The Influence of Lifestyle Factors on the Long-Term Health-Related Quality of Life in Breast Cancer Survivors and in Comparison to a Control Cohort

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Abstract

Background: In 2020, breast cancer (BC) was the most diagnosed cancer globally as well as in Germany. Due to the demographic ageing and the improvement of cancer therapy, an increase in long-term breast cancer survivors (BCS) was observed. 90% of the BCSs reported late and long-term sequelae caused by the disease and its treatment, which reduced their health-related quality of life (HRQoL). However, adjustable factors, such as lifestyle factors (LSF), on the long-term HRQoL were not conclusively studied yet, and often these were not compared to a control group. Findings on this topic could help to develop interventions to support and improve the quality of life (QoL) of long-term BCSs.

Aim: This thesis aimed to investigate which LSF determine the HRQoL in long-term BCSs at approximately 5 and ≥10 years post-diagnosis, and to compare them to cancer-free controls 10 years post-recruitment.

Methods: This thesis included women who participated in the MARIE study, a German population-based cohort study composed of 3813 breast cancer women aged 50-74 years at diagnosis (2002-2005), and 7341 age-matched breast cancer-free women. Information on social-economic status, lifestyle factors, and medical history and conditions were collected at baseline (BL) in a face-to-face interview. HRQoL was estimated with the EORTC QLQ-C30 questionnaire. To analyse the influence of the LSFs, such as physical activity, smoking behaviour, and alcohol consumption, two linear regression models were created. Model 1 was a generalized linear mixed model with an interaction between time-point assessment and LSFs using the participant number as a random effect variable. This model investigated the influence of the LSFs on the long-term HRQoL of cases at 5 and ≥10 yeas post-diagnosis to check whether LSFs had a different effect on the HRQoL at different time-point. Model 2 was a linear regression with an interaction between case-control status and LSFs, which was used to investigate LSFs as determinants of HRQoL of cases to controls ≥10 years post-recruitment. This model was used to look at whether the LSFs had a different influence on the HRQoL of the cases from the controls.

Results: LFSs influenced differently the HRQoL of cases at FU1 and FU2, and controls at FU2. Transport PA (walking and cycling) influenced the most subscale of the QoL of cases, although it lost significance at FU2, while alcohol consumption had the least impact on the HRQoL. At FU2, all LSFs influenced similarly many subscales of QoL of cases and controls. Just LSFs related to smoking behaviour influenced differently the HRQoL and had an influence just in the control group.

Conclusion: LSFs determined the HRQoL of cases at FU1 but lost importance at FU2. Just smoking behaviour influenced differently some subscale of the HRQoL of cases and controls at FU2, but in general, LSFs still determined the HRQoL. Researchers and clinicians should be aware of these determinants of QoL in order to develop interventions to support the needs of long-term BCSs.

Table of Content

ABSTRACT I

TABLE OF CONTENT III

LIST OF FIGURES IV

LIST OF TABLES V

ABBREVIATION VII

1. INTRODUCTION 1

2. BACKGROUND 2

2.1 Breast Cancer Epidemiology 2

2.2 Quality of Life 2

2.3 Lifestyle Factors 3

3. RESEARCH QUESTION 5

4. METHODS 5

4.1 Data Source and Study Population 5

4.2 Health Related Quality of Life Measurement 9

4.3 Lifestyle Factors 10

4.4 Confounders 11

4.5 Statistical Analysis 12

5. RESULTS 13

5.1 Descriptive and Frequencies 13

5.2 Model 1 - Generalized Linear Mixed Model with Random Effect 17

5.3 Model 2 - Linear Regression with Interaction 27

6. DISCUSSION 34

6.1 Methodology Discussion 34

6.2 Discussion of the Results 35

6.3 Strength and Limitations 37

7. CONCLUSION 38

REFERENCES 39

APPENDIX: TIMELINE OF THE MARIE STUDY 44

ACKNOWLEDGEMENT 45

List of Figures

Fig. 1: Flowchart for the exclusion criteria for the cases from BL to FU1, from BL to FU2, and the complete participants. 8
Fig. 2: Flowchart for the exclusion criteria for the controls from BL to FU2. 9
Fig. 3: Interaction between time-point and transport PA for Global Health Status. 18
Fig. 4: Interaction between time-point and smoking status for Cognitive Functioning. 19
Fig. 5: Interaction between time-point and transport PA for Cognitive Functioning. 20
Fig. 6: Interaction between time-point and transport PA for Emotional Functioning. 21
Fig. 7: Interaction between time-point and transport PA for Physical Functioning. 22
Fig. 8: Interaction between time-point and transport PA for Role Functioning. 23
Fig. 9: Interaction between time-point and smoking status for Social Functioning. 25
Fig. 10: Interaction between time-point and current sport status for Social Functioning. .. 26
Fig. 11: Interaction between time-point and transport PA for Social Functioning. 27
Fig. 12: Interaction between case-control status and smoking status for Emotional Functioning. 29
Fig. 13: Interaction between case-control status and smoking status for Physical Functioning. 31
Fig. 14: Interaction between case-control status and smoking status for Role Functioning. 33

