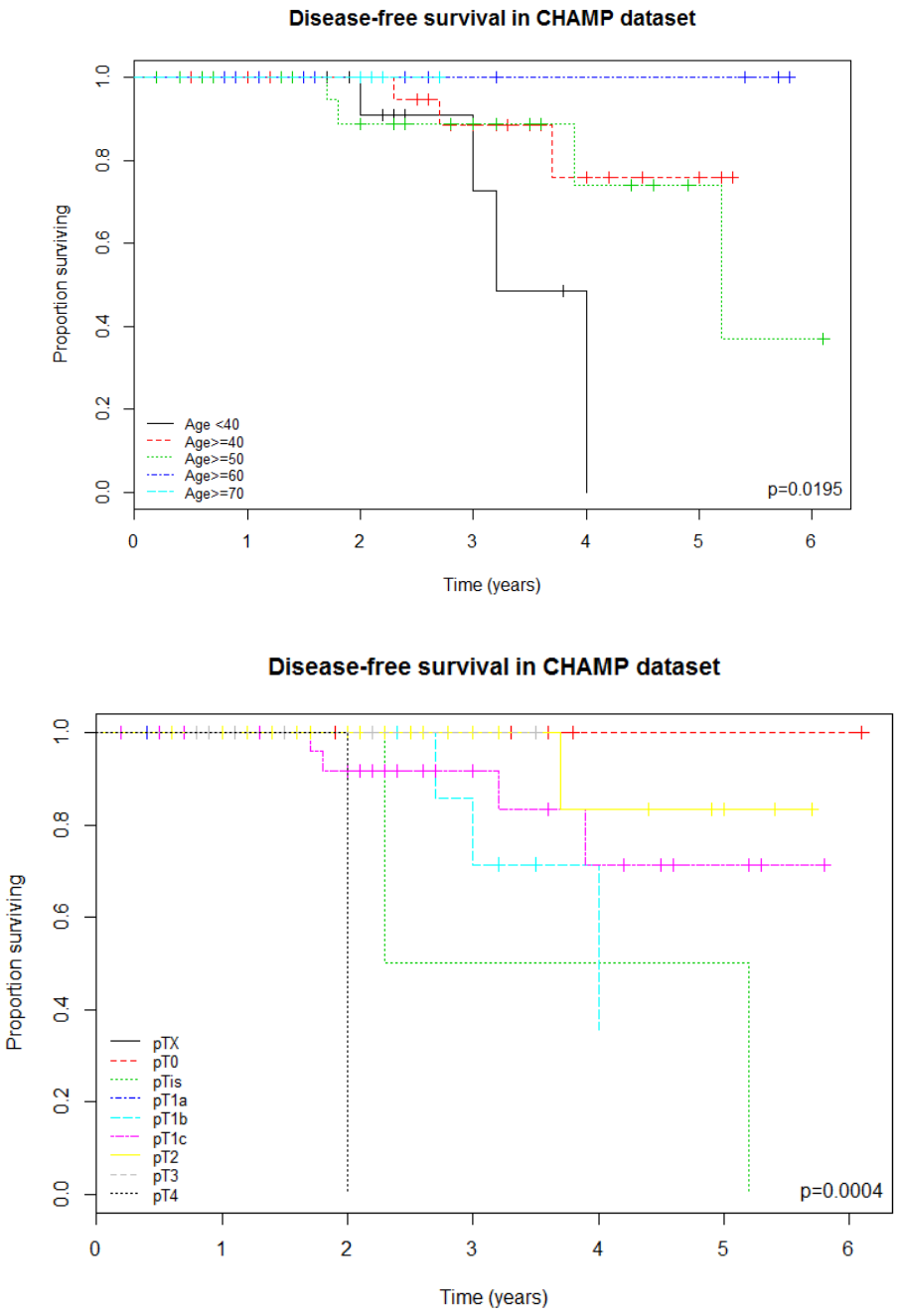


Figure A18 Kaplan–Meier overall survival curves for selected variables

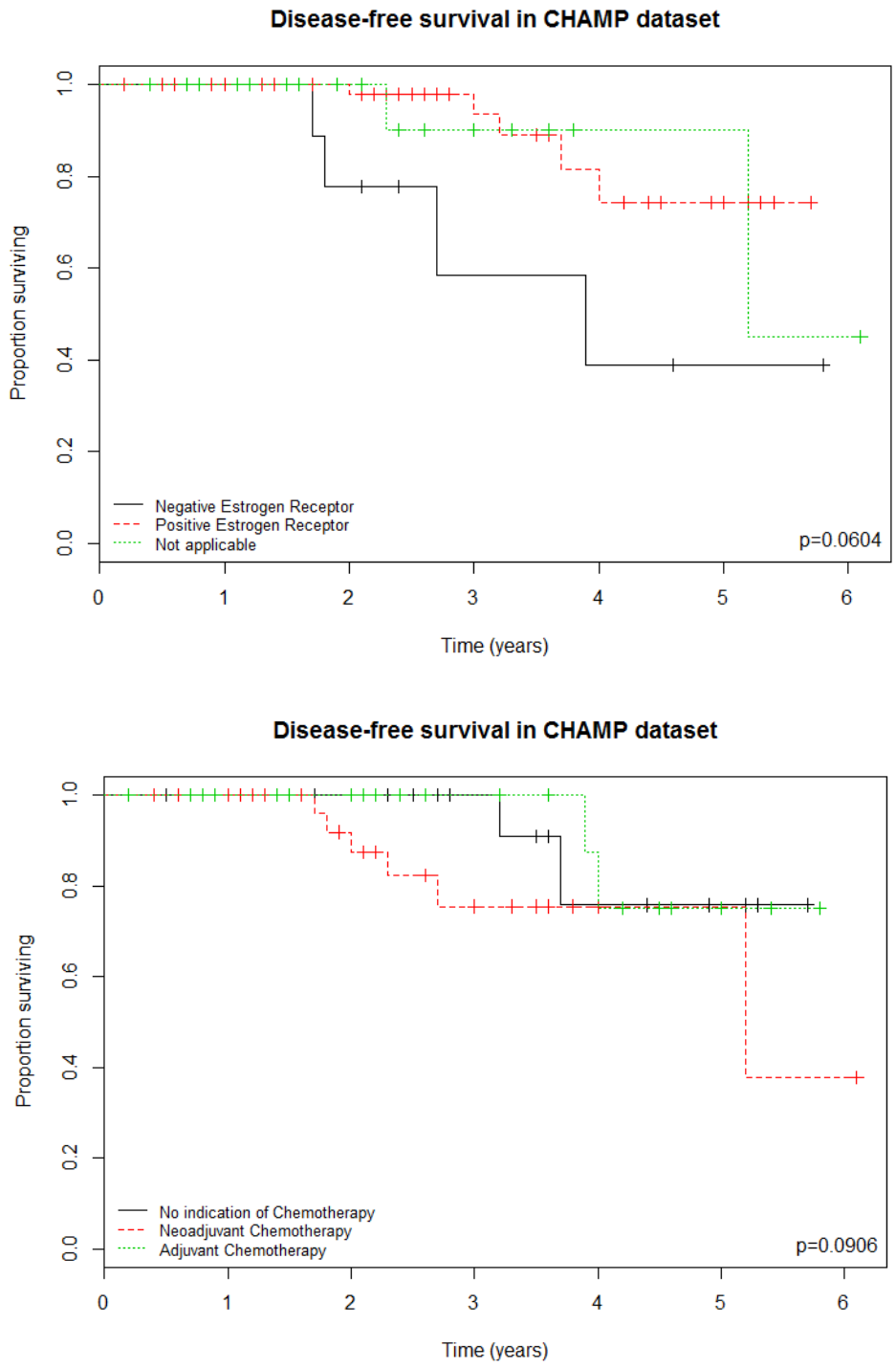
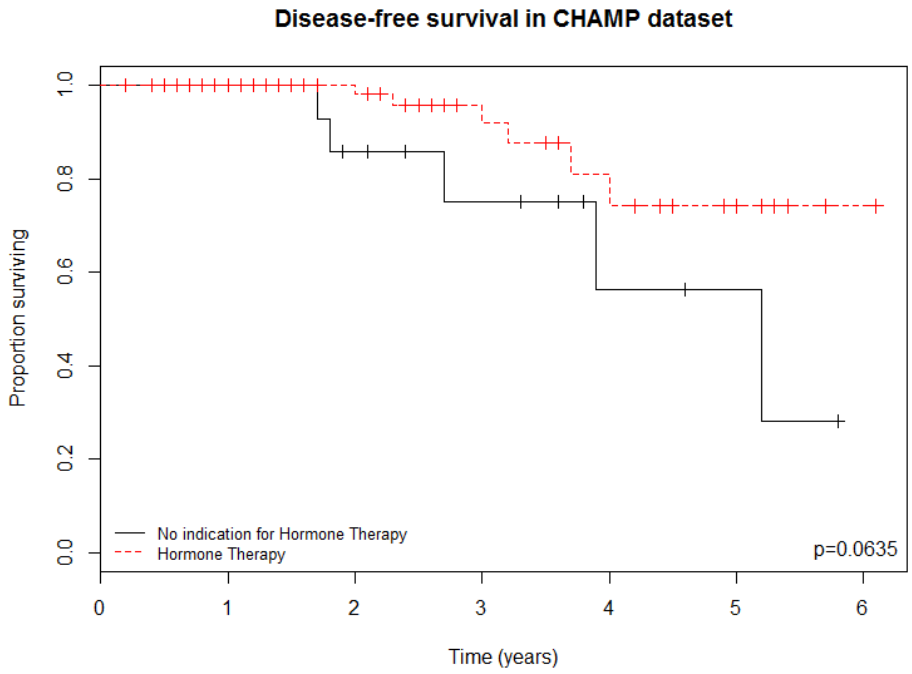


Figure A19 Kaplan–Meier overall survival curves for selected variables



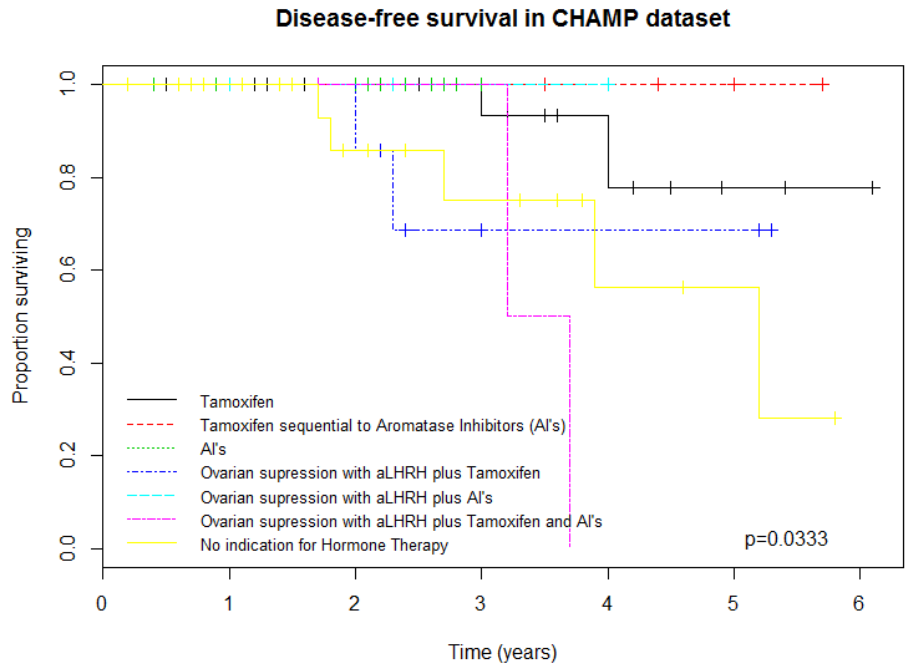


Figure A20 Kaplan–Meier overall survival curves for selected variables

A3 Handling Missing Values

A common problem in statistical analysis is the handling of missing values. The simplest way of dealing with it is to discard the observations that contain them. However, this method is applicable only when there are a few missing values. For example, in the case of the HUS retrospective data no complete case exists even after removing variables with a high percentage of missing values (note that the total number of relevant variables is around 1400). Rather than removing the observations with missing data, another approach is to fill in or "impute" the missing values. The choice of the most appropriate technique is problem specific and related to the variable of interest.

Our general strategy to analyze and handle missing data within BOUNCE retrospective and prospective datasets includes the following steps:

Step 1. Understand our data and identify patterns/reasons for missing data

Missing values in BOUNCE data may occur for a number of reasons: a) attrition due to study dropout and death, b) skip pattern in survey and data collection design, e.g. certain questions are only asked to respondents who have given a certain answer to a previous question, c) random data collection issues, i.e. no data have been collected from some respondents at specific time points, d) respondent refusal/non-response, i.e. some answers have intentionally or randomly not be provided by the respondents at a given time point

Step 2. Understand distribution of missing data

In general there are three probabilities of missingness: a) values are missing completely at random (MCAR), i.e. some questions are answered from a random sample of the original set; in this case the missing value is completely independent both of the observable variable or another variable in the dataset, b) values are missing at random (MAR), i.e. the missing values depends on and, hence, can be accounted for by other variables in the dataset where there is complete information; for example married women are less likely to report sexual functioning, and c) values are missing not at random (MNAR), i.e. the probability of a missing value depends on the observable variable; for example respondents with high depression are less likely to report depression level.

Step 3. Decide on the best method for handling the missing data

Using the knowledge gained about the reason and distribution of missing data, we can decide on the best analysis strategy to yield the least biased estimates. In some cases the filling in of variables might be straightforward for example, the missing menopause status is postmenopausal if the patient was postmenopausal at the time of diagnosis and over 60 years of age, or the number of cigarettes for non smokers is zero. Furthermore, patients with records up to a specific time point will be excluded from any analysis covering a larger period.

In the rest of the cases, depending on the variable of interest we can choose between the following options:

a) Delete observations with missing values using either pairwise or listwise deletion.
b) Impute data: a variety of imputation approaches exists ranging from extremely simple to rather complex. An indicative list of the most typical techniques is given below:
    - Single Imputation Methods
        - Mean/mode substitution, dummy variable method, single regression
    - Model-Based Methods
        - Maximum Likelihood, Multiple imputation

A4 Conclusions

The preliminary analyses presented in this chapter have led to an in depth quantitative exploration and exploitation of the retrospective data provided by two participating clinical centres. The results produced are essentially consistent with both literature and common sense. The entire process has offered the opportunity for an excellent familiarization of BOUNCE modellers with the handling of fundamental BOUNCE data types. The same and similar data types will also be collected and analysed during the implementation of the prospective BOUNCE pilot study. More importantly, the work outlined in this chapter has generated valuable hints which will partly guide and enlighten the data analysis and interpretation of the prospective pilot study. It is noted that the statistical analysis techniques have been selected based on a literature review on the more popular techniques to solve this kind of problems.. A more complete investigation and evaluation of techniques is planned in the next steps of the data analysis efforts (deliverable D4.2).

The analyses presented so far have been focused on coping and posttraumatic growth rather than on resilience operationalized as potential, process and outcome. In addition they have been bound by several other limitations. In order to be able to predict resilience as defined by potential, process and outcome (e.g., functioning and wellbeing), the examination of a broad spectrum of factors clustered into the three major categories of *biomedical*, *psychosocial* and *functional* parameters is needed. Thus the BOUNCE Pilot Study is being designed in order to test resilience in an integrated and comprehensive way. To this end all lessons learned from the analysis and exploration of the retrospective data will be fully exploited.

Through the BOUNCE pilot study, we will be able to test general and specific predictive models regarding the resilience trajectories. In chapter 7 [H], we present the BOUNCE pilot study-and how the computational models of resilience can lead to relevant prediction models of post cancer adaptation and resilience that can be tested by the prospective research.