List of Tables

Tab. 1: Descriptive of the population characteristics and lifestyle factors of cases at FU1 and FU2, and controls at FU2. 14
Tab. 2: Mean of the quality of life, and functional scales for cases at FU1 and FU2, and controls at FU2. 16
Tab. 3: Association between packs of cigarettes per year and Global Health Status. 17
Tab. 4: Interaction between time-point and transport PA for Global Health Status. 17
Tab. 5: Interaction between time-point and smoking status for Cognitive Functioning. 18
Tab. 6: Interaction between time-point and transport PA for Cognitive Functioning. 19
Tab. 7: Interaction between time-point and transport PA for Emotional Functioning. 20
Tab. 8: Association between LSFs (packs of cigarettes per year and current sport status) and Physical Functioning. 21
Tab. 9: Interaction between time-point and transport PA for Physical Functioning..... 22
Tab. 10: Interaction between time-point and transport PA for Role Functioning..... 23
Tab. 11: Association between alcohol consumption and Social Functioning. 24
Tab. 12: Interaction between time-point and smoking status for Social Functioning..... 24
Tab. 13: Interaction between time-point and current sport for Social Functioning. 25
Tab. 14: Interaction between time-point and transport PA for Social Functioning. 26
Tab. 15: Association between alcohol consumption and Global Health Status. 28
Tab. 16: Association between LSFs (current sport status and transport PA) and Cognitive Functioning. 28
Tab. 17: Association between packs of cigarettes per year and Emotional Functioning. 28
Tab. 18: Interaction between case-control status and smoking status for Emotional Functioning. 29
Tab. 19: Association between LSFs (alcohol consumption, current sport status, and transport PA) and Physical Functioning. 30
Tab. 20: Interaction between case-control status and packs of cigarettes per year for Physical Functioning. 30
Tab. 21: Interaction between case-control status and smoking status for Physical Functioning. 31
Tab. 22: Association between LSFs (alcohol consumption, current sport status, and transport PA) and Role Functioning. 32

Tab. 23: Interaction between case-control status and packs of cigarettes per year for Role Functioning. 32
Tab. 24: Interaction between case-control status and smoking status for Role Functioning. 33
Tab. 25: Association between LSFs (alcohol consumption and transport PA) and Social Functioning. 34

Abbreviation

ACS	American Cancer Society
AIRC	American Institute for Cancer Research
BC	Breast Cancer
BCP	Breast Cancer Patient
BCS	Breast Cancer Survivor
BL	Baseline
BMI	Body Mass Index
BZgA	Bundeszentrale für Gesundheitliche Aufklärung (in **English**: Federal Centre for Health Education)
CCI	Charlson Comorbidity Index
CI	Confidential Interval
EORTC	European Organization for Research and Treatment of Cancer
FU1	Follow-Up 1
FU2	Follow-Up 2
HRQoL	Health-Related Quality of Life
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
LSF	Lifestyle Factor
MARIE	Mammakarzinom-Risikofaktoren-Erhebung (in **English**: Mammary Carcinoma Risk Factor Investigation)
MET	Metabolic Equivalent of Task
PA	Physical Activity
QLQ-C30	Quality of Life Questionnaire Core-30
QoL	Quality of Life
RKI	Robert Koch Institute
SAS	Statistical Analysis System
WCRF	World Cancer Research Fund
WHO	World Health Organisation

1. Introduction

According to the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), breast cancer (BC) was the most diagnosed cancer globally as well as in Germany with respectively 2.3 million and 69 697 new diagnosed cases in 2020 [1], meaning that 1 in 8 women was expected to develop BC in the course of a lifetime [2].

Due to demographic ageing, an increase in the number of BC diagnoses is expected [3]. Furthermore, the progressive improvement of BC therapy led to a decrease in mortality rates [4], leading to an increase in life expectancy and a growing number of long-term cancer survivors. However, 90% of breast cancer survivors (BCS) reported late and long-term sequelae that can impact the physical, psychosocial, emotional health, and well-being, and reduce patient's health-related quality of life (HRQoL) [5], which after 10 years post-diagnosis, was still not comparable to the HRQoL of a BC-free population [6].

Some known long-term side effects of BC surgery and external radiation therapy are lymphedema, axillary web syndrome, rotator cuff syndrome, and fatigue. Chemotherapy instead, often caused nausea and vomiting, hair loss, fatigue as short-term side effects, while in long-term could cause memory problems, peripheral neuropathy, heart problems, sleep disorders, as well as fatigue [5,7]. However, adjustable factors, such as lifestyle factors (LSFs), on the long-term HRQoL were not conclusively studied yet. For this reason, research in finding factors that determine the HRQoL became of significant concern.

Previous studies showed that a 12-months lifestyle modification, such as having a healthier diet, practising physical activity (PA), and not smoking, could improve the HRQoL in BCSs [8,9]. Many studies investigated the effect of PA on the HRQoL of breast cancer patients (BCP) [10–12], but just few studies investigated the effect of alcohol consumption [13,14] and smoking behaviour [9,15–17]. However, to the author knowledge, no other study investigated LSFs as determinants of HRQoL of cases to a control group at ≥10 years post-diagnosis.

In this thesis, effects of different LSFs such as PA, alcohol consumption, and smoking behaviour on HRQoL of long-term (5 years post-diagnosis) and very long-term (≥10 years post-diagnosis) were investigated. Furthermore, the association of LSFs on HRQoL in BCPs were compared to that of age-matched controls similarly followed up for ≥10 years.

2. Background

2.1 Breast Cancer Epidemiology

Cancer is the second leading cause of death globally and in Germany, in fact, it is responsible for about 10 million deaths annually, meaning that about 1 in 6 deaths is due to cancer [2,18]. According to the statistics released by the International Agency for Research on Cancer (IARC) in December 2020, BC is now the world's most diagnosed cancer, with 2.3 million new cases including both genders of all ages (11.7% of all cancer diagnoses), followed by the 2.2 new lung cancer cases (11.4% of all cancer diagnosis), and 1.9 new colorectum cancer cases (10.0% of all cases diagnosis) [1]. A similar percentage was observed in Germany with 69 697 new reported cases (11.1% of all cancer diagnoses in both sexes and 24.5% of all cancer diagnoses in females) [1].

With the demographic ageing of the population, an increase in BC incidence rate is expected, and often, this disease was not fatal and the survival rates among this population were growing due to improvements in treatment and care [2,3].

2.2 Quality of Life

Quality of Life (QoL) is a growing important health goal, and it is based on both subjectivity and multidimensionality. It can refer to the perception of an individual on their position in life and living conditions in a broad-ranging concept, which includes physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment [19–21]. HRQoL, instead, includes just the aspects which are part of the physical and mental health of an individual [22,23].

The increasing recognition of the importance of the impact of healthcare interventions on the lives of patients led to a fast development of measures for QoL and HRQoL, which are important targets of healthcare programs and interventions for patients with chronic, disabling, or life-threatening diseases who have conditions that are likely to have an impact on their physical, psychological, and social wellbeing [24,25]. As measurements of QoL and HRQoL are patient-centred, they could be used to develop personalized therapeutic approaches and therapeutic strategies that are tailored to the patient's needs [25].

As 90% of BCSs reported side effects related to their treatment, different studies focused on the measurements and analysis of their QoL in the short- and long-term. Previous studies compared the HRQoL of BCPs (cases) and women without cancer (controls) from diagnosis

to 10 years post-diagnosis [6,26] and from diagnosis to 15 years post-diagnosis [27]. At diagnosis and 1-year post-diagnosis, BCPs reported a significant lower HRQoL compared to controls. Although by 2 years there were no longer significant differences between the two groups, many subgroups of BCPs continued to have a lower HRQoL [26]. Even after 10 years post-diagnosis, the HRQoL of cases couldn't be completely compared to that of controls [6], but 15 years from diagnosis the QoL of BCSs was no longer different from that of controls [27].

It was clear that BCSs reported a significant lower HRQoL compared to controls right after the diagnosis and treatment, nevertheless, this could improve with time, but this was rarely investigated.

2.3 Lifestyle Factors

Studies showed that LSFs, such as PA, diet, and smoking behaviour, affected the HRQoL, as a healthy lifestyle was associated with better QoL [8,9]. A study found that a 12-months lifestyle modification in diet, physical activity, and vitamin D intake improved global health status, physical, role, and social functioning, and reduced fatigue, nausea and vomiting, dyspnoea, constipation, and financial problems [8]. Similar results were found in another study where cancer survivors following lifestyle behaviour recommendations from the American Cancer Society (ACS), such as sufficient PA (150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity activity each week), eat at least 5 servings of fruits and vegetables a day, and not smoking cigarettes had a better HRQoL. The association between the adherence to the ACS recommendation and HRQoL were cumulative, meaning that cancer survivors meeting more lifestyle recommendation reported a higher QoL [9]. But nothing is known about LSFs as determinants of HRQoL in long-term BCSs.

2.3.1. Physical Activity

PA was an important LSF determinant of the HRQoL. Organisations such as the ACS and the WHO recommend adults and people with chronic diseases, such as cancer, to practice at least 150 minutes of moderate PA per week [28,29]. Many investigated the effect of both short and long PA intervention as well as different types of exercise on the HRQoL of BCS. A study showed that a 4-weeks intervention of stretching, aerobic, and strengthening exercises improved the global health status, physical functioning, role functioning, emotional functioning, fatigue, pain, nausea and dyspnoea of BCPs [10]. While a study

investigating the effect of a 12-months PA intervention on the QoL 5 years from BL observed that BCSs who improved their PA behaviour in this time period, also reported better global health status, physical, social, role functioning, and fatigue [11]. Another study investigated how different PA interventions such as water exercise interventions, pilates, and yoga could also influence differently the HRQoL. After 1 year, they observed a significant increase in QoL in participants of all groups [12], meaning that any kind of PA could improve the QoL. Nevertheless, little is known about the effect of PA on the long-term HRQoL of BCPs compared to a control group.