A5. References

Saarto T, Penttinen HM, Sievänen H, Kellokumpu-Lehtinen PL, Hakamies-Blomqvist L, Nikander R, Huovinen R, Luoto R, Kautiainen H, Järvenpää S, Idman I, Utriainen M, Vehmanen L, Jääskeläinen AS, Elme A, Ruohola J, Palva T, Vertio H, Rautalahti M, Fogelholm M, Blomqvist C and Luoma ML, Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors. Anticancer Res. 2012; 32(9):3875-84.

Hamama-Raz, Y., Perry, S., Pat-Horenczyk, R., Bar-Levav, R., Stemmer, S. (2012). Factors affecting participation in group intervention in patients after adjuvant treatment for early-study breast cancer. Acta Oncologica, 51, 208-214.

Pat-Horenczyk, R., Perry, S., Hamama-Raz, Y., Ziv, Y., Schramm-Yavin, S., Stemmer, S.M. (2015). Posttraumatic Growth in Breast Cancer Survivors: Constructive and Illusory Processes. Journal of Traumatic Stress, 28, 214-222. DOI: 10.1002/jts.22014. June 2015, 28, 214–222

Hamama-Raz, Y., Pat-Horenczyk, R., Perry, S., Ziv, Y., Bar-Levav, R., & Stemmer, S. M. (2016). The Effectiveness of Group Intervention on Enhancing Cognitive Emotion Regulation Strategies in Breast Cancer Patients: A 2-Year Follow-up. Integrative cancer therapies, 15(2), 175-182. DOI: 10.1177/1534735415607318.

Pat-Horenczyk, R., Saltzman, L. Y., Hamama-Raz, Y., Perry, S.., Ziv, Y., Ginat-Frolich, R., & Stemmer, S. M. (2016). Stability and Transitions in Posttraumatic Growth Trajectories among Cancer Survivors: LCA and LTA Analyses. Psychological Trauma: Theory, Research, practice and policy, 8(5), 541-5419. DOI: 10.1037/tra0000094.

Foa EB., Cashman L, Jaycox L, Perry K, The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnostic Scale. Psychological Assessment 1997:9(4), 445-451.

Radloff LS, The CES-D Scale: A Self-Report Depression Scale for Research in the General Population, Applied Psychological Measurement 1977:1(3):385 – 401.

Garnefski N, Kraaij V, Cognitive Emotion Regulation Questionnaire: Development of a short 18-item version (CERQ-short).Personality and Individual Differences 2006:41:1045-1053.

Bonanno, G. A., Pat-Horenczyk, R., & Noll, J. (2011). Coping flexibility and trauma: The Perceived Ability to Cope With Trauma (PACT) scale. *Psychological Trauma: Theory, Research, Practice, and Policy, 3*(2), 117-129.

Tedeschi, R. G., & Calhoun, L. G. (1996). The Posttraumatic Growth Inventory: Measuring the positive legacy of trauma. *Journal of Traumatic Stress, 9*(3), 455-472

Block, J., & Kremen, A. M. (1996). IQ and ego-resiliency: Conceptual and empirical connections and separateness. *Journal of Personality and Social Psychology, 70*, 349–361.

Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM.
Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002 Aug;32(6):959-76.

Weathers F, Litz B, Keane T, Palmieri T, Marx B.P, Schnurr P. The PTSD Checklist for DSM-5 (PCL-5) 2013

Cavaco S, Gonçalves A, Pinto C, et al. Trail Making Test: Regression-based Norms for the Portuguese Population, Archives of Clinical Neuropsychology, 2013:28(2):189–198, https://doi.org/10.1093/arclin/acs115.

Gonçalves C, Pinho MS, Cruz V, et al., The Portuguese version of Addenbrooke's Cognitive Examination–Revised (ACE-R) in the diagnosis of subcortical vascular dementia and Alzheimer's disease, Aging, Neuropsychology, and Cognition, 2015:22:4:473-485.

Stroop JR, Studies of interference in serial verbal reactions. Journal of Experimental Psychology, 1935:18(6), 643.

Golden CJ, Freshwater SM, Stroop Color and Word Test: Revised examiner's manual. Wood Dale, IL: Stoelting Co, 2002.

Fernandes S, Stroop: Teste de cores e palavras: Manual. Lisbon, Portugal: Cegoc, 2013.

Santos SC, Silva DR, Adaptação do State-Trait Anxiety Inventory (STAI) – Form Y para a população portuguesa: Primeiros dados. Revista Portuguesa de Psicologia, 1997:32:85-98.

6 [Q]. An Abstract Conceptual Approach to the Quantification of Resilience as a Function of the Biomedical, the Psychosocial and the Functional Statuses of the Patient [Code Letter: Q]

One of the main goals of the BOUNCE project is to quantify the notion of resilience by rendering it a "*measurable quantity*" like any physical quantity (e.g. temperature). A comprehensive approach to the definition of resilience is available in deliverables D2.1 and D2.1 of the BOUNCE project.

Three broad categories (clusters) of patient's data i.e their biomedical data, their psychosocial data and their functional data are the key deterninants of resilience. An abstract conceptual approach to the quantification of resilience as a function of the biomedical, the psychosocial and the functional statuses of the patient is proposed through the use of a simple diagram in Table Q1. The values or characterizations of the three statuses of the patient can generally refer to the same and/or different time points. A tentative and hypothetical preliminary numerical quantification of resilience for the various combinations of the BMS, PSS and FUS statuses is presented in the same Table Q1. The precise values of resilience in "Resilience Degrees (RD)" – in a scale of 1 RD to 10 RD - for each BMS, PSS and FUS combination are to be determined by the BOUNCE project by applying a host of statistical and machine learning methods on the available data and especially on the data to be generated by the prospective BOUNCE pilot study.

If the resilience value is above a threshold (which might be e.g. 7 RD) no action might be required. If it lies between say 5 RD and 7 RD, then a light action might be required (e.g. more physical exercise, more strict diet etc.). If it is say below 5 RD then "emergency" measures might need to take place (e.g. psychological interventions, psychiatric examinations, further biomedical examinations and tests etc.).

TABLE Q1 A tentative and hypothetical numerical quantification of resilience for the various combinations of the BMS, PSS and FUS statuses. The precise values of resilience in Resilience Degrees (RD) - in a scale of 1 RD to 10 RD - for each BMS, PSS and FUS combination will be one of the outcomes of the implementation of the BOUNCE project. It is noted that the values or characterizations of the three statuses of the patient can generally refer to the same and/or different time points. More refined gradings of the three statuses can be adopted.

BIOMEDICAL STATUS (BMS)	PSYCHOSOCIAL STATUS (PSS)	FUNCTIONAL STATUS (FUS)	(TENTATIVE) RESILIENCE IN RESILIENCE DEGREES (RD)
GOOD	GOOD	GOOD	10
GOOD	GOOD	INTERMEDIATE	9
GOOD	GOOD	BAD	8
GOOD	INTERMEDIATE	GOOD	9
GOOD	INTERMEDIATE	INTERMEDIATE	8
GOOD	INTERMEDIATE	BAD	6
GOOD	BAD	GOOD	7
GOOD	BAD	INTERMEDIATE	6
GOOD	BAD	BAD	5
INTERMEDIATE	GOOD	GOOD	7
INTERMEDIATE	GOOD	INTERMEDIATE	7
INTERMEDIATE	GOOD	BAD	6
INTERMEDIATE	INTERMEDIATE	GOOD	7
INTERMEDIATE	INTERMEDIATE	INTERMEDIATE	5
INTERMEDIATE	INTERMEDIATE	BAD	5
INTERMEDIATE	BAD	GOOD	5
INTERMEDIATE	BAD	INTERMEDIATE	5
INTERMEDIATE	BAD	BAD	4
BAD	GOOD	GOOD	4
BAD	GOOD	INTERMEDIATE	4
BAD	GOOD	BAD	3
BAD	INTERMEDIATE	GOOD	4
BAD	INTERMEDIATE	INTERMEDIATE	3
BAD	INTERMEDIATE	BAD	2
BAD	BAD	GOOD	3
BAD	BAD	INTERMEDIATE	2
BAD	BAD	BAD	1

7 [H]. A Preliminary Framework of Factor Correlation Hypotheses Regarding Resilience. [Code Letter: H]

The aim of this chapter is to briefly present the possible relationships between the variables included in the BOUNCE "Pilot Study" and, thus, the potential overall prediction model to be used in order to achieve the main goal of the study. An in depth approach to the definition of resilience is provided in deliverables D2.1 and D2.1 of the BOUNCE project.

H1. An overview of the Factors Included in the Pilot Study

The main goal of the pilot study is to identify the factors that can predict the medical and psychological outcomes at different time points (possibly at 3-month intervals, from month 3 after surgery to month 18, end of study).

Medical outcomes refer to survivorship, possible metastases etc. Psychological outcomes refer to three major indices. Namely, quality of life, physical functioning, and mental health. Due to the potentially strong correlations among these variables, a composite, general psychological outcome might also be examined. Table H1 presents the general variables/concepts included in each category of factors. It is noted that several variables (and the corresponding scales) are comprised of sub-scales not presented in this Table. For example, the personality scale consists of 5 distinct sub-scales, each providing a different score; illness representations is a group of 7 separate specific illness-related perceptions.

TABLE H1. The General Variables/Concepts in Each Category of Factors Included in the Pilot Study

Main Outcomes	Well-being indicators (minor outcomes)	Illness related self-regulation	Events	Moderators/ facilitators	Lifestyle
Medical…	Impact of events/PTSD	Illness representations	Trauma history	Personality traits	Health habits
Functioning	Post-traumatic growth	Self-rated health	Medical events	Socio-demographics	Adherence to medical advice
Mental health	Body image	Illness related coping behavior	Personal events	Resilience	
Quality of life	Distress			Self-efficacy	
	Mood			Social support	
[Resilience]	Fear of recurrence			Family resilience	
	Resilience (bounce back)			Coping style	
				Emotion regulation	
				Self-esteem	
				Optimism	
				Care satisfaction	
				Spirituality	
				Sense of coherence	
				Mindfulness etc.	
				Medical/illness variables…	

Study Variables

H2. The Basic Theoretical Background (the Mechanism)

The Common-Sense Model (CSM) of illness-related self-regulation (Leventhal, Halm, Horowitz, Leventhal, & Ozakinci, 2005; Leventhal, Weinman, Leventhal, & Phillips, 2008) will stand as the basic theoretical model for the formation of the prediction model and the identification of predictive factors, since it is the most respected and evaluated relevant theory so far. The core of this theory is that patients, after examining several sources of information, both external (e.g., examination results, other persons' experience) and internal (e.g., felt symptoms, personal knowledge and experience, goals and habits), as well as considering several factors, develop their personal understanding of illness and therapy (i.e., their illness representations). These representations guide patients' action plans and coping behavior which, in turn, impact adaptation to illness, well-being and health outcomes. This self-regulation process is affected/moderated by a series of personal and environmental variables (e.g., personality, family, health care system, other stressful events). It is a dynamic mechanism based on constant feedback loops. There is ample evidence for the validity of this model (e.g., Hagger, Koch, Chatzisarantis, & Orbell, 2017).

With respect to the potential role of resilience in the illness-related self-regulation process, as described by the CSM, and according to the ways resilience has been defined in the BOUNCE final proposal,

- **Resilience-as-Trait may**

1. be predictive of specific parts of the self-regulation process. For example, high levels of baseline resilience may be related to a more positive representation of illness (e.g., as a more controllable condition), more functional coping behaviors (e.g., making plans, adhering to medical advice), better outcomes (e.g., fewer psychological symptoms);

2. affect the basic self-regulation mechanism by moderating/regulating the associations between the different aspects of this process. For example, high levels of resilience may enhance the positive relation of control over illness to adherence to medical advice and, thus, outcomes. It may also 'prevent' the negative association between a perception of low control over illness with avoidance and helplessness.

- **Resilience-as-Process could be Inferred from**

1. the observation of positive adaptation to illness and better outcomes, despite negative events (e.g., therapy side-effects, negative examination results; see also, Figure H1);

2. the observation of the positive impact of other factors (e.g., optimism, self-efficacy) on the self-regulation process (i.e., on the associations between the different aspects of this process), in the form of positive-outcome-promoting or negative-outcome-preventing moderating effects.

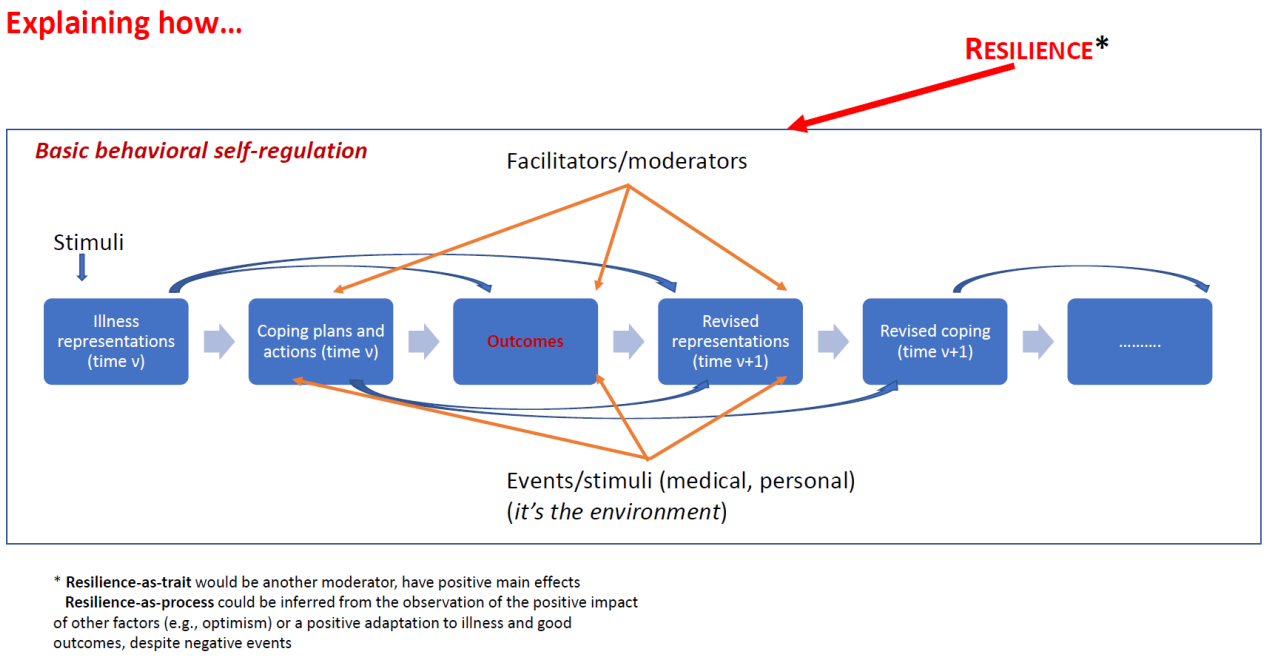


Figure H1. The illness-related self-regulation model which will serve as the basic theoretical background for the analyses of the Pilot Study data.

H3. Prediction Models

In order to fulfil the main aim of the "pilot study", two "prediction" models are proposed; an overall/general one, and a resilience-trajectory specific one.

H3.1. The Overall Prediction Model

Based on the hypothesis that previous medical and psychological factors may determine or at least predict subsequent well-being and health outcomes, this overall model includes the following hypothesized significant relationships:

1. Medical and psychological outcomes at 3, 6, 9, 12, 15, 18-month time points are predicted by a number of variables regarding (i) well-being indicators, (ii) resilience, (iii) illness related self-regulation, (iv) psychological and (v) medical moderators/facilitators of resilience, and (vi) lifestyle, as well as by (vii) their interactions (see also Figure H2 and Figure H3).

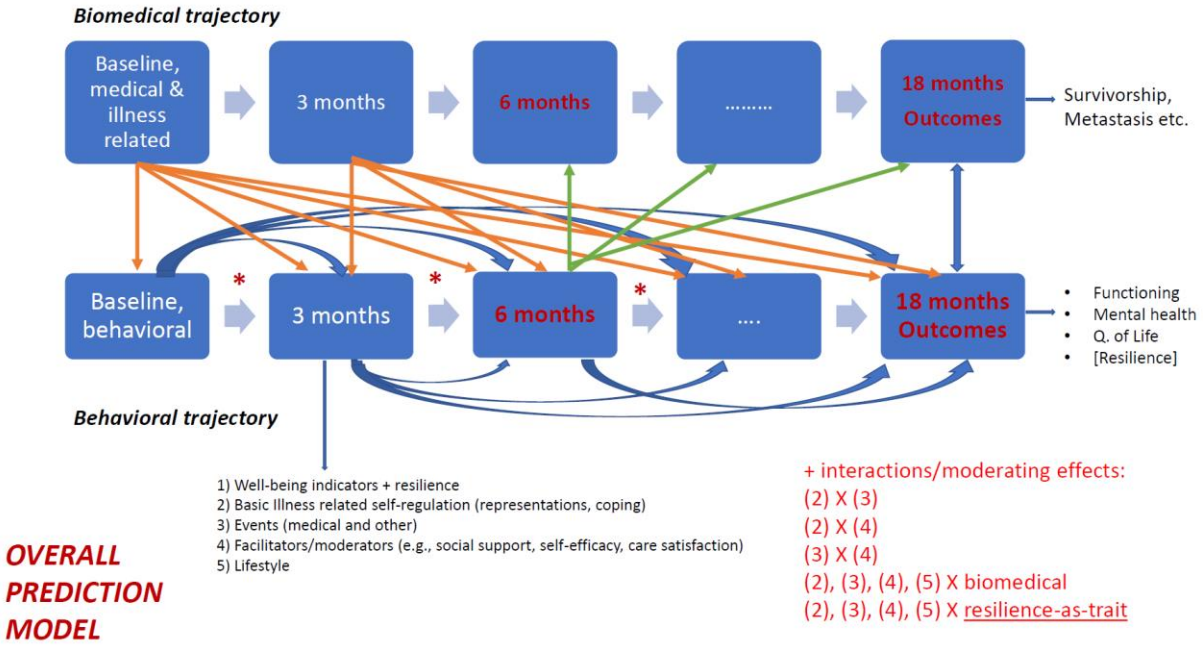


Figure H2. The overall prediction model – basic time points and possible relationships.

Our aim is to identify those variables or interactions that can more accurately predict final (i.e., at 18 months) and intermediate (i.e., at 3, 6, … 15 months) outcomes.

Outcomes may be predicted not only (1) by the variables (or their interactions) assessed at the immediately previous time-point, but also (2) by the factors (or their interactions) assessed at all previous time-points and baseline, as well as (3) by the interactions between variables assessed at different time-points.

2. Of special interest is the potential interplay between the medical and psychological variables of the study.

a. For example, it is possible for a medical event or changes in a significant biomedical index to lead to subsequent changes in illness self-regulation and psychological outcomes.
b. Likewise, it is possible and, therefore, should be examined whether there is an interaction between psychological variables, such as illness representations or self-efficacy, and crucial medical variables, such as therapy side-effects, regarding their impact on health outcomes.

3. The process of adaptation to illness is probably characterized by a choreography of dynamic changes in the several aspects of this process. In other words, it is possible that changes in the basic self-regulatory spiral (illness representations, coping behaviors, reappraisals etc.) are associated with corresponding changes to the ways that facilitating factors (such as, self-efficacy) change over time, and for both of these patterns of change to be associated with variations in health outcomes. Hence, the examination of the potential impact of the dynamic changes in different variables (or a set of the most important of them) on corresponding changes in health outcome scores is needed.

The specific pathways through which adaptation to illness takes place are of great importance. The realization of these pathways will permit a more lucid description of the ways that self-regulation and related factors impact health outcomes. In this way, a more accurate prediction of future outcomes is possible. A basic pathway has already been described in Section H2 and Figure H1. Additional pathways could be examined, based on the theoretical proximity of the various concepts and the plausibility of processes as described by several psychological theories (e.g., the social cognitive models which suggest a close relationship between perceptions and thoughts, feelings, behaviors, and health outcomes; e.g., Bandura, 1989) and research. Some only paradigmatic (as the list can be quite long) pathways are provided below:

- Medical events – (changes in) self-efficacy – (changes in) adherence to medical advice – (changes in) health outcomes

- Medical events – (changes in) optimism – (changes in) coping behaviour(e.g., positive attitude) – (changes in) health outcomes

- Illness emotional representations – emotion regulation – social support – health outcomes

- Illness representation of treatment control – fear of recurrence – distress – health outcomes

- Sense of coherence – self-rated health – coping behaviour– health outcomes

In the development of the above-mentioned prediction model, two issues should be considered:
a. Brief assessment of basic factors will take place every month as well.
b. There is a possibility of particularly high correlations between certain variables/factors (possibly indicative of confounding, although great effort has been made to avoid such a danger, and although all concepts are different in theory). For instance, it is possible for self-rated health and overall quality of life to be very highly correlated to each-other and to mood (although they stand for quite different concepts).

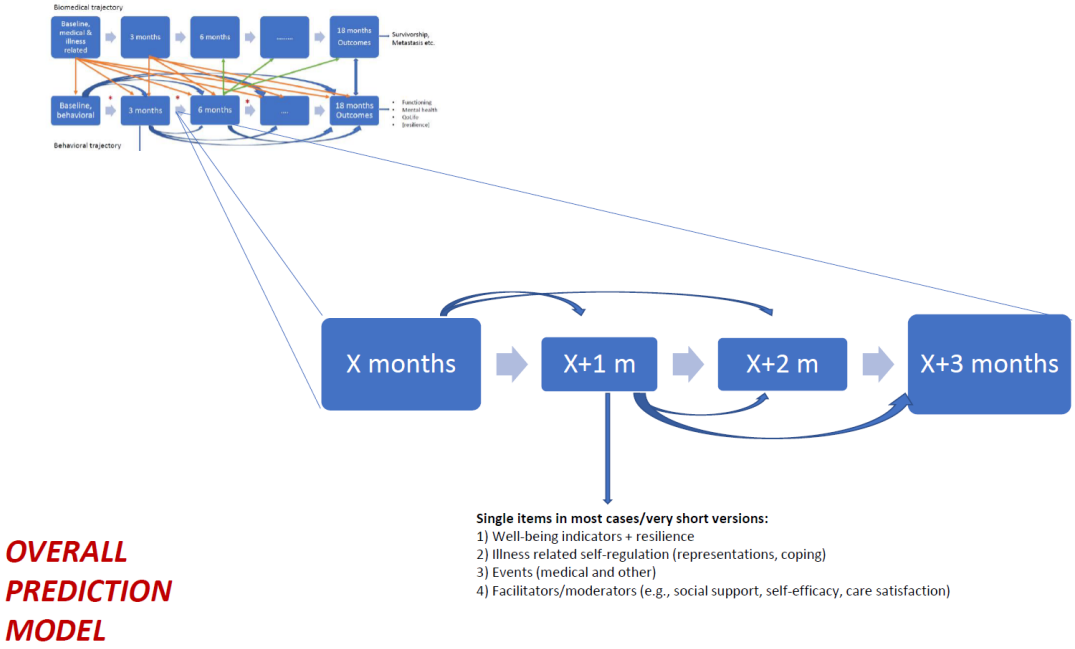


Figure H3. The overall prediction model – intermediate time points.

H3.2. The Resilience Trajectory Prediction Model

This model is supplementary to the previous main one. It has two goals:

1. To identify:

a. the (different types of) trajectory over time (i.e., months 1 to 18) for the main outcomes (or the composite outcome indexes) in order to detect the time-point(s) that is (are) critical for inclusion in (or exclusion from) a specific type of trajectory (specifically, the resilience trajectory);

b. the possible transitions from one specific type of trajectory to another;

c. detect the critical factors that precede inclusion in a specific type of trajectory (e.g., changes in important variables; significant events).

2. To examine the links between the resilience-specific trajectory (for each outcome) and the trajectories of crucial variables (such as, illness representations, self-efficacy, mood and distress), so as to test whether the latter predict the former. That is, whether there is one or more sensitive to change variable(s) which can predict the resilience-specific trajectory of each outcome.

H4. Concluding Remarks

1. In addition to what was mentioned above, BOUNCE will examine the possible differences between the four clinical sites as far as the above-mentioned prediction models is concerned.

2. Due to possible limitations (e.g., restrictions in analyses imposed by the final number of participants), it is likely that not all of the above described relationships or specific prediction models will be testable. In such a case, we should probably focus on certain of them which appear the most important ones for the purposes of the BOUNCE project. As such, we propose the relationships depicted in points 1 and 2 of Section H3.1, as well as in point 1 of Section H3.2.

H.References

Bandura, A. (1989). Human agency in social cognitive theory. American Psychologist, 44, 1175-1184.

Hagger, M. S., Koch, S., Chatzisarantis, N. L. D., & Orbell, S. (2017). The common-sense model of self-regulation: Meta-analysis and test of a process model. Psychological Bulletin, 143, 1117-1154.

Leventhal, H., Halm, E., Horowitz, C., Leventhal, E. A., & Ozakinci, G. (2005). Living with chronic illness: A contextualized, self-regulation approach. In S. Sutton, A. Baum, & M. Johnston (Eds.), The SAGE handbook of health psychology (pp. 197–240). London, UK: Sage.

Leventhal, H., Weinman, J., Leventhal, E. A., & Phillips, L. A. (2008). Health psychology: The search for pathways between behaviourand health. Annual Review of Psychology, 59, 477–505.

8 [M]. Temporal Data Mining [Code Letter: M]

Association rule mining, data classification and data clustering are common machine learning techniques for discovering relations in data.

One major problem that arises during the mining process is treating data with a temporal feature i.e. the attributes related with the temporal information present in the database. Traditional data mining techniques would treat temporal data as an unordered collection of events, ignoring its temporal information. However, the temporal attributes require different pre-processing procedures and handling.

The aim of the present chapter is to present a brief overview of techniques that deal with temporal data mining. These comprise a pool of candidate techniques to be applied in the framework of BOUNCE for both retrospective and prospective datasets.

M1. Prediction

The task of time-series prediction has to do with forecasting (typically) future values of the time series based on its past samples (Shahnawaz et al 2011). For this purpose, we need to build a predictive model for the data. The autoregressive family of models can be used to predict a future value as a linear combination of earlier sample values, provided the time series is stationary. Linear non-stationary models like autoregressive–moving-average (ARMA) models have also been found useful in many economic and industrial applications where some suitable variant of the process can be assumed to be stationary. Another popular work-around for non-stationary data is to assume that the time series is piece-wise stationary. The series is then broken down into smaller pieces called "frames" within each of which, the stationary condition can be assumed to hold true and then separate models are trained for each frame. In addition to this standard ARMA family of models, there are many nonlinear models for time series prediction e. g., neural networks. The prediction problem for symbolic sequences has also been addressed in Artificial Intelligence using various rule models such as the disjunctive normal form model, the periodic rule model etc. Based on the models, sequence-generating rules are obtained that state some properties that constrain which symbol can appear next in the sequence.

In many cases, prediction may be formulated as classification, association rule finding or clustering problems. Generative models can also be used effectively to predict the evolution of time series.

M2. Classification of Temporal Data

Temporal classification is a task of classification of sequences (time series data) into given categories. The algorithm tries to predict the most likely value of the temporal variable given the other variables, from a training dataset in which the target variable is given for each observation, and a set of assumptions representing one's prior knowledge of the problem (Lin et al 2002).

The sequence classification methods can be divided into three large categories (Xing et al 2010).

- The first category is feature based classification, which transforms a sequence into a feature vector and then applies conventional classification methods. Feature selection plays an important role in this kind of methods.

- The second category is sequence distance based classification. The distance function which measures the similarity between sequences determines the quality of the classification significantly.

- The third category is model based classification, such as using the Hidden Markov Model (HMM) and other statistical models to classify sequences.

There are three major challenges in sequence classification. First, most of the classifiers, such as decision trees and neural networks, can only take input data as a vector of features. However, there may be no explicit features in sequence data. Second, even with various feature selection methods, we can transform a sequence into a set of features, the feature selection is far from trivial. The dimensionality of the feature space for the sequence data can be very high and the computation can be costly. Third, besides accurate classification results, in some applications, we may also want to get an interpretable classifier. Building an interpretable sequence classifier is difficult since there are no explicit features.

Over the years, sequence classification applications have seen the use of both pattern based as well as model based methods (Shahnawaz et al 2011). In a typical pattern based method, prototype feature sequences are available for each class. The classifier then searches over the space of all prototypes, for the one that is closest or most similar to the feature sequence of the new pattern. Typically, the prototypes and the given features vector sequences are of different lengths. Thus, in order to score each prototype sequence against the given pattern, sequence aligning methods like Dynamic Time Warping are needed. Another popular class of sequence recognition techniques is a model based method that use Hidden Markov Models (HMMs).

Since traditional classification algorithms are difficult to apply to sequential examples, mostly because there is a vast number of potentially useful features for describing each example, an interesting improvement consists of applying a preprocessing mechanism to extract relevant features (Antunes and Oliveira 2001). One approach to implement this idea consists of discovering frequent subsequences, and then using them, as the relevant features to classify sequences with traditional methods, like Naive Bayes or Winnow.

Classification is relatively straightforward if generative models are employed to model the temporal data (Antunes and Oliveira 2001). Deterministic and probabilistic models can be applied in a straightforward way to perform classification since they give a clear answer to the question of whether a sequence matches a given model.

Indicative examples of time series classification involves the use of semi-supervised learning (Wei and Keogh,2006). Semi-supervised learning is an appealing method in areas where labeled data is hard to collect.

Another approach is a Dynamic Bayesian Network (DBN), a Bayesian network which relates variables to each other over adjacent time steps. This is often called a Two-Timeslice BN (2TBN) because it assumes that at any point in time T, the value of a variable can be calculated from the internal regressors and the immediate prior value (time T-1) (Wikipedia).

M3. Temporal Cluster Analysis

Temporal clustering targets separating the temporal data into subsets that are similar to each other and are able to represent the different sequences. There are two fundamental problems of temporal clustering: to define a meaningful similarity measure between sequences, and, to choose the number of temporal clusters (if we do not know the cluster numbers).

Considering that K is known, if a sequence is viewed as being generated according to some probabilistic model, for example by a Markov model, clustering may be viewed as modeling the data sequences as a finite group of K sequences in the form of a finite mixture model. Through the EM (Expectation Maximization) algorithm their parameters could be estimated and each K group would correspond to a

cluster (Antunes and Oliveira 2001). Learning the value of K, if it is unknown, may be accomplished by a Monte-Carlo cross validation approach.

A different approach proposes to use a hierarchical clustering method to cluster temporal sequences databases (Antunes and Oliveira 2001). The algorithm used is the COBWEB, and it works on two steps: first grouping the elements of the sequences, and then grouping the sequences themselves. Considering a simple time series, the first step is accomplished without difficulties, but to group the sequences is necessary to define a generalization mechanism for sequences. Such mechanism has to be able to choose the most specific description for what is common to different sequences.

Another method proposed in literature for clustering time series data utilizes fuzzy logic. Fuzzy clusters provide the flexibility of allowing an object or changes in time series variables to participate in multiple clusters.