2.3.2. Alcohol Consumption

According to the ACS Guideline and the recommendation from the Federal Centre for Health Education (BZgA), alcohol consumption should be avoided or should be limited to a maximum of 1 drink (12g of alcohol) per day for women [28,30]. Although the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AIRC) advised to avoid drinking alcohol as there was no threshold for the level of consumption below which there wasn't an increase in the risk of developing cancer [31]. The effect of alcohol consumption on the HRQoL of BCPs has been seldom investigated. One study investigated the relationship between sleep disturbance, symptoms, and alcohol use in BCPs and couldn't find an association between alcohol consumption and symptoms severity [13]. In another recent study was observed strong evidence between alcohol intake and role limitation due to emotional problems, but weak evidence for an effect of role limitation due to physical health [14]. Nevertheless, to the author's knowledge, the effect of alcohol consumption on the HRQoL of long-term BCSs is still unknown and this hasn't been compared to controls.

2.3.3. Smoking Behaviour

Few studies investigated the association between smoking behaviour and QoL in BCPs. Studies found out that cancer survivors, including BCPs, who are currently smoking, had a poorer physical functioning, mental health, and role emotional compared to non-smokers, while former smokers reported poorer physical functioning, mental health, and general health compared to non-smokers [9,15]. The smoking status was assessed at BL and in a follow-up 15 years after [15]. Another study with an average follow-up of 2.2 years investigated the side effects of tamoxifen by smoking status and discovered that compared to never smokers, a significantly greater percentage of current smokers reported nausea,

depression and migraines [17]. Furthermore, a study investigated the association of smoking abstinence and QoL over time (follow-ups at 2, 6, and 12 months after BL), including depression, pain, and fatigue in cancer patients, such as gynaecologic, breast, thoracic, head and neck, and genitourinary cancer patients. This study found out that more days of abstinent was associated with lower depression at all follow-ups, lower fatigue at 12 months, and better QoL in general. Although pain decreased over time, this side effect was not associated with the smoking abstinence length [16]. This LSF was rarely investigated in the QoL of just BCPs and it is still unclear whether the behaviour determines differently the HRQoL over time and compared to a control group.

3. Research Question

This thesis aimed to investigate the effects of lifestyle factors, such as alcohol consumption, smoking behaviour, and physical activity on HRQoL in long-term breast cancer survivors at approximately 5 and ≥10 years post-diagnosis, and in comparison to women without a breast cancer diagnosis ≥10 years after recruitment. The following main research questions were examined:

- Do lifestyle factors differently influence the HRQoL of patients with breast cancer at 5 and ≥10 years after diagnosis?
- Do lifestyle factors differently influence the HRQoL of patients with breast cancer compared to women without breast cancer ≥10 years after diagnosis/recruitment?

4. Methods

4.1 Data Source and Study Population

This thesis included women who participated in the MARIE study. The MARIE study, an acronym of the German words **Ma**mmakarzinom-**Ri**sikofaktoren-**E**rhebung (in English: Mammary Carcinoma Risk Factor Investigation), was initially a population-based case-control study [32], which later became a longitudinal cohort study with follow-ups of the participants about every 5 years.

The MARIE study (BL) was carried out in the two German regions of Hamburg and Rhine-Neckar-Karlsruhe between August 2002 and September 2005, which included menopausal women aged 50-74 years. The patients (cases) had a histologically confirmed first primary invasive (stage I to IV, ICD-10: C50) or *in situ* (stage 0, ICD-10: D05) breast cancer,

diagnosed between January 1st, 2001 and July 31st, 2005 [32]. Participants without breast cancer diagnosis (controls) were randomly drawn from the population registries and were matched to the cases based on the birth year and study regions, with a ratio of two controls-to-one case.

During the face-to-face interview, information on socioeconomic status, lifestyle factors, medical history and conditions, and use and duration of specific medication were collected. Pathology reports were used to draw information on the histological characteristics of the primary breast cancer, while medical records were used to draw information about the treatment and clinical course to establish clinical events. At recruitment, 3813 cases and 7341 controls completed the standardized interview.

In 2009 and 2014, the cases were re-contacted to participate in the first and second follow-up (FU1 and FU2), while the controls were re-contacted in 2011/2012 and 2016. During both follow-ups, the cases' self-reported HRQoL status was assessed using the EORTC QLQ-C30 questionnaire from the European Organization for Research and Treatment of Cancer (EORTC) through telephone interviews and questionnaires sent by post. At BL, the HRQoL data was not collected, therefore the HRQoL pre-diagnosis, during treatment phases, and 1-year post-surgery data were asked to the cases at FU1. The information on HRQoL of controls was collected just at FU2.

The end of the follow-up was determined by the decease, emigration, or last contact. At FU1, 510 (13.4%) cases were deceased, and 3 (0.1%) emigrated. By FU2, 902 (23.7%) of the cases were deceased, 11 (0.3%) were lost to follow-up, and 5 (0.1%) emigrated in total, while by FU2, 817 (11.1%) controls deceased, 89 (1.1%) were lost in follow-up, and 21 (0.3%) emigrated.