M4. Temporal Pattern Discovery - Association Rules

Temporal pattern discovery deals with the discovery of temporal patterns of interest in time series or temporal sequences, where the interest is determined by the domain and the application. For example: Patients who are on drug X for over a month, sometimes start suffering from severe headaches after a month. This is a temporal association rule, but also a potentially causal rule (Mitsa, 2010).

The discovery of relevant association rules is one of the most important methods used to perform data mining on transactional databases (Shahnawaz et al 2011). An effective algorithm to discover association rules is the apriori and various implementations have been applied in the clinical domain (Potamias et al.). Association rule discovery is an important task in data mining in which we extract the relation among the attribute on the basis of support and confidence. The association rule discovery can be extended to temporal association. However, the manipulation of temporal sequences requires that some adaptations are made to the apriori algorithm.

The presence of a temporal association rule may suggest a number of interpretations (Roddick & Spiliopoulou, 2002):

- The earlier event plays some role in causing the later event.
- There is a third (set of) events that cause both other events,
- The confluence of events is coincidental.

The first interpretation is associated with the concept of causal rule, i.e. a relationship in which changes in one part of the modeled reality cause subsequent changes in other parts of the domain. Causal rules are common targets of scientific investigation within the medical domain, where the search for factors that may cause or aggravate particular medical conditions is a fundamental objective. In this domain, KDD (Knowledge Discovery in Database) tools can be applied at a preliminary stage, namely, to discover associations that can be observed as candidate causal rules. The tests for causality follow in a subsequent stage, involving expert guidance and extensive statistical tests (Roddick & Spiliopoulou, 2002).

While the concept of association rule discovery is the same for temporal and non-temporal rules, algorithms designed for conventional rules cannot be directly applied to extract temporal rules (Roddick & Spiliopoulou, 2002). The reason is that classical association rules have no notion of order, while time implies an ordering. This ordering affects the statistical properties of the data and the semantics of the rules being extracted from them. Moreover, patients are associated with both static properties, such as gender, and temporal properties, such as age or current medical treatments, any or all of which may be taken into account during mining.

Fuzzy temporal association rules arise from the use of fuzzy sets to describe quantitative temporal and/or not temporal attributes of items in a database, and/or to introduce fuzzy temporal specifications (Carinena, 2014)

M. References

Antunes, C. and Oliveira, A. 2001. Temporal data mining: An overview. In Proceedings of the KDD Workshop on Temporal Data Mining. 1--13.

Purificacion Carinena, Fuzzy temporal association rules: combining temporal and quantitative data to increase rule expressiveness, WIREs Data Mining Knowl Discov 2014, 4:64–70. doi: 10.1002/widm.1116

Wei L., Keogh E.,2006. Semi-supervised time series classification. In: The Proceedings of the Twelfth International Conference on Knowledge Discovery and Data Mining Philadelphia (KDD2006),USA,pp.748–753.

W. Lin, M. A. Orgun and G. J. Williams, An overview of temporal data mining, Proc. 1st Australian Data Mining Workshop (ADM02), eds. S. J. Simoff, G. J. Williams and M. Hegland (2002) pp. 83–90

Theophano Mitsa. Temporal Data Mining, 1st Edition, Chapman & Hall, CRC (2010)

Potamias, G., Koumakis, L., & Moustakis, V. (2005). Mining XML Clinical Data: the HealthObs System. Ingénierie des systèmes d'information, 10(1), 59-79.).

J.F. Roddick, M. Spiliopoulou, A survey of temporal knowledge discovery paradigms and methods, IEEE Trans. Knowledge Data Eng., 14 (4) (2002), pp. 750-767

Mohd. Shahnawaz, Ashish Ranjan, Mohd Danish —Temporal Data Mining: An Overviewǁ(IJEAT) ISSN: 2249 – 8958, vol - 1, Issue -1, Oct 2011

Srivatsan Laxman and P S Sastry, A survey of temporal data mining, Sadhana Vol. 31, Part 2, April 2006, pp. 173–198.

https://en.wikipedia.org/wiki/Dynamic_Bayesian_network retrieved on 23/5/2018

Z. Xing, J. Pei, and E. Keogh. A brief survey on sequence classification. ACM SIGKDD Explorations,Volume 12, Issue 1, pages 40-48, June 2010, ACM Press.

9 [C]. Conclusions [Code Letter: C]

The central theme of this document has been the proposition and the formulation of preliminary factor correlation hypotheses related to the quantification and the prediction of the quantity of resilience in the case of breast cancer. To this end a series of background and foreground steps have been taken and described.

A brief outline of the retrospective data originating from the participating clinical centres has been presented. The latter include: the Helsinki University Hospital Comprehensive Cancer Centre (HUS), Helsinki, Finland, the Hebrew University School of Social Work and Social Welfare (HUJI), Jerusalem, Israel, the European Institute of Oncology (IEO), Milan, Italy and the Champalimaud Clinical Centre (CHAMP), Lisbon, Portugal.

A literature survey of various factor correlations with particular emphasis on the aims of the studies, the methodologies and the associations identified has been included. Several representative correlation and statistical analyses and their results using retrospective BOUNCE data sets have been presented. All analyses in this document refer to the datasets provided by HUS, HUJI and CHAMP. Correlations among various factors at various time points have been identified and presented using correlation matrices. The work outlined has led to an in depth quantitative exploration and exploitation of the provided retrospective data. The results produced are essentially consistent with pertinent literature. Moreover, the whole work outlined has offered the opportunity for an excellent familiarization of BOUNCE modellers with the handling of basic data types to be also generated and analysed during the prospective BOUNCE pilot study.

An abstract conceptual approach to the quantification of resilience as a function of the biomedical, the psychosocial and the functional statuses of the patient has been briefly outlined.

Subsequently, a preliminary framework of factor correlation hypotheses has been presented. An overview of the factors included in the pilot study of BOUNCE has been provided and a basic theoretical background has been outlined. In order to best address the main aim of the "pilot study", two "prediction" models have been proposed; an overall/general one, and a resilience-trajectory specific one.

An outline of the temporal data mining approach adopted has also been made. Several appendices include representative data sharing agreements and the descriptions of the inhomogeneous data provided by the participating clinical centres.

The work presented in this document constitutes a solid basis for the further implementation of the BOUNCE project. Additional analyses on the eventual correlations among various factors of interest will be reported in deliverable D4.2 when further retrospective data will have been made available by the participating clinical organizations.

APPENDICES [Code Letter: P]

P. APPENDIX I

INDICATIVE DATA SHARING AGREEMENTS

P. APPENDIX 1A DATA SHARING AGREEMENT BETWEEN THE HELSINKI UNIVERSITY HOSPITAL COMPREHENSIVE CANCER CENTRE (HUS) AND THE INSTITUTE OF COMMUNICATION AND COMPUTER SYSTEMS (ICCS)

To: BOUNCE Consortium
From: BREX-trial study group
Date: 9.2.2018
Subject: NOTICE AND AGREEMENT OF DATA CONFIDENTIALITY AND ACCESS RIGHTS

This is to notify the BOUNCE consortium that the data from the Breast Cancer BREX research study including 573 patients treated at Helsinki University Hospital (HUS), that is made available for the BOUNCE project is marked confidential according to Article 10.1 of the Consortium Agreement.

As such, HUS reiterates that the data can only be used by person who have signed this agreement for the specific task for which it was made available to any individual consortium member and should not be distributed to others not involved in the task, or to a third party not involved in the project. Furthermore, the data or any result from its analysis shall not be published without the prior written approval of HUS.

All other conditions stated in the Consortium Agreement concerning a Party to the consortium agreement shall also apply and be binding upon the individual receiving the data here in question.

(ICCS)

I, undersigned, **Georgios S. Stamatakos, Research Professor at ICCS-NTUA** born on the **10th July 1963** in **Amykles, Sparta, Greece** and working in the **Institute of Communication and Computer Systems – National Technical University of Athens**
declare by the present consent form to subscribe to the project: Predicting effective adaptation to breast cancer to help women to BOUNCE back (Grant agreement number 777167), called BOUNCE in this document.
I have read, I understand and I agree to subscribe to the terms stated in this notice and agreement- which form a part
of this document (Version 1.0, February 2018), I further commit to keep any and all information received under this signed document confidential and shall use the data received, if containing patient data, only as consented by the patient and within those limits. I shall be entirely responsible for the use of the data and liable of any damages caused by such use or breach of this document.
I understand that two original copies of this agreement will be produced and will be kept by me and HUS respectively.
Name of the user; **Georgios Stamatakos**
Name of the representative**: Georgios Stamatakos**
Signature of the user/ its representative: .....
Date (please date your own signature): **16 February 2018**

(FORTH)

I, undersigned ....., (title) born on the....., in..... and working in ...../on behalf of .....(please cancel if not applicable) declare by the present consent form to subscribe to the project: Predicting effective adaptation to breast cancer to help women to BOUNCE back (Grant agreement number 777167), called BOUNCE in this document.

I have read, I understand and I agree to subscribe to the terms stated in this notice and agreement- which form a part
of this document (Version 1.0, February 2018), I further commit to keep any and all information received under this signed document confidential and shall use the data received, if containing patient data, only as consented by the patient and within those limits. I shall be entirely responsible for the use of the data and liable of any damages caused by such use or breach of this document. I understand that two original copies of this agreement will be produced and will be kept by me and HUS respectively.
Name of the user: .....
Name of the representative: .....
Signature of the user/ its representative: .....
Date (please date your own signature): .....

(SiLo)

I, undersigned ....., (title) born on the....., in..... and working in ...../on behalf of .....(please cancel if not applicable) declare by the present consent form to subscribe to the project: Predicting effective adaptation to breast cancer to help women to BOUNCE back (Grant agreement number 777167), called BOUNCE in this document.
I have read, I understand and I agree to subscribe to the terms stated in this notice and agreement- which form a part
of this document (Version 1.0, February 2018), I further commit to keep any and all information received under this signed document confidential and shall use the data received, if containing patient data, only as consented by the patient and within those limits. I shall be entirely responsible for the use of the data and liable of any damages caused by such use or breach of this document. I understand that two original copies of this agreement will be produced and will be kept by me and HUS respectively.
Name of the user: .....
Name of the representative: .....
Signature of the user/ its representative: .....
Date (please date your own signature): .....

PAULA POHJONEN-SAUSELA
HELSINKI UNIVERSITY HOSPITAL CCC
27 Feb. 2018

G. Stamatakos (ICCS)

Attachment 1: Background included

According to the Grant Agreement (Article 24) Background is defined as "data, know-how or information (…) that is needed to implement the action or exploit the results". Because of this need, Access Rights have to be granted in principle, but Parties must identify and agree amongst them on the Background for the project. This is the purpose of this attachment.

PARTY 1

As to Helsingin ja Uudenmaan sairaanhoitopiirin kuntayhtymä (HUS), it is agreed between the Parties that, to the best of their knowledge (*please choose)*,

Option 1: The following background is hereby identified and agreed upon for the Project. Specific limitations and/or conditions, shall be as mentioned hereunder:

Describe Background	Specific limitations and/or conditions for implementation (Article 25.2 Grant Agreement)	Specific limitations and/or conditions for Exploitation (Article 25.3 Grant Agreement)
BREX-study trial data	Data is only available for tasks related to WP3, WP 4 and WP5 for persons who have signed a Notice and Agreement of Data Confidentiality and Access Rights. The data can only be used by a person who has signed the above mentioned agreement, and only for the specific task for which it was made available and shall not be distributed to others not involved in the task, or to a third party not involved in the task. Furthermore, the data or any result from its analysis shall not be published without the prior written approval of HUS. Data is available only during the BOUNCE project and one year after its end for purposes of completing the task and must be destroyed afterwards.	Data is only available for tasks related to WP3, WP4 and WP5 for persons who have signed a Notice and Agreement of Data Confidentiality and Access Rights. The data can only be used by a person who has signed the above mentioned agreement, and only for the specific task for which it was made available, and shall not be distributed to others not involved in the task, or to a third party not involved in the task. Furthermore, the data or any result from its analysis shall not be published without the prior written approval of HUS. Data is available only during the BOUNCE project for purposes of completing the task and must be destroyed afterwards.

This represents the status 9.2.2018.

Signed by the BOUNCE representatives of the data using partners

Institute of Communication and Computer Systems (ICCS)

Georgios S. Stamatakos Athens, 16 February 2018

Foundation for Research and Technology Hellas (FORTH)

Singular Logic Anonymi Etaireia Pliroforiakon Systimaton kai Efarmogon Pliroforikis (SiLo)

PAULA POLHONEN-SAARELA, HELSINKI UNIVERSITY HOSPITAL CCC
27 Feb. 2018

P.APPENDIX 1B DATA SHARING AGREEMENT BETWEEN THE HEBREW UNIVERSITY SCHOOL OF SOCIAL WORK AND SOCIAL WELFARE AND THE INSTITUTE OF COMMUNICATION AND COMPUTER SYSTEMS (ICCS)

[The original of the following scanned document has already been signed by the representative of the HUJI team]

כללית מעל 100 שנה הכי טובה למשפחה

מרכז רפואי רבין בילינסון · השרון

To: BOUNCE Consortium
From: Building Resilience in Breast Cancer Patients
Date: 9.2.2018
Subject: NOTICE AND AGREEMENT OF DATA CONFIDENTIALITY AND ACCESS RIGHTS

This is to notify the BOUNCE consortium that the data from the Breast Cancer research study including 198 patients treated at **Davidoff Center, Rabin Medical Center, Petach-Tikva, Israel in collaboration with the Hebrew University of Jerusalem (HUJI)** that is made available for the BOUNCE project is marked confidential according to Article 10.1 of the Consortium Agreement.

כללית מעל 100 שנה הכי טובה למשפחה

מרכז רפואי רבין בילינסון · השרון

Attachment 1: Background included

According to the Grant Agreement (Article 24) Background is defined as "data, know-how or information that is needed to implement the action or exploit the results". Because of this need, Access Rights have to be granted in principle, but Parties must identify and agree amongst them on the Background for the project. This is the purpose of this attachment.

PARTY 4 - HUJI
The following background is hereby identified and agreed upon for the Project. Specific limitations and/or conditions, shall be as mentioned here under:

Describe Background	Specific limitations and/or conditions for implementation (Article 25.2 Grant Agreement)	Specific limitations and/or conditions for Exploitation (Article 25.3 Grant Agreement)
Building Resilience in Breast Cancer Patients Sample: In the study participated 198 females diagnosed with breast cancer (age range 26-72) Stages of breast cancer: Stage I (n=47) Stage II (N=107), Stage III (N= 37) Five waves of measurement starting in 2011, with a follow-up study conducted after 5-7 years in 2017	Data is only available for tasks related to WP4 for persons who have signed a Notice and Agreement of Data Confidentiality and Access Rights. The data can only be used by a person who has signed the above mentioned agreement, and only for the specific task for which it was made available and shall not be distributed to others not involved in the task, or to a third party not involved in the task. Furthermore, the data or any result from its analysis shall not be published without the prior written approval of **Davidoff Center, Rabin Medical Center, Petach-Tikva, Israel in collaboration with the Hebrew University of Jerusalem (HUJI)** - Data is available only during the BOUNCE project and one year after its end for purposes of completing the task and must be destroyed afterwards.	Data is only available for tasks related to WP4 for persons who have signed a Notice and Agreement of Data Confidentiality and Access Rights. The data can only be used by a person who has signed the above mentioned agreement, and only for the specific task for which it was made available, and shall not be distributed to others not involved in the task, or to a third party not involved in the task. Furthermore, the data or any result from its analysis shall not be published without the prior written approval of **Davidoff Center and HUJI.** Data is available only during the BOUNCE project for purposes of completing the task and must be destroyed afterwards.