Between BL and FU1, and between BL and FU2, cases alive until that time-point were excluded if they were diagnosed with another malignant tumour before breast cancer diagnosis (n=189; n=155), had a cancer stage IIIb or higher (n=214; n=153), or developed metastases (n=136; 102), had a recurrence (n= 64; n= 41), or secondary tumour (n=83; n= 104). Controls were excluded if they were diagnosed with any cancer before recruitment (n= 303), developed breast cancer during follow-up (n=218), or had a missing breast cancer diagnosis status (n= 3346).

Furthermore, the global health status was missing for 829 cases at FU1, 979 cases at FU2, and 51 controls at FU2. The lifestyle factors were missing for 43 cases at FU1, 201 cases at

FU2, and 354 controls at FU2. 16 cases at FU1, 17 cases at FU2, and 19 controls at FU2 also had missing comorbidity.

The final study population was composed of 1726 cases at FU1 and 1143 cases at FU2. 951 patients were present in both FU1 and FU2. The final study population of controls was composed of 2123 participants at FU2.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of the University of Heidelberg and the University of Hamburg. All subjects gave written informed consent before participation in the study.

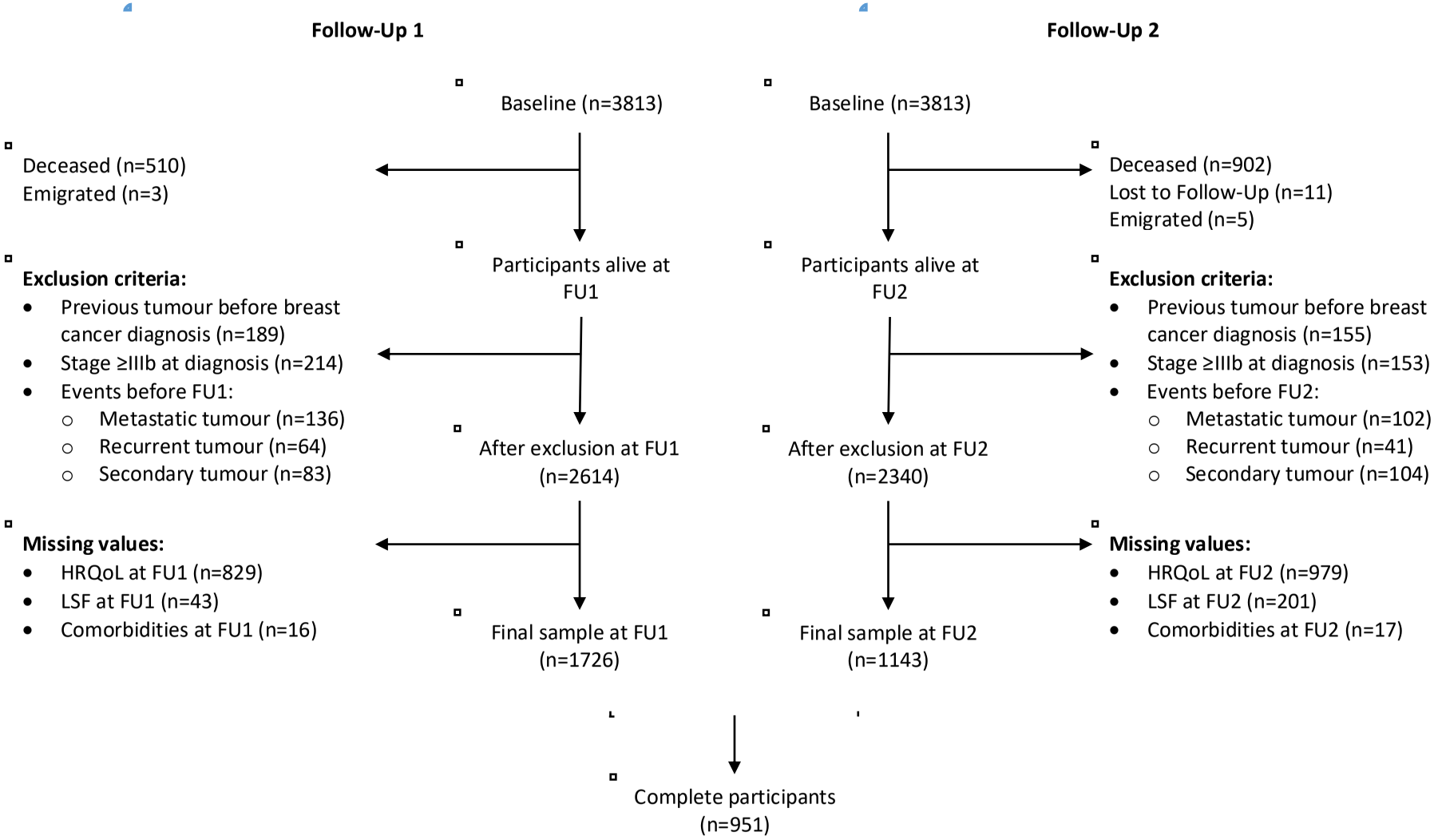


Fig. 1: Flowchart for the exclusion criteria for the cases from BL to FU1, from BL to FU2, and the complete participants.

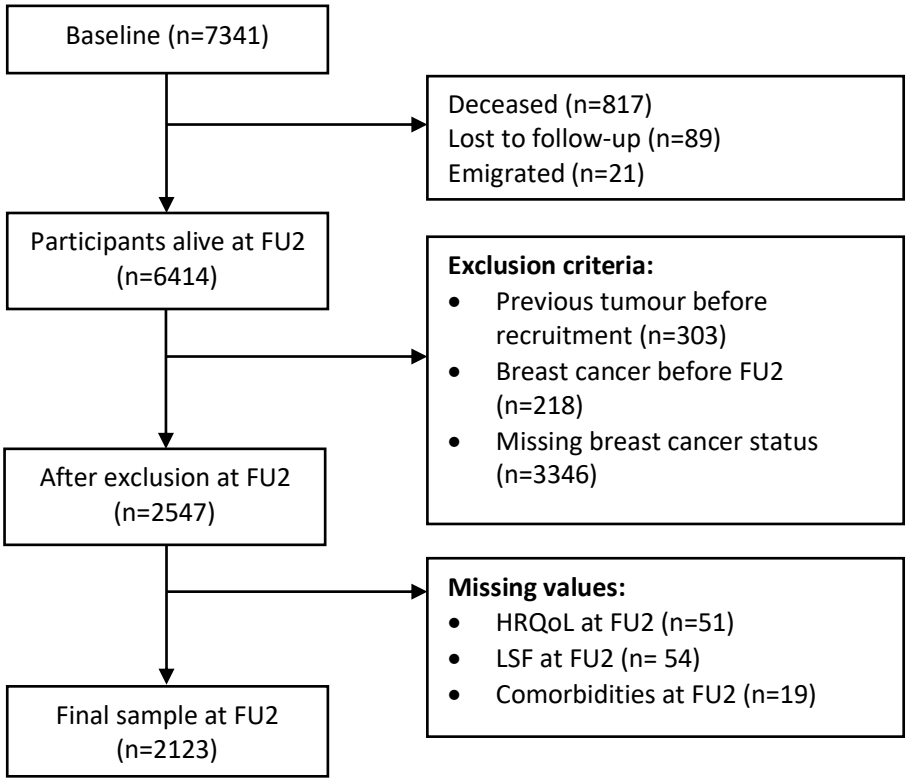


Fig. 2: Flowchart for the exclusion criteria for the controls from BL to FU2.

4.2 Health Related Quality of Life Measurement

The EORTC QLQ-C30 – version 3.0 questionnaire was used to assess the health-related quality of life of patients with breast cancer. This is a validated cancer-specific questionnaire that reflects the multidimensionality of QoL, and is appropriate for self-administration, which was tested in a cross-cultural setting [33]. The EORTC QLQ-C30 is composed of a total of 30 items, including 5 multi-items for functional scales, which assess the physical, role, emotional, cognitive, and social functions, 3 multi-items for symptom scales to assess fatigue, nausea and vomiting, and pain, 6 single-items to assess dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties, and 2 items which assess the global health status / HRQoL [33]. In conformity with the EORTC QLQ-C30 Scoring Manual 3rd Edition, all scales and single-item measures were transformed linearly in order to standardise the raw scores with a range score from 0 to 100, thus a higher score for a functional scale and global health status / HRQoL represents a better and higher level of functioning and general health and quality of life. Conversely, a higher score for a symptom scale represents

a higher level of symptoms [34]. In this thesis, just the global health status and functioning scales were analysed.

4.3 Lifestyle Factors

Physical Activity. Information about recreational and transport physical activity (PA) was collected at BL, FU1, and FU2. At BL, participants were asked to provide information for when they were aged 30-49 years and ≥50 years, while for the follow-ups, PA was assessed for the year before the interview.

Participants were asked if they were currently practising any kind of sport and to list 3 (at BL) and 4 (at FU1 and FU2) recreational physical activities. A regular PA participation was considered "currently practising sports", while a lack of participation was classified as "not practising sports".

Furthermore, the participants were asked how many hours per week they usually spent walking and cycling. Cycling hours in winter and summer were asked separately. For the analysis, the mean cycling hours per week were calculated as the average of the cycling hours in winter and summer, when both were present. When cycling hours in summer was missing, but hours in winter was present, then it was presumed that the hours in summer was equal to the hours in winter, as it was assumed that nobody would only cycle in winter. If cycling hours in winter were missing, but the hours in summer existed, then the winter hours were counted as 0. The transport PA was calculated as the sum of walking and cycling per week, which later is dichotomised with a cut point at 2.5 h/week, based on the recommendation from the ACS and WHO of practising at least 150 minutes of moderate PA per week [28,29].

Alcohol Consumption. Data about alcohol consumption was collected at BL, FU1, and FU2. During the BL interviews, participants provided information about the daily, weekly, or monthly intake of different alcoholic beverages, such as beer, wine, and spirits in littles or centilitres for when they were aged 30-49 years, 50-59 years and ≥60 years, while for the follow-ups, alcohol consumption was assessed for the year previous to the interview.

The average alcohol consumption was calculated in grams per day, and the alcohol intake was categorized as 0g-0.5g, 0.5g-6g, 6g-12g, and ≥12g. This was based on the recommendation from the BZgA of a limit consumption of 12g per day for women [30].