This represents the status 19.2.2018.

Signed by the BOUNCE representatives of the data using partners

Institute of Communication and Computer Systems (ICCS)

G.S. Stamatakos

22 March 2018

P. APPENDIX 2

P.Appendix 2A HUS retrospective data description and coding

Note: Variables have been translated into English

Variable	Coding	Available at month
Patient number	Number	0
Birthdate	Date	0
Randomisation date	Date	0
Randomisation group	Exercise, Control	0
Menarche age	Age	0
Menopause status before adjuvant therapy	Postmenopausal (amenorrhea >12 months) Premenopausal	0
Menopause age before adjuvant therapy	Age	0
Last menstruation date before adjuvant therapy	Date	0
Hormone replacement therapy	Yes, No	0
Breast surgery	Mastectomy, Breast-conserving, Biopsy	0
Breast re-operation	Mastectomy, Breast-conserving, Other	
Breast re-operation specify	Free text	
Axillary surgery	Dissection, Sentinel node biopsy	0
Axillary re-operation	Dissection, Oher	
Axillary re-operation specify	Free text	
Tumor diameter	Number	0
Investigated lymph nodes	Number	0
Metastatic lymph nodes	Number	0
pT	T1, T2, T3, T4, Tis,Tx	0
pN	N0, N0i+, N1, N1mi, N2, N3	0
Histological type	Lobular, Ductal, Other	0
Histological grade	G1, G2, G3	0
ER	Positive, Negative	0
PR	Positive, Negative	0
Her2 IHC	Negative, +, ++, +++, Not done	0
Her2 FISH	Negative, Positive, Not done	0
Adjuvant CT	Yes, No	0
Adjuvant CT start weight	Number	0
Adjuvant CT start height	Number	0
Adjuvant CT start BSA	Number	0
CT regimen	1.6CEF, 2.3D+3CEF, 3.3DX+3CEX, 4.MUU	0

Neoadjuvant therapy	Yes, No	**0**
Herceptin	Yes, No	**0**
ET	Yes, No	**0**
ET agent	Astrozole, Exemestan, Letrazole, Tamoxifen, Other	**0**
ET Start date	Date	**0**
Radiotherapy (RT)	Yes, No	**0**
RT breast	Residual breast tissue, Scar	**0**
RT lymph nodes	Yes, No	**0**
RT total dose	Number	**0**
RT fraction dose	Number	**0**
RT booster	Yes, No	**0**
RT booster total dose	Number	**0**
Date of start	Date	**0**
Marital status	1. married or cohabitation 2. not married 3. divorced 4. widow 9. ND 10. other	0, 6, 12, 18, 24, 30, 36
Student years	Number	0
Births	Number	0
First birth	Date (Year)	0
State of health	1. good 2. quite good 3. middle level 4. quite bad 5. bad 9. ND 10. other	0, 6, 12, 18, 24, 30, 36
Disability	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Myocardiac infarction	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Cardiac insufficiency	1. yes 2. no 9. ND	
Arrhytmia	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Other cardiac disease	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Hypertension	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Thrombosis	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Stroke	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Rhematoid arthritis	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Arthrosis	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Other joint disease	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Back disease	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Fracture	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Osteoporosis	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Psychatric disease	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Which psyciatric disease	1. psychosis 2. depression 3. anxiety 4. drug abuse 5. other 9. ND	0, 6, 12, 18, 24, 30, 36
Which psyciatric disease 2	1. psychosis 2. depression 3. anxiety 4. drug abuse 5. other 9. ND	0, 6, 12, 18, 24, 30, 36
Which psyciatric disease 3	1. psychosis 2. depression 3. anxiety 4. drug abuse 5. other 9. ND	0, 6, 12, 18, 24, 30, 36
Diabetes	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Severe headache	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Urinary symptoms	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Degree of disability in work	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36

Degree of disability in leisure time	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Back pain	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Neck pain	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Proximal shoulder pain	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Distal shoulder pain	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Hip pain	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Knee pain	scale 0 to 10, 11 ND	0, 6, 12, 18, 24, 30, 36
Reduced amount of fat	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Changed amount of fat	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Increased vegetables	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Reduced sugar	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Reduced salt	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Lost weight	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Increased exercise	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Reduced alcohol	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Reduced smoking	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Alcohol use last 6 m	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Beer	Number	0, 6, 12, 18, 24, 30, 36
Long drink	Number	0, 6, 12, 18, 24, 30, 36
Strong alcvolohol	Number	0, 6, 12, 18, 24, 30, 36
Wine	Number	0, 6, 12, 18, 24, 30, 36
Cider or light wine	Number	0, 6, 12, 18, 24, 30, 36
Frequency of alcohol use	1. never 2. less than once a month 3 once a months 4. once a week 5 daily or almost daily 9. ND 10. other	0, 6, 12, 18, 24, 30, 36
Present smoking	1. yes, daily 2. occasionally 3. never 9. ND	0, 6, 12, 18, 24, 30, 36
Daily number of cigarrettes	Number	0, 6, 12, 18, 24, 30, 36
Type of work	1. agricultural 2. factory, mine, construction or similar 3. Office, non-manual work, service 4. study or school 5. housewife 6. retired 7. unemploid 9. ND 10. other	0, 6, 12, 18, 24, 30, 36
Duration of working day	Number	0, 6, 12, 18, 24, 30, 36
competitive sport	1. yes 2. no 9. ND	0, 6, 12, 18, 24, 30, 36
Competitive sport age	Age (from to)	0, 6, 12, 18, 24, 30, 36
Exercise work duration	Number	0, 6, 12, 18, 24, 30, 36
Physical strain at work	1. mainly sitting 2. walking quite a lot 3 walking and lifting a lot 4. heavy physical work 9. ND 10. other	0, 6, 12, 18, 24, 30, 36
Exercise at leisure time before breast cancer	1. watching television 2. walking bicycling 3. proper exercise 4. competitive exercise 9. not done 10. other answer	0, 6, 12, 18, 24, 30, 36

Exercise at leisure time before breast cancer, other	1. watching television 2. walking bicycling 3. proper exercise 4. competetitve exercise 9. not done 10. other answer	0, 6, 12, 18, 24, 30, 36
Type of exercise, mostly 1	1. ball game 2. gym 3. other gymnastics 4. running walking 5. swimming, water exercise 6. other 9. ND	0, 6, 12, 18, 24, 30, 36
Type of exercise, mostly 2	1. ball game 2. gym 3. other gymnastics 4. running walking 5. swimming, water exercise 6. other 9. ND	0, 6, 12, 18, 24, 30, 36
CRF Visits Menstrual cycle after therapy	Amenorrhea >12 months (postmenopausal) Unknown, Amenorrhea 6-12 months, Irregular, Regular (every 3-4 weeks)	0
CRF Visits Menopause status cause specify	Free text	0
Age	Number	0
Hospital in patient	1. yes 2. no 9. ND	6, 12, 18, 24, 30, 36
Hospital in patient, times	Number	6, 12, 18, 24, 30, 36
Hospital in patient, days	Number	6, 12, 18, 24, 30, 36
Doctor's appointment	1. yes 2. no 9. ND	6, 12, 18, 24, 30, 36
Number of doctor's appointments	Number	6, 12, 18, 24, 30, 36
Treatment due to mental problems	1. yes 2. no 9. ND	6, 12, 18, 24, 30, 36
Physiotherapy	1. yes 2. no 9. ND	6, 12, 18, 24, 30, 36
Physiotherapy, times	Number	6, 12, 18, 24, 30, 36
Duration of working day hours	Number	6, 12, 18, 24, 30, 36
Duration of working day-minutes	Number	6, 12, 18, 24, 30, 36
Change of work due to disease	1. yes 2. no 9. ND	6, 12, 18, 24, 30, 36
Amount of leisure time exercise	1. None 2. Some times per year 3. 1-3 times per month 4. Once a week 5. 2-3 times per week 6. 4-5 times per week 7. more than 5 times per week 9. ND (no data) 10. other	6, 12, 18, 24, 30, 36
Type of exercise, mostly	1. ball game 2. gym 3. other gymnastics 4. running walking 5. swimming, water exercise 6. other 9. ND	6, 12, 18, 24, 30, 36
At work last 6 m	1. yes 2. no 9. ND	6, 12, 18, 24, 30, 36
Work situation now	1 at work, sick leave ended 2 at sick leave, which started 3 presently not at work 9 ND 10 other	6, 12, 18, 24, 30, 36
Physical strain at work	1. mainly sitting 2. walking quite a lot 3 walking and lifting a lot 4. heavy physical	0, 6, 12, 18, 24, 30, 36

	work 9. ND 10. other	
Physical strain at work, other	1. mainly sitting 2. walking quite a lot 3 walking and lifting a lot 4. heavy physical work 9. ND 10. other	6, 12, 18, 24, 30, 36
Exercise on way to work before breast cancer	1. not working or working at home 2. I do not walk or bicycle daily 3. less than 15 min daily 4. 15-29 min daily 5. 30-44 min daily 6. 45-59 min daily 7. more than 1 hour daily 9. ND 10. other	0
Exercise on way to work	1. not working or working at home 2. I do not walk or bicycle daily 3. less than 15 min daily 4. 15-29 min daily 5. 30-44 min daily 6. 45-59 min daily 7. more than 1 hour daily 9. ND 10. other	6, 12, 18, 24, 30, 36
Exercise on way to work, other	1. not working or working at home 2. I do not walk or bicycle daily 3. less than 15 min daily 4. 15-29 min daily 5. 30-44 min daily 6. 45-59 min daily 7. more than 1 hour daily 9. ND 10. other	6, 12, 18, 24, 30, 36
CRF VisitsWHO	Number	0, 12, 36
CRF Visits Height	Number	0, 12, 36
CRF Visits Weight	Number	0, 12, 36
CRF Visits Pulse	Number	0, 12, 36
CRF Visits BP systolic	Number	0, 12, 36
CRF VisitsBP diastolic	Number	0, 12, 36
CRF Visits Menopause status changed	Yes, No, Unknown	12, 36
CRF Visits Menopause status unknown reason	Free text	12, 36
CRF Visits Menopause age	Number	12, 36
CRF Visits Menopause status cause	Chemical, Surgical, Natural, Other	12, 36
CRF Visits Menstrual cycle	Amenorrhea >12 months (postmenopausal) Unknown, Amenorrhea 6-12 months, Irregular, Regular (every 3-4 weeks)	12, 36
CRF Visits ET changed	No changes, Changed	12, 36
CRF Visits Fracture region	Free text	0, 12, 36
CRF Visits Diabetes	Yes, No	0, 12, 36
CRF Visits Cardiovascular disease	Yes, No	0, 12, 36
CRF Visits Coronary heart disease	Yes, No	0, 12, 36
CRF Visits Coronary stroke	Yes, No	0, 12, 36
CRF Visits Hypertension	Yes, No	0, 12, 36
CRF Visits Musculoskeletal morbidity	Yes, No	0, 12, 36
CRF Visits Total cholesterol	Number	0, 12, 36
CRF Visits Glucose	Number	0, 12, 36
Fyys akt kyselySeurantakerta kk		
Light exetcise total min	Number	0, 6, 12, 18, 24, 30, 36

Moderately heavy exercise total min	Number	0, 6, 12, 18, 24, 30, 36
Heavy exercise total min	Number	0, 6, 12, 18, 24, 30, 36
Very heavy exercise total min	Number	0, 6, 12, 18, 24, 30, 36
Figure of eight run 1 time	Number	0, 12, 36
Figure of eight run 2 time	Number	0, 12, 36
Figure of eight number of cycles	Number	0, 12, 36
Walking test result	Number	0, 12, 36
Waist circumference	Number	0, 12, 36
C30Strenuous activities	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Long walk	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Short walk	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Rest or sitting	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Help with eating dressing washing	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Difficulties in daily activities	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Difficulties in leisure time activities	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Short of breath 1	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Pain	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Need to rest	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Insomnia	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Weakness	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Appetite loss	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Nausea	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Vomitting	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Constipation	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Diarrhea	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Fatigue	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Distracting pain	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Difficulty concentrating	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Tense	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36

C30Worry	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Irritable	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Depressed	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Difficulty remembering	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Disturbance in family life	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Disturbance in social activities	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Financial difficulties	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Health status	1. Very poor - 7. Excellent 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30Quality of life	1. Very poor - 7. Excellent 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Seurantakerta kk	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Dry mouth	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Taste different	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Irritated eyes	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Hair loss	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Upset by hair loss	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Ill or unwell	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Hot flushes	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Headaches	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Physically less attractive	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Less feminine	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Hard to look at yourself naked	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Dissatisfied with your body	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Worried about future health	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Sexual interest	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Sexual activity	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Sexual enjoyment	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Pain in arm shoulder	1. Not at all 2. A little 3. Quite a bit 4. Very	0, 3, 6, 12, 18, 24, 30,

	much 9. ND	36
BR23Swollen arm or hand	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Difficulty raising arm	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Pain in affected breast	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Swollen affected breast	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Oversensitive affected breast	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BR23Skin problems in affected breast	1. Not at all 2. A little 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Wake up at night	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Frightened or panic	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Miserable or sad	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Anxious outside home	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Lost interest	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Get palpitations	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Still enjoy the same things	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Life is not worth living	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Tense	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Good appetite	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Restless	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ More irritable	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WH Worry about growing	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Headaches	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ More tired	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Dizzy spells	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Breasts tender or uncomfortable	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Pain in back or limps	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36

WHQ Hot flushes	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ More clumsy	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Lively and excitable	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Abdominal cramps or discomfort	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Sick or nauseous	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Lost interest in sex	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Feelings of well-being	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Heavy periods	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Night sweats	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Bloated stomach	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Difficult to sleep	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Feel pins in hands or feet	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Satisfied with my sexual relationship	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Physically attractive	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Difficult to concentrate	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Uncomfortable sex due to vaginal dryness	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ More frequent urination	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Poor memory	1. Yes definitely 2. Yes sometimes 3 No not much 4. No not at all 9. ND	0, 3, 6, 12, 18, 24, 30, 36
WHQ Living with some symptoms is difficult	1. Yes 0. No 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Fatigued	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Weak all over	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Listless	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Tired	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Trouble starting things	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Trouble finishing things	0. Not at all 1. A little bit 2. Somewhat 3.	0, 3, 6, 12, 18, 24, 30,

	Quite a bit 4. Very much 9. ND	36
FACIT Energy	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Able to do usual activities	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Need sleep during day	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Too tired to eat	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Need help for usual activities	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Frustrated about being tired to do things	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
FACIT Limit social activity because tired	0. Not at all 1. A little bit 2. Somewhat 3. Quite a bit 4. Very much 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Mood sadness	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Future pessimism	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Past failure	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Dissatisfaction	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI How do you like yourself	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Disappointment	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Suicidal thoughts	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Social withdrawal	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Indecisiveness	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Body image	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Changes in sleep	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Tiredness or fatigue	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Changes in appetite	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
BDI Anxious or tense	1- 5 scale 9. ND	0, 3, 6, 12, 18, 24, 30, 36
C30 Global QoL	0-100 score *A high score represents a high QoL*	0, 3, 6, 12, 18, 24, 30, 36
C30 Physical functioning	0-100 score *A high score represents a healthy level of functioning*	0, 3, 6, 12, 18, 24, 30, 36
C30 Role functioning		
C30 Emotional functioning		
C30 Cognitive functioning		
C30 Social functioning		
C30 Fatigue	0-100 score *A high score represents a high level of symptomatology*	0, 3, 6, 12, 18, 24, 30, 36
C30 Nausea and vomiting		