Smoking Behaviour. The smoking status at BL and both follow-ups were assessed during in-person and telephone interviews, respectively. Participants were classified as "current smoker" if they were smoking within the year before the interview, "ex-smoker" if they had stopped smoking at least 1 year before the interview, or as "never smoker" if they had never smoked.

Furthermore, the number of packs of cigarettes smoked per year was calculated for 3 time periods: from the beginning of the smoking phase until diagnosis, from diagnosis until FU1, and from FU1 until FU2.

4.4 Confounders

Different confounders were considered such as age group, Body Mass Index (BMI), autonomy in occupation, and the Charlson Comorbidity Index (CCI). These variables were used to adjust the models for the statistical analysis in order to address potential confounding.

Age Group. The study population was divided into three groups based on the age at diagnosis for cases and age at recruitment for controls: ≤58 years, 59-63 years, and ≥64 years.

Occupation Autonomy. During the initial interview at BL, the autonomy in occupation, information about the occupation title, leadership responsibility, and occupational description was asked. Then these were categorised into three groups: low, medium, and high.

Body Mass Index (BMI). At BL and both follow-ups, the weight and the height of the participants were asked, and the BMI was calculated. The participants were classified as underweight if the BMI was < 22.5, normal if the BMI was between 22.5-25, overweight if it was between 25-30, and obese if the BMI was ≥ 30. The underweight and normal weight categories were different from the one suggested by the WHO, in which underweight was considered a BMI below 18.5, and normal weight was a BMI between 18.5-24.9 [35]. This decision was taken based on the fact that none of the participants reported a BMI below 18.5.

Charlson Comorbidity Index (CCI). The CCI was developed in 1987 by Mary Charlson and it was used as a weighted index to predict the mortality risk of a patient with a chronic disease within a year of hospitalisation. Each comorbidity was weighted from 1 to 6 and they were summed to have a CCI score [36].

During each interview, the participants were asked which diseases their doctors diagnosed them with. In the MARIE study, the CCI included the following comorbidities and scores: heart attack (1 point), heart failure (1 point), peripheral arterial disease (1 point), cerebrovascular diseases (1 point), dementia (1 point), chronic lung disease (1 point), collagenosis (1 point), peptic ulcer disease (1 point), mild liver disease (1 point), moderately severe and severe liver disease (3 points), diabetes without (1 point) / with (2 points) end-organ damage, hemiplegia (2 points), moderately severe and severe kidney disease (2 points), AIDS (6 points), tumour without metastases (2 points), leukaemia (2 points), lymphoma (2 points), and metastatic solid tumour (6 points).

Time-Point. As participants were followed through the entire study period, the time-point variable was created to recognise if the information was from the FU1 (time-point=1) or FU2 (time-point=2).

Case-Control Status. The variable was used to recognise if a participant was in the case or control group.

4.5 Statistical Analysis

Analyses were performed using SAS Statistic Software - Version 9.4 (SAS Institute Inc., Cary, NC, USA). Firstly, participants with missing data on exposure (LSF), comorbidities, and global health status were excluded, as the model would automatically remove them during the analysis. The statistical significance level was determined at $\alpha=0.05$.

Backward Stepwise. Initially, the backward stepwise was used to investigate the importance of covariables and to decide which confounder to include in the model at a significance of $\alpha=0.1$. Family status, living situation, and education were excluded, while the age group, occupation status, BMI, and CCI were kept.

Descriptive and Frequencies. The descriptive of the population characteristics such as the frequencies of the age group, occupation status, BMI and CCI were calculated for the cases at FU1 and FU2, and controls at FU2. Age group and occupational status were information obtained at BL, while the BMI and CCI were calculated for BL and each follow-up. For the cases, cancer characteristics at BL, e.g. grading, nodal status, stage, and tumour size, were calculated for both the datasets at FU1 and FU2. The frequencies of categorical variables

such as grams of alcohol consumed per day, current sport status, transport PA, and smoking status were calculated. Furthermore, the mean of continuous variables, such as the number of packs of cigarettes smoked per year and the HRQoL scales, were calculated.

Model 1 – Generalized Linear Mixed Model with Random Effect. The following model was used to analyse the LSFs as determinants of the HRQoL of cases at FU1 and FU2. The datasets of cases at these two follow-ups were merged in a long format, meaning that every participant had two lines: one for the FU1 and one for the FU2, for this reason, the participant number was used as random effect variable, and a time-point variable was created. In this model, the main effect of LSFs independent of time of assessment, as well as the interaction between follow-ups and LSFs on HRQoL were analysed, and the model was adjusted with the confounders. The model was run multiple times, and the no-significant interactions between time-point and LSFs were removed one by one starting with the interaction with the highest *p*-value until all the remaining interactions were significant. The singular LSFs and confounders were not changed and stayed in the model no matter the significance.