C30 Pain		
C30 Dyspnea		
C30 Insomnia		
C30 Appetite loss		
C30 Constipation		
C30 Diarrhea		
C30 Financial impact	0-100 score *A high score represents a high level of problem*	0, 3, 6, 12, 18, 24, 30, 36
BR23 Body image	0-100 score *A high score represents a healthy level of functioning*	0, 3, 6, 12, 18, 24, 30, 36
BR23 Sexual functioning		
BR23 Sexual enjoyment		
BR23 Future perspective		
BR23 Systemic therapy side effects	0-100 score *A high score represents a high level of symptomatology*	0, 3, 6, 12, 18, 24, 30, 36
BR23 Breast symptoms		
BR23 Arm symptoms		
BR23 Upset by hair loss		
WHQ Depressed mood	0-1 score *0 is an indicator of "poor health status" and 1 is an indicator of "good health status"*	0, 3, 6, 12, 18, 24, 30, 36
WHQ Somatic symptoms		
WHQ Memory/concentration		
WHQ Vasomotor Symptoms		
WHQ Anxiety/fears		
WHQ Sexual behaviour		
WHQ Sleep Problems		
WHQ Menstrual symptoms		
WHQ Attractiveness		
BDI Depression	0-39 score *The higher the score, the higher the depression*	0, 3, 6, 12, 18, 24, 30, 36
FACIT score	0-52 score *The higher the score, the better the QoL*	0, 3, 6, 12, 18, 24, 30, 36
FACIT score prorated for missing items		
BMI	Number	0, 12, 36
Figure 8 time	Number	0, 12, 36
MetH	Number	0, 6, 12, 18, 24, 30, 36
MetHheavy	Number	0, 6, 12, 18, 24, 30, 36

P.Appendix 2B HUJI Retrospective Data Description

The demographic and medical data (collected at T1):

Variable name	Meaning	Coding
Workshop	Whether participated in the intervention workshop	0. No 1. Yes
NotFinish	Whether dropped out of the workshop	99. Not Applicable 0. No, 1. Yes
H_T2	Has T2 data?	0. No, 1. Yes
H_T3	Has T3 data?	0. No, 1. Yes
H_T4	Has T4 data?	0. No, 1. Yes
H_T5	Has T5 data?	0. No, 1. Yes
H_T6	Has T6 data?	0. No, 1. Yes
Age	Age at diagnosis	Number
Children	Number of children	Number
DiagnDate	Date of diagnosis	Date
Stage	Disease stage	1. I, 2. II , 3. III
Protocol	Treatment protocol	0. Adria, 1. no Adria, 2.DD(Dose dense?)
Treatment	Treatment Type	1. Chemo, 2. Radio, 3.Both
Herceptin	Herceptin	0. No, 1. Yes
Hormonal	Hormonal	0. No, 1. Yes
TreatEnd	Date of treatment end (not including Herceptin and Hormonal)	Date
City	Whether lives in a city (vs rural area)	0. No, 1. Yes
Married	Whether married (vs. single)	0. No, 1. Yes
ISRAELI	Whether born in Israel (vs. immigrant)	0. No, 1. Yes
Child	Has Children?	1. Yes, 2. No
EducQue	Education	1-7
WorkStat	Work Status	1. Not employed, 2.Part-time, 3.Full- time
RNotWork	Reason for not working	99. Not Applicable, 1-6
IWork	Income from work	0. No, 1. Yes
IBit	Income from Social Security disability pension	0. No, 1. Yes
IOth	Income from pension or from another source	0. No, 1. Yes
Religious	Definition of religious faith/ Level of religious faith	1.Religious, 2. Traditional, 3. Secular
SressTod	Today distress level	0-7.7 Continuous scale
ResTod	Level of Perceived Resilience Today	0-7.7 Continuous Scale
HopeTod	Amount of hope for the future	0-7.7 Continuous Scale
OperDate	Operation Date	Date
Genetic	Genetic Testing was Performed	1. Yes, 2. No
Carrier	If a Genetic Test Performed - are you a Carrier	1. Yes, 2. No
History	Family history of breast cancer	1. Yes, 2. No
Heat	Heat Waves	0. No, 1. Yes
Mood	Mood Swings	0. No, 1. Yes
Sleep	Sleep Problems	0. No, 1. Yes
Fat	Obesity	0. No, 1. Yes

Body	Decrease in comfort with the body	0. No, 1. Yes
Sex	Disruption in Sexuality	0. No, 1. Yes
FemSense	Interference with a sense of femininity	0. No, 1. Yes
HeatH	How Affected: Heat waves	0-4 score
MoodH	How Affected: Mood swings	0-4 score
SleepH	How Affected: Sleep problems	0-4 score
FatH	How Affected: Obesity	0-4 score
BodyH	How Affected: Decrease in comfort with the body	0-4 score
SexH	How Affected: Disruption in sexuality	0-4 score
FemseneH	How Affected: Interference with a sense of femininity	0-4 score

Psychosocial measures:

Variable name	Meaning	Coding	Collected at month
PTSD - The Posttraumatic Stress Diagnostic Scale			
pds1	Intrusive images	0. Not at all or only one time 1. Once a week or less/once in a while 2. 2 to 4 times a week/half the time 3. 5 or more times a week/almost always	0,3,6,12,24
pds2	Nightmares		
pds3	Reliving of the trauma		
pds4	Emotionally upset when reminded of the trauma		
pds5	Physical reactions when reminded of the trauma		
pds6	Trying not to think, talk, or have feelings about the trauma		
pds7	Trying to avoid activities, places, or people		
pds8	Memory loss		
pds9	Loss of interest		
pds10	Feeling distant or cut off		
pds11	Feeling emotionally numb		
pds12	Lack of future plans		
pds13	Difficulty sleeping		
pds14	Irritability		
pds15	Difficulty concentrating		
pds16	Overly alert		
pds17	Easily startled		
Functional impairment items			
func1	Work	6-point scale 0 (Not influenced at all) to 5 (Severely influenced)	0,3,6,12,24
func2	Housekeeping and related obligations		
func3	Relations with friends		
func4	Leisure activities		
func5	Studies		
func6	Relations with family members		
func7	Sexual functioning and relations		
func8	General life satisfaction		
func9	General level of functioning		
CES-D – depression			
cesd1	Bothered	0. Rarely or None of the Time (Less than 1 Day) 1. Some or Little of the Time (1-2 Days) 2. Occasionally or a Moderate Amount of Time (3-4 Days) 3. Most or All of the Time (5-7 Days)	0,3,6,12,24
cesd2	Poor appetite		
cesd3	Blues		
cesd4	As good as others		
cesd5	Poor concentration		
cesd6	Depressed		
cesd7	Everything is effort		
cesd8	Hopeful		
cesd9	Failure		
cesd10	Fearful		
cesd11	Restless sleep		
cesd12	Happy		
cesd13	Less talk		
cesd14	Lonely		
cesd15	People were unfriendly		
cesd16	Enjoying life		
cesd17	Crying spells		
cesd18	Sad		
cesd19	People dislike me		
cesd20	Not get going		

Feeling Today			
SressTod	Overall self-report of stress "today"	0-10 Continuous Scale	0,3,6,12,24
ResTod	Overall self-report of resilience "today"	0-10 Continuous Scale	0,3,6,12,24
HopeTod	Overall self-report of hope "today"	0-10 Continuous Scale	0,3,6,12,24
Ego resilience Scale			
ego1	Generous with friends	1.Does not apply at all 2. Applies slightly 3. Applies somewhat 4. Applies very strongly	0,3,6,12,24
ego2	Quickly recover from being startled		
ego3	Enjoy new situations		
ego4	Give favorable impression		
ego5	Enjoy trying new foods		
ego6	Energetic		
ego7	Take different paths		
ego8	Curious		
ego9	Most of the people I meet are likable.		
ego10	Think carefully before acting		
ego11	Like new things		
ego12	Daily life full of interesting things		
ego13	"Strong" personality		
ego14	Get over quickly		
CERQ – Cognitive Emotion Regulation Questionnaire			
cerq1	Acceptance item 1	1. (almost) never 2. some-times 3. regularly 4. often 5. (almost) always	0,3,6,12,24, follow-up
cerq2	Focus on thought/rumination item 1		
cerq3	Positive reappraisal item 1		
cerq4	Self-blame item 1		
cerq5	Acceptance item 2		
cerq6	Focus on thought/rumination item 2		
cerq7	Positive refocusing item 1		
cerq8	Positive reappraisal item 2		
cerq9	Catastrophizing item 1		
cerq10	Other-blame item 1		
cerq11	Positive refocusing item 2		
cerq12	Refocus on planning item 1		
cerq13	Putting into perspective item 1		
cerq14	Self-blame item 2		
cerq15	Refocus on planning item 2		
cerq16	Putting into perspective item 2		
cerq17	Catastrophizing item 2		
cerq18	Other-blame item 2		
PACT - The Perceived Ability to Cope with Trauma			
flex1	Keep my schedule and activities as constant as possible	7-point scale 1 (Not at all able) to 7 (Extremely able)	0,3,6,12,24, follow-up
flex2	Comfort other		
flex3	Look for a silver lining		
flex4	Stay focused on my current goals and plans		
flex5	Find activities to help me keep the event off my mind		
flex6	Let myself fully experience some of the painful emotions linked with the event		
flex7	Spend time alone		
flex8	I would be able to laugh		

flex9	Try to lessen the experience of painful emotions		
flex10	Reduce my normal social obligations		
flex11	Alter my daily routine		
flex12	Reflect upon the meaning of the event		
flex13	Distract myself to keep from thinking about event		
flex14	Face the grim reality head on		
flex15	Enjoy something that I would normally find funny or amusing		
flex16	Focus my attention on or care for the needs of other people		
flex17	Remind myself that things will get better		
flex18	Keep myself serious and calm		
flex19	Remember the details of the event		
flex20	Pay attention to the distressing feelings that result from the event		
PTGI - The Posttraumatic Growth Inventory			
ptg1	changed priorities about what is important	0. I did not experience this change as a result of my crisis. 1. I experienced this change to a very small degree as a result of my crisis. 2. I experienced this change to a small degree as a result of my crisis. 3. I experienced this change to a moderate degree as a result of my crisis. 4. I experienced this change to a great degree as a result of my crisis. 5. I experienced this change to a very great degree as a result of my crisis.	0,3,6,12,24, follow-up
ptg2	*An* appreciation for the value of my own life.		
ptg3	I developed new interests		
ptg4	A feeling of self-reliance.		
ptg5	A better understanding of spiritual matters		
ptg6	Knowing that I can count on people in times of trouble.		
ptg7	I established a new path for my life.		
ptg8	A sense of closeness with others.		
ptg9	A willingness to express my emotions		
ptg10	Knowing I can handle difficulties		
ptg11	I' m able to do better things with my life.		
ptg12	Being able to accept the way things work out.		
ptg13	Appreciating each day		
ptg14	New opportunities are available which wouldn't have been otherwise		
ptg15	Having compassion for others.		
ptg16	Putting effort into my relationships.		
ptg17	I'm more likely to try to change things which need changing.		
ptg18	I have a stronger religious faith.		
ptg19	I discovered that I'm stronger than I thought I was.		
ptg20	I learned a great deal about how wonderful people are.		
ptg21	I accept needing others		
K6 – Kessler Psychological Distress Scale			
distress1	feel nervous	1. none of the time 2. a little of the time	follow-up
distress2	feel hopeless		
distress3	feel restless or fidgety		

distress4	feel so depressed	3. some of the time, 4. most of the time 5. all of the time	
distress5	feel that everything was an effort		
distress6	feel worthless		
PCL 5 – Posttraumatic Stress Disorder Check-List			
pcl1	Intrusive memories	1. Not at all 2. A little bit 2. Moderately 4. Quite a bit 5. Extremely	follow-up
pcl2	Disturbing dreams		
pcl3	Reliving of the stressful experience		
pcl4	Emotionally upset when reminded of the stressful experience		
pcl5	Physical reactions when reminded of the stressful experience		
pcl6	Avoid thoughts, feelings, or physical sensations about the stressful experience		
pcl7	Avoid activities, conversations, places, or people		
pcl8	Memory loss		
pcl9	Negative thoughts about yourself, other people, or the world		
pcl10	Blaming yourself or someone else		
pcl11	Strong negative feelings		
pcl12	Loss of interest		
pcl13	Feeling distant or cut off		
pcl14	Having trouble experiencing positive feelings		
pcl15	Irritability		
pcl16	Too risky		
pcl17	Overly alert		
pcl18	Easily startled		
pcl19	Difficulty concentrating		
pcl20	Difficulty sleeping		
CERQ	Average of CERQ scores	1-5	0,3,6,12,24, follow-up
FLEX	Average of PACT scores	1-7	0,3,6,12,24, follow-up
PTG	Average of PTGI scores	0-5	0,3,6,12,24, follow-up
EGO	Average of EGO scores	1-4	0,3,6,12,24
PDS	Average of PTSD scores	0-3	0,3,6,12,24
FUNCT	Average of functional scores	0-5	0,3,6,12,24
CESD	Average of CES-D scores	0-3	0,3,6,12,24
CERQPOS	Average of scores for CERQ – Positive coping strategies (acceptance, positive refocusing, refocus on planning, positive reappraisal, and putting into perspective)	1-5	0,3,6,12,24, follow-up
CERQNEG	Average of scores for CERQ – Negative coping strategies (selfblame, rumination, catastrophizing, and other blame)	1-5	0,3,6,12,24, follow-up
TODAY	Average of TODAY scores	0-10	0,3,6,12,24
DISTR	Average of Kessler scores	1-5	follow-up
PCL	Average of PCL-5 scores	1-5	follow-up

P.Appendix 2C IEO Retrospective Data Description

	PHR	Database
Age	X	
Height	X	
Weight (BMI)	X	
Education	X	
Socioeconomic status	X	
nulliparity or pregnancy	X	
occupational status	X	
past/current smoking	X	
Frequency and amount of alcohol consumption	X	
Frequency and type of physical activity	not regularly	
TNM stage	X	X
nodal status	X	X
date of first diagnostic sampling	X	X
surgery type and side	X	X
menopausal status	X	X
early age menstruation	X	X
breastfeeding	X	
family history	X	
tumour biology (estrogen, progesterone and HER2 receptor expression, grade and state, vascular invasion, margins)	X	X
ki67	X	X
basic laboratory tests (CBC, Hb, creatinine, bilirubine CRP, ALT)	X	
imaging results (mammography, CT, ultrasound)	X	
genetic risk factors	X	
RMI, mammograph, ecography in BRCA cases	X	
amount of counselling (and support sessions) received during cancer treatment	X	
psychotropic medication	X	
disease free survival	X	X
Type of treatment (chemotherapy/HT/RT)	X	X
Psychological dimensions/measures		
Distress levels (Distress thermometer)	X	X
emotion regulation (Emotion Thermometers)	not to all patients	
life events and stressors	only for patients receiving psy support	
quality of life (EORTC QLQ-C30 or FACT-B)	not to all patients	
impact of cancer-event (IES, impact event scale)	not to all patients	
positive and negative mood (POMS)	not to all patients	
Patient Reported symptoms (IBCSG patient reported symptomps form)	not to all patients	
FACIT Fatigue scale	not to all patients	

F.A.R.E Family Resilience	not to all patients	
HADS (Hospital Anxiety and Depression Scale)	not to all patients	
MoCA	not to all patients (for patients >70)	
instrumental activities of daily living	not to all patients (for patients >70)	
Activity daily living	not to all patients (for patients >70)	
care-giver's reaction assessment instrument	not to all patients (for patients >70)	

P. Appendix 2D CHAMP Retrospective Data Description

Biological Variables

Variable	Type of variable	Coding
SOCIO-DEMOGRAPHIC DATA		
Date of birth	Time	
Marital Status	Ordinal	1.Married, 2. Single, 3.Common-law partner, 4.Divorced, 5.Widow
Education level (years)	Ordinal	
DIAGNOSIS DATA		
Date of diagnosis/biopsy	Time	
Hystologic Type	Ordinal	1.Invasive, NST, 2.Invasive, Lobular, 3.Mixed, NST and Lobular, 4.Histologically special types, 5.Ductal carcinoma in situ (DCIS), 6.Not applicable/Undetermined
Grade	Ordinal	1.Grade 1, 2.Grade 2, 3.Grade 3, 4.Not applicable/Undetermined
Estrogen receptor	Ordinal	1.Negative., 2.Positive, 3.Not applicable/Undetermined
Progesteron receptor	Ordinal	1.Negative., 2.Positive, 3.Not applicable/Undetermined
HER- 2 receptor	Ordinal	1.Negative., 2.Positive, 3.Not applicable/Undetermined
Ki67	Continuous	
IMAGING DATA		
Date	Time	
Type of Imaging	Ordinal	1.Ultrasound + Mammogram, 2.Mammogram only, 3.Ultrasound only
Tumor Size (cT)	Ordinal	1.TX, 2.T0, 3.Tis, 4.T1a, 5.T1b, 6.T1c, 7.T2, 8.T3, 9.T4
Lymph node involvement (cN)	Ordinal	1.Nx, 2.N0, 3.N1mi, 4.N1a, 5.N1b, 6.N1c, 7.N2, 8.N3
Multifocality / Multicentrality	Ordinal	1.No, 2.Yes
Distant metastases (cM)	Ordinal	1.M0, 2.M1, 3.Mx
GENETIC RISK FACTORS		
Family history	Ordinal	1.No known family history of cancer 2.Any family history of breast and/or ovarian cancer 3.Any family history of cancer other than breast and ovarian
Genetic test	Ordinal	1.Negative test, 2.Not available, 3.BRCA 1 positive, 4.BRCA 2 positive, 5.Positive for other tests, 6.Positive result of uncertain significance
PATHOLOGY (Post-surgery)		
pT	Ordinal	1.TX, 2.T0, 3.Tis, 4.T1a, 5.T1b, 6.T1c, 7.T2, 8.T3, 9.T4
pN	Ordinal	1.Nx, 2.N0, 3.N1mi, 4.N1a, 5.N1b, 6.N1c, 7.N2, 8.N3

Hystologic Type	Ordinal	1. Invasive, NST, 2. Invasive, Lobular, 3.Mixed, NST and Lobular/other histological types 4.Histologically special types 5.Ductal carcinoma in situ (DCIS) 6.Not applicable/Undetermined
Grade	Ordinal	1.Grade 1, 2.Grade 2, 3.Grade 3, 4.Not applicable/Undetermined
Estrogen receptor	Ordinal	1.Negative., 2.Positive, 3.Not applicable/Undetermined
Progesteron receptor	Ordinal	1.Negative., 2.Positive, 3.Not applicable/Undetermined
HER- 2 receptor	Ordinal	1.Negative., 2.Positive, 3.Not applicable/Undetermined
Ki67	Continuous	
Margins	Ordinal	1.Free Margins, 2.Positive margins with indication for surgery 3.Positive margins with no indication for surgery, 4.Not applicable/Undetermined
Lymphovascular invasion	Ordinal	1.Present, 2.Absent, 3.Suspected, 4.Not applicable/Undetermined
Genomic test	Ordinal	1.Not done,,2.Luminal low-risk, 3.Luminal intermediate or high-risk 4.Not applicable/Undetermined
Molecular classification	Ordinal	1.Luminal A like, 2.Luminal B like, 3.Luminal B, HER 2 enriched 4.HER 2 enriched, 5.Basal, 6.Undetermined
Staging results - AJCC 7th Ed.	Ordinal	1.0, 2.1a, 3.1b, 4.IIa, 5.IIb, 6.IIIa, 7.IIIb, 8.IIIc, 9.IV, 10.Undetermined
SURGERY		
Date	Time	
Breast surgery	Ordinal	1.Lumpectomy, 2.Mastectomy
Axillary management	Ordinal	1.Sentinel lymph node biopsy (SLNB) 2.Axillary lymph node dissection (ALND) 3.ALND after SLNB
RADIATION THERAPY		
Radiation therapy- type	Ordinal	1.No indication for adjuvant radiotherapy 2.Local therapy (breast) 3.Local-regional therapyl (breast + lymph nodes)
Starting date	Time	11/11/1111 Not applicable
End date	Time	11/11/1111 Not applicable
Total dose	Continuous	1111 Not applicable
Number of fractions (number of daily sessions)	Continuous	1111 Not applicable
Boost		1111 Not applicable
SYSTEMIC TREATMENT		
Type of Systemic Treatment	Ordinal	1.No indication for systemic treatment 2.Adjuvant/Neoadjuvant Chemotherapy only 3.Adjuvant/Neoadjuvant Chemotherapy plus biologicals 4.Adjuvant/Neoadjuvant Chemotherapy plus biologicals and endocrine therapy (ET) 5.Adjuvant/Neoadjuvant Chemotherapy plus ET

		6.ET only 7.Biologicals only
Adjuvant/Neoadjuvant Chemotherapy Start Date	Time	11/11/1111. Not applicable
Adjuvant/Neoadjuvant Chemotherapy End Date	Time	11/11/1111. Not applicable
Type of Chemotherapy	Ordinal	1.Anthracyclines and taxanes 2.Taxanes only 3.Anthracyclines only 4.Anthracyclines and taxanes and platinums 5.Not applicable (no indication for Chemotherapy)
Adjuvant/Neoadjuvant Hormone Therapy Start Date	Time	11/11/1111.Not applicable
Adjuvant/Neoadjuvant Hormone Therapy Start Date	Time	11/11/1111.Not applicable
Type of Hormone Therapy	Ordinal	1.Tamoxifen 2.Tamoxifen sequential to Aromatase Inhibitors (AI's) 3.AI's 4.Ovarian supression with aLHRH plus Tamoxifen 5.Ovarian supression with aLHRH plus AI's 6.Ovarian supression with aLHRH plus Tamoxifen and AI's 7.Not applicable (no indication for Hormone Therapy)
Biologics ADJ/NEO Start Date	Time	11/11/1111. Not applicable
Biologics ADJ/NEO End Date	Time	11/11/1111. Not applicable
Type of Biologicals	Ordinal	1.Trastuzumab 2.Trastuzumab plus pertuzumab 3.Not applicable (no indication for Biologicals)
Patient options	Ordinal	1.Followed the plan, 2.Reffused ET, 3.Refused CT, 4.Reffused biologicals
Participation in clinical trials	Ordinal	1.No, 2.Yes
FOLLOW UP		
Relapse	Ordinal	1.Without relapse, 2.Local/regional relapse, 3.Distant relapse 4.Local and distant relapse
Date of relapse	Time	11/11/1111. Not applicable
Current disease status	Ordinal	1. Alive and desease free 2.Alive with relapsed disease 3.Dead, not related to relapse 4.Dead, related to relapsed disease 5.Lost to follow up
Date of last follow up	Time	

Pshycological variables

Variable	Type of variable	Range/Relevant information
Date of psychological assessment	Time	
Distress thermometer	Continuous	0 - 10
HADS	Continuous	0 - 42
Symbol Search (subtest WAIS-III)	Continuous	1-19 Standardized result (mean value = 10; standard deviation = 3)
Digit Span (subtest WAIS-III)	Continuous	
Trail Making Test A	Ordinal	Results presented in percentile score.
Trail Making Test B	Ordinal	
Stroop test_Word Task	Continuous	3-98 T score Standardized result (mean value = 50; standard deviation = 10)
Stroop test_Color Task	Continuous	
Stroop Test_Color-Word Task	Continuous	
Beck Depression Inventory (BDI-II)	Continuous	0 - 63 Standardized result (mean value = 8.8 ; standard deviation = 7.8)
STAI_State subscale	Continuous	20-80 Standardized result (mean value Mean value (females) = 39.2 ; Standard deviation (females) = 10.2
STAI_Trait subscale	Continuous	
EORTC QLC 30	Continuous	0-100 Results presented in percentage format
Mini Mental Status	Continuous	0 - 30 Standardized result considering the patient's age and schooling
Addenbrookes Cognitive Examination Revised (ACE-R)	Continuous	0 - 100 Standardized result considering the patient's age and schooling

P. APPENDIX 3 Literature on the Reported Associations Among Various BOUNCE Related Factors

This appendix contains a concise summary of pertinent literature focusing on the associations among various BOUNCE related factors observed so far.

TABLE P3.1 Psychological Factors

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
WOMEN'S HEALTH QUESTIONNAIRE: USER MANUAL. BY ISABELLE GIROD, LINDA ABETZ CHRISTINE DE LA LOGE, CHRISTINE FAYOL-PAGET	Assess WHQ scores according to age groups in general population (n=6060). Four age groups are considered: <49, 49-53, 53-58, >=58. Assess WHQ scores according to menopausal status in general population (n=6060). Peri or pre-menopause status and post-menopause status are considered.	All dimensions are related to age. For Menstrual Symptoms, Sexual Behaviour and Attractiveness this relation is linear; for Menstrual symptoms older are the women better are their Health status and inversely for Sexual Behaviour and Attractiveness dimensions. For most of the dimensions, the group 49 and younger has the highest health status. Health status, for all dimensions is related to the menopausal condition. Women in peri- or pre-menopause have a better health status than the women in post-menopause for all dimensions except for Menstrual Symptoms.
DONOVAN K ET AL. CANCER. (2012)	Review paper	Treatments commonly associated with menopausal symptoms in women with breast cancer include chemotherapy and endocrine therapy. The effects of endocrine therapy on urinary symptoms are not yet known Less vitality, worse physical quality of life, worse social life, and worse overall quality of life were significantly associated with more urinary symptoms in the post-treatment period. With respect to sexuality, more urinary incontinence and worse urinary problems were significantly associated with adverse effects on sexuality in the post-treatment period.
MATZKA M ET AL. PLOS ONE (2016)	Assess the prevalence of symptoms and supportive care needs of oncology patients undergoing chemotherapy, radiotherapy or chemo-radiation therapy in a tertiary oncology service. Resilience was assessed using the 10-item Connor-Davidson Resilience Scale (CD-RISC 10), social support was evaluated using the 12-item Multidimensional Scale of Perceived Social Support (MSPSS) and both psychological distress and activity level were measured using corresponding subscales of the Rotterdam Symptom Checklist (RSCL).	Resilience was negatively associated with psychological distress, and positively associated with activity level. The relationship between resilience and psychological distress was moderated by age but not social support. Cancer patients with higher resilience, particularly older patients, experience lower psychological distress.

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
RISTEVSKA-DIMITROVSKA G ET AL. OPEN ACCESS MACED J MED SCI. (2015)	• Examine the relationship between resilience and quality of life in breast cancer patients. • QoL was measured in 218 consequent breast cancer patients, with EORTC - QLQ Core 30 questionnaire, and EORTC QLQ-BR23. The resilience was measured with Connor Davidson Resilience Scale.	Psychological resilience affects different aspects of health-related quality of life. More resilient patients have significantly better quality of life in almost all aspects of QoL. The global quality of life was positively correlated with the levels of resilience. All functional scales (physical, role, emotional, cognitive and social functioning was in a positive correlation with resilience. The symptoms severity (fatigue, nausea and vomitus, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) was in negative correlation with resilience. Less resilient breast cancer patients reported worse body image and future perspective and suffered from more severe adverse effects of systemic therapy, and arm/breast symptoms.
SYROWATKA A ET AL. BREAST CANCER RES TREAT. (2017)	• Review paper • Synthesize the published literature around predictors of distress in female breast cancer survivors to help guide targeted intervention to prevent distress.	Breast cancer and treatment-related predictors were more advanced cancer at diagnosis, treatment with chemotherapy, longer primary treatment duration, more recent transition into survivorship, and breast cancer recurrence. Manageable treatment-related symptoms associated with distress included menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. Sociodemographic characteristics that increased the risk of distress were younger age, non-Caucasian ethnicity, being unmarried, and lower socioeconomic status. Comorbidities, history of mental health problems, and perceived functioning limitations were also associated. Modifiable predictors of distress were lower physical activity, lower social support, and cigarette smoking.
SCHLEGELA RJ ET AL. PSYCHOL HEALTH. (2012)	Examine whether income, marital status, presence of children in the home, education, travel distance, age and rurality interact with time to predict psychological health over the first year post diagnosis. 225 breast cancer patients receiving radiation treatment completed four surveys over the course of 13 months that included measures of both their physical health and depressive symptoms. Depressive symptoms were measured using the Center for Epidemiologic Studies-Depression Scale	Women who were not married, had children living in the home or had to travel long distances to receive radiation treatment reported higher levels of depressive symptoms across the entire study. Women with lower incomes reported increased depressive symptoms, but only after the completion of treatment. Younger women reported elevated depressive symptoms during initial treatment, but this effect dissipated after the completion of treatment.
WÖCKEL A ET AL. QUAL LIFE RES. (2017)	Explore the changes in QoL from diagnosis to conclusion of adjuvant therapy and to identify	Global QoL improved between t1 and t3, while physical functioning, emotional functioning and fatigue deteriorated.

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
	predictive factors of QoL. Before surgery (t1), before onset of adjuvant treatment (t2) and after completion of adjuvant chemo-orradiotherapy (t3), patients with primary breast cancer (n = 759) completed the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, Charlson Comorbidity Index, Patient Health Questionnaire and Perceived Involvement in Care Scales.	QoL before surgery was more often poor in patients <60 years and in those with comorbid mental illnesses Forty-seven percentage reported good global QoL both at t1 and at t3. QoL improved in 28%, worsened in 10% and remained poor in 15%. Compared to patients with consistently good global QoL, a course of improving QoL was more often seen in patients who had received a mastectomy and in those with intense fear of treatment before surgery. A course of decreasing QoL was more often found in patients who were treated with chemotherapy. QoL stayed poor in patients with chemotherapy, mastectomy and intense fear. There was no evidence that radiotherapy, progressive disease or perceived involvement impact the course of QoL. Concluding, younger age and comorbid mental illnesses are associated with poor QoL pre-therapeutically. QoL is more likely to stay or become poor in patients who receive chemotherapy.
HO PJ ET AL. BMJ OPEN. (2018)	Review paper Summarize the evidence on determinants of health-related quality of life (HRQL) in Asian patients with breast cancer.	Patients with comorbidities, treated with chemotherapy, with less social support and with more unmet needs have poorer HRQL. HRQL improves over time. Discordant results in studies were found in the association of age, marital status, household income, type of surgery, radiotherapy and hormone therapy and unmet sexuality needs with poor global health status or overall well-being.
JUNG-WON LIM ETHNICITY & HEALTH (2016)	(1) Identify the occurrence of comorbidities among Chinese- and Korean-American breast cancer survivors (BCS), (2) examine whether health-related quality of life (HRQOL) scores varied with the occurrence of specific comorbidities, and (3) investigate the mediating effect of comorbidities on the relationship between life stress and HRQOL. Data were drawn from the parent study, a cross-sectional study investigating HRQOL in 86 Chinese- and 71 Korean-American BCS in Southern California.	HRQOL differences based on the occurrence of a specific comorbidity were evident for arthritis, eye/vision problems, dental and gum problems, lymphedema, and psychological difficulties. Structural equation modeling demonstrated that the nature of the outcome variable, either physical or mental HRQOL, influenced the overall patterns of the findings. For example, life stress was significantly associated with the total number of comorbidities and in turn influenced physical HRQOL. In terms of mental HRQOL, arthritis, dental and gum problems, chronic pain, heart disease, lymphedema, and psychological difficulties mediated
TANG Z ET AL. PLOS ONE. (2016)	Investigate the associations between diabetes and quality of life (QOL) among breast cancer survivors	Diabetes, both of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) significantly reduced QOL. This effect of diabetes on QOL is independent of tumour size, regional lymph node

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
	Cross-sectional survey was conducted at 34 Cancer Recovery Clubs across China from May 2014 to January 2015. Quality of life was measured by the Quality of Life Questionnaire- Core 30 (EORTC QLQ-C30) and the Quality of Life Questionnaire-Breast Cancer Module 23 (QLQ-BR23, simplified Chinese version). Information on social-demography, diagnosis and treatment of tumours, and diabetes mellitus were collected by self-reported questionnaires.	metastasis, distant metastasis and tumour stage index (TNM). After adjusting for different socialdemography, diagnosis and treatment of the tumour, the tumour's stage and other chronic comorbidities, breast cancer survivors with diabetes got significantly lower scores in functional dimensions (including physical, role, emotional and social functionings measured by EORTC QLQC30; body image (BRBI) and future perspective (BRFU) measured by QLQ-BR23, as well as economic difficulties than those without diabetes. Diabetic patients also obtained higher scores in symptom dimensions, including fatigue, nausea and vomiting, pain, dyspnoea, insomnia, constipation and diarrhoeameasured by EORTC QLQ-C30; side effects, breast symptoms and upset by hair lossmeasured by QLQ-BR23. Compared to patients with T1DM, those with T2DMare likely to suffer more by loss of functioning.
FU MR ET AL. J PERS MED. (2015)	Evaluate the association of comorbidities on breast cancer survivors' quality of life A prospective design was used to recruit 140 women before cancer surgery, 134 women completed the study. Comorbidities were assessed using self-report and verified by medical record review and the Charlson Comorbidity Index (CCI) before and 12-month after cancer surgery. Quality of life was evaluated using Short-Form Health Survey (SF-36 v2).	Numbers of comorbidities by patients' self-report and weighted categorization of comorbidities by CCI had a similar negative correlation with overall quality of life scores as well as domains of general health, physical functioning, bodily pain, and vitality. Comorbidities, specifically hypertension, arthritis, and diabetes, were associated with poorer quality of life in multiple domains among breast cancer survivors.

P3.1. References

Kristine A. Donovan, Alice R. Boyington, Roohi Ismail-Khan, Jean F. Wyman, Urinary Symptoms in Breast Cancer: A Systematic Review, Cancer. 2012 Feb 1; 118(3): 582–593. doi: 10.1002/cncr.26324

Matzka M, Mayer H, Köck-Hódi S, Moses- Passini C, Dubey C, Jahn P, et al. (2016) Relationship between Resilience, Psychological Distress and Physical Activity in Cancer Patients: A Cross-Sectional Observation Study. PLoS ONE 11 (4): e0154496. doi:10.1371/journal.pone.0154496

Gordana Ristevska-Dimitr0vska, Izabela Filov, Domnika Rajchanovska, Petar Stefanovski, Beti Dejanova , Resilience and Quality of Life in Breast Cancer Patients, Open Access Maced J Med Sci. 2015 Dec 15; 3(4):727-731. http://dx.doi.org/10.3889/oamjms.2015.128

Ania Syrowatka, Aude Motulsky, Siyana Kurteva, James A. Hanley, William G. Dixon, Ari N. Meguerditchian, Robyn Tamblyn, Predictors of distress in female breast cancer survivors: a systematic review, Breast Cancer Res Treat. 2017; 165(2): 229–245. doi: 10.1007/s10549-017-4290-9

Rebecca J. Schlegela, Mark A. Manningb, Lisa A. Molixc, Amelia E. Talleyb, and B. Ann Bettencourtb, Predictors of depressive symptoms among breast cancer patients during the first year post diagnosis, Psychol Health. 2012 ; 27(3): 277–293. doi:10.1080/08870446.2011.559232.

Wöckel A, Schwentner L, Krockenberger M, Kreienberg R, Janni W, Wischnewsky M, Thorsten K, Felix F, Riccardo F, Blettner M, Singer S., Predictors of the course of quality of life during therapy in women with primary breast cancer. Qual Life Res. 2017 Aug;26(8):2201-2208. doi: 10.1007/s11136-017-1570-0. Epub 2017 Apr 6.
Ho PJ, Gernaat SAM, Hartman M, Verkooijen HM. Health-related quality of life in Asian patients with breast cancer: a systematic review. BMJ Open. 2018 Apr 20;8(4):e020512. doi: 10.1136/bmjopen-2017-020512.

Jung-won Lim (2016): The impact of comorbidity on the relationship between life stress and health-related quality of life for Chinese- and Korean-American breast cancer survivors, Ethnicity & Health, DOI: 10.1080/13557858.2016.1246428
Tang Z, Wang J, Zhang H, Sun L, Tang F, Deng Q, et al. (2016) Associations between Diabetes and Quality of Life among Breast Cancer Survivors. PLoS ONE 11(6): e0157791. doi:10.1371/journal.pone.0157791

Fu MR, Axelod D, Guth AA, Cleland CM, Ryan CE, Weaver KR, Qiu JM, Kleinman R, Scagliola J, Palamar JJ, Melkus GD. Comorbidities and Quality of Life among Breast Cancer Survivors: A Prospective Study. J Pers Med. 2015 Jun 26;5(3):229-42. doi: 10.3390/jpm5030229.

TABLE P3.2. Clinical outcome

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
NAKAJIMA ET AL. ADVANCES IN RADIATION ONCOLOGY (2018)	Determine clinical outcomes and identify reliable prognostic factors in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy followed by mastectomy and postmastectomy radiotherapy. 5-year locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) rates were assessed.	Estrogen receptor positivity and ypN0 were significant prognostic factors for better LRFS, while lympho-vascular invasion and clinical stage IIIC were independent prognostic factors for worse LRFS. The number of axillary node metastases after surgery was an independent prognostic factor of DMFS and OS. Patients with hormone receptor and HER2 positivity had significantly better 5-year LRFS rates.
CANDIDO DOS REIS ET AL. BREAST CANCER RESEARCH (2017)	Refit the PREDICT prognostic model (online tool) using the original cohort of cases from East Anglia with updated survival time in order to take into account age at diagnosis and to smooth out the survival function for tumour size and node status.	• There is an increase in risk of breast cancer specific mortality in younger and older patients with ER positive disease, with a substantial increase in risk for women diagnosed before the age of 35. • In ER negative disease the risk increases slightly with age. • The association between breast cancer specific mortality and both tumour size and number of positive nodes was non-linear with a more marked increase in risk with increasing size and increasing number of nodes in ER positive disease.
PAREDES-ARACIL E ET AL. SCI REP. (2017)	• Develope a predictive model specific for breast cancer mortality at 5 and 10 years. • The study included 287 patients diagnosed with breast cancer in a Spanish region in 2003–2016.	• Prognostic factors included in the predictive model were age, personal history of BC, grade, TNM stage and multicentricity.
SARFATI ET AL. CA CANCER J CLIN (2016)	• Review paper • Cancer patients	• Comorbidity has consistently been found to have an adverse impact on cancer survival. The magnitude of the association is variable, depending on how comorbidity is measured, the measure of survival used, the cancer studied, and the population included. • The impact of comorbidity tends to increase with increasing severity of comorbidity, although not necessarily in a linear fashion. • The (relative) impact of comorbidity tends to be greater for cancers with a better prognosis. This is because those who have cancer associated with a high mortality rate will be more likely to die from their cancer regardless of other concomitant disease compared with patients who have a less severe prognosis.
KIDERLEN ET AL. ANN ONCOL. (2013)	The aim of this study was to assess the impact of diabetes on relapse-free period (RFP) and overall mortality in elderly breast cancer patients. Overall, 3124 patients with non-metastasized breast cancer were included.	RFP was better for patients with diabetes compared with patients without diabetes, irrespective of other comorbidity and most evident in patients aged ≥75 years. The overall survival was similar for patients with diabetes only compared with patients without comorbidity, while patients with diabetes and additional comorbidity had the worst overall survival.

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
		When taking competing mortality into account, RFP was better in elderly breast cancer patients with diabetes compared with patients without diabetes. Moreover, patients with diabetes without other comorbidity had a similar overall survival as patients without any comorbidity. Possibly, unfavourable effects of (complications of) diabetes on overall survival are counterbalanced by beneficial effects of metformin on the occurrence of breast cancer recurrences.
W SUN ET AL. ONCOTARGET (2016)	Develop nomograms for long-term survival (5-year, 10-year) of luminal breast cancer Patients with luminal breast cancer from the Surveillance, Epidemiology, and End Results (SEER) database (n= 176,082). Stage I-III	Patients younger than 40 years at diagnosis had the highest cumulative incidences of death resulting from breast cancer (CIDBC), while patients between 50 and 59 years old at diagnosis had the lowest CIDBC than other ages. Black patients had the highest CIDBC, while white and "other" patients had similar lower CIDBC. There was no significant difference between different lateralities. Patients with infiltrating lobular carcinoma, histologic grade I, negative lymph node or positive ER/PR status had lower CIDBC, and patients with infiltrating ductal carcinoma, histologic grade III, more than 3 positive lymph nodes or negative ER/PR status had higher CIDBC. Receiving radiation decreased CIDBC.
A ABADI ET AL. IRAN J CANCER PREV (2014)	Evaluate the association between different treatments and survival time of breast cancer patients 15830 women diagnosed with breast cancer in British Columbia, Canada.	For patients under age 50 years old and over age 50 with stage I cancer, the highest hazard was related to radiotherapy and chemotherapy respectively. For both groups of patients with stage II cancer, the highest risk was related to radiotherapy. For both groups of patients with stage III cancer, the highest risk was for surgery. For patients of age 50 years or less with stage IV cancer, none of the treatments were statistically significant. In group of patients over age 50 years old with stage IV cancer, the highest hazard was related to surgery.
FISHER ET AL. ANN ONCOL. (2015)	Assess the all-cause and breast cancer-specific survival rates of non metastatic breast cancer patients surgically treated with mastectomy, BCS alone and BCS plus radiotherapy among surgically treated breast cancer patients diagnosed in Alberta, Canada. 14 633 patients were included in this study.	Stage II and III patients who received mastectomy had a higher all-cause and breast cancer-specific mortality hazard compared with those who received BCS plus radiotherapy, adjusting for patient and clinical characteristics. BCS alone was consistently associated with poor survival.
BRENNER ET AL. CANCER CAUSES	Review paper Propose a model identifying three main areas of lifestyle factors (energy imbalance, inflammation, and	Increased risks for overall mortality and breast cancer-specific mortality associated with increasing body mass index or waist–hip ratio. Larger effect sizes for breast cancer mortality are

REFERENCE	AIM OF THE STUDY/METHODOLOGY	ASSOCIATIONS IDENTIFIED
CONTROL. 2016	dietary nutrient adequacy) that may influence survival in BCYW.	associated with obesity among pre-menopausal compared to postmenopausal women. One of the biologic mechanisms through which obesity could affect cancer survival is by altering the insulin resistance (IR) pathway. • Physical activity has been consistently associated with improved survival and other breast cancer-specific outcomes in breast cancer patients. The risk of breast cancer specific mortality for young active women (aged 20–54, ≥5 h of recreational activity per week) was reduced compared to young inactive women. This estimate was adjusted for cancer stage and BMI, but not for treatment. • High levels of alcohol consumption may be associated with increased risk of breast cancer recurrence. • Sleep disturbance and insomnia may impact both quality of life and survival outcomes after a breast cancer diagnosis. Sleep affects many of the inflammatory factors that are implicated in our proposed biologic model such as cytokine production, adipokine production, and immune responses. • There is some evidence to suggest that high post diagnostic fruit, vegetable, whole grain, and protein intake decrease the risk of mortality following breast cancer, while high animal fat intake increases the risk. • The role of specific dietary components, including vitamins, fatty acids, and alcohol consumption, or overall dietary patterns, have also been evaluated, but findings are inconclusive. • Dietary fat intake has been extensively researched in relation to breast cancer risk, but the evidence remains inconclusive. Dietary fat intake might influence risk of breast cancer through the promotion of oxidative stress, hormonal dysregulation, or inflammatory signaling. These same mechanisms are implicated in breast cancer progression and recurrence. Dietary intake of folate, phytoestrogens and vitamin D may influence recurrence and survival.

P3.2. References

Naomi Nakajima, Masahiko Oguchi, Yasuko Kumai, Masahiro Yoshida, Hirotaka Inoda, Takuji Iwase, Yoshinori Ito, Futoshi Akiyama, Shinji Ohno, Teruhito Mochizuki, Clinical outcomes and prognostic factors in patients with stage II-III breast cancer treated with neoadjuvant chemotherapy followed by surgery and postmastectomy radiotherapy in the modern treatment era, Advances in Radiation Oncology (2018), https://doi.org/10.1016/j.adro.2018.04.006.

Candido dos Reis et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation Breast Cancer Research (2017) 19:58 DOI 10.1186/s13058-017-0852-3

Paredes-Aracil E, Palazón-Bru A, Folgado-de la Rosa DM, Ots-Gutiérrez JR, Compañ-Rosique AF, Gil-Guillén VF. A scoring system to predict breast cancer mortality at 5 and 10 years, Sci Rep. 2017 Mar 24;7(1):415. doi: 10.1038/s41598-017-00536-7

Kiderlen M, de Glas NA, Bastiaannet E, et al. Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis. Ann Oncol. 2013;24:3011-3016.

Diana Sarfati, MBChB, Bogda Koczwara, BMBS, MBioethics; Christopher Jackson, MBChB, The Impact of Comorbidity on Cancer and Its Treatment, CA CANCER J CLIN 2016;66:337–350
Abadi A, Yavari P, Dehghani-Arani M, Alavi-Majd H, Ghasemi E, Amanpour F, Bajdik C., Cox models survival analysis based on breast cancer treatments. Iran J Cancer Prev. 2014 Summer;7(3):124-9.

Fisher S, Gao H, Yasui Y, Dabbs K, Winget M. Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system. Ann Oncol. 2015 Jun;26(6):1161-9. doi: 10.1093/annonc/mdv107. Epub 2015 Feb 23.

Sun W, Jiang YZ, Liu YR, Ma D, Shao ZM., Nomograms to estimate long-term overall survival and breast cancer-specific survival of patients with luminal breast cancer. Oncotarget. 2016 Apr 12;7(15):20496-506. doi: 10.18632/oncotarget.7975.

Brenner DR, Brockton NT, Kotsopoulos J, Cotterchio M, Boucher BA, Courneya KS, Knight JA7, Olivotto IA, Quan ML, Friedenreich CM, Breast cancer survival among young women: a review of the role of modifiable lifestyle factors., Cancer Causes Control. 2016 Apr;27(4):459-72. doi: 10.1007/s10552-016-0726-5. Epub 2016 Mar 12.

P. APPENDIX 4 ABBREVIATIONS

CHAMP	Fundação D. Anna de Sommer Champalimaud e Dr. Carlos Montez Champalimaud (Champalimaud Clinical Center - CCC)
DFS	Disease Free Survival
FORTH	Foundation for Research and Technology – Hellas
GCP	Good Clinical Practice
HUJ	Hebrew University school of Social Work and Social Welfare
HUS	Helsinki University Hospital Comprehensive Cancer Center
ICCS	Institute of Communication and Computer Systems
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEO	European Institute of Oncology
NHG	NHG Consulting
NOONA	Noona Healthcare
OS	Overall Survival
QoL	Quality of Life
SiLo	SINGULARLOGIC ANONYMI ETAIREIA PLIROFORIAKON SYSTIMATON KAI EFARMOGON PLIROFORIKIS
WHO	World Health Organization