Model 2 - Linear Regression. This model analyses the influence of LSFs on the HRQoL of cases and controls at FU2, and the dataset of these two study populations at FU2 were merged. In this model, the main effects of LSFs independent of the case-control status and the effect of the interaction between case-control status and each LSF on each HRQoL scale were analysed, and the model was adjusted for possible confounders. In this case, the model was run multiple times, and the no-significant interactions between case-control-status and LSFs were removed one by one starting with the less significant interactions. All the remaining interactions were significant with a *p*-value of ≤0.5. The singular LSF and confounders were not changed and stayed in the model no matter the significance

5. Results

5.1 Descriptive and Frequencies

Characteristics of the Population Sample. In total, there were 1726 cases at FU1, 1143 cases at FU2, and 2123 controls at FU2. As shown in Table 1, half of the cases had moderate grading at diagnosis (50.87% at FU1 and 50.39% FU2) and had a nodal status equal to 0 (69.81% case at FU1 and 69.64% cases at FU2). As all patients with a tumour stage greater than IIIb were excluded, most of the patients in this population sample had a cancer stage I

(50.93% cases at FU1 and 51.62% cases at FU2) and a tumour size smaller than 2 cm (61.82% cases at FU1 and 62.64% cases at FU2).

At diagnosis, most of the women, 35.57% (n= 614) cases at FU1, 36.05% (n=412) cases at FU2, and 39.24% (n=833) controls at FU2, were aged between 59 and 64 years, and 40.90% (n=706) cases at FU1, 43.13% (n=493) cases at FU2, and 44.98% (n=955) controls at FU2 had a medium occupational status. 35.75% (n=617) cases at FU1, 35.70% (n=408) cases at FU2, and 35.07% (n=744) controls at FU2 were overweight and had a BMI between 25 and 30, while 65.64% (n=1133) cases at FU1, 55.64% (n=636) cases at FU2, and 54.45% (n=1156) controls at FU2 didn't have any comorbidity, therefore their CCI score was equal to 0 (Tab.1).

Lifestyle Factors. For cases, the majority (43.74% at FU1 and 38.93% at FU2) consumed between 0 g and 0.5 g of alcohol per day, participated regularly in a sports activity (62.46% at FU1 and 69.20% at FU2), and did enough transport PA (87.31% at FU1 and 83.55% at FU2). Most of the cases were never smokers (54.00% at FU1 and 53.11% at FU2), while current smokers (9.10% at FU1 and 8.40% at FU2) represented the smallest group. The average number of packs of cigarettes smoked per year for cases was 0.34 packs at FU1, and 0.27 packs at FU2 (Tab.1).

Most of the controls at FU2 (34.24%) consumed between 0.5g and 6g of alcohol per day, participated regularly in a sports activity (67.78%) and did enough transport physical activity (88.27%). The majority were never smokers (51.91%), while current smokers (8.76%) also represented the smallest group. The average number of packs of cigarettes smoked per year for controls was 0.26 packs (Tab.1).

Tab. 1: Descriptive of the population characteristics and lifestyle factors of cases at FU1 and FU2, and controls at FU2.

		Cases FU1 (partial)*		**Cases FU2 (partial)***		**Controls (FU2)**	
		n	**%**	***n***	**%**	***n***	**%**
Grading**	Missing	6	0.35	3	0.26	-	-
	Low	377	21.84	248	21.70	-	-
	Moderate	878	50.87	576	50.39	-	-
	High	354	20.51	236	20.65	-	-
	in situ	111	6.43	80	7.00	-	-
Nodal Status**	0	1205	69.81	796	69.64	-	-
	1 - 3	338	19.58	225	19.69	-	-
	4 - 9	72	4.17	42	3.67	-	-
	in situ	111	6.43	80	7.00	-	-
Stage**	Ia/Ib	879	50.93	590	51.62	-	-
	IIa/IIb	650	37.66	425	37.18	-	-

		Cases FU1 (partial)*		Cases FU2 (partial)*		Controls (FU2)	
		n	**%**	***n***	**%**	***n***	**%**
	IIIa	86	4.98	48	4.20	-	-
	in situ	111	6.43	80	7.00	-	-
Tumour Size**	<2cm	1067	61.82	716	62.64	-	-
	2-5cm	516	29.90	332	29.05	-	-
	>5cm	32	1.85	15	1.31	-	-
	in situ	111	6.43	80	7.00	-	-
Age Group**	<59 years	496	28.74	390	34.12	760	35.80
	59 - 64 years	614	35.57	412	36.05	833	39.24
	>64 years	616	35.69	341	29.83	530	24.96
Occupation Status**	Low	564	32.68	328	28.70	559	26.33
	Medium	706	40.90	493	43.13	955	44.98
	High	456	26.42	322	28.17	609	28.69
BMI	<22.5	351	20.34	274	23.97	491	23.13
	22.5 - <25	474	27.46	311	27.21	543	25.58
	25 - <30	617	35.75	408	35.70	744	35.04
	≥30	284	16.45	150	13.12	345	16.25
Charlson Comorbidity Index	0	1133	65.64	636	55.64	1156	54.45
	1	444	25.72	349	30.53	597	28.12
	2	122	7.07	111	9.71	234	11.02
	3	23	1.33	31	2.71	76	3.58
	4	3	0.17	11	0.96	38	1.79
	5	1	0.06	3	0.26	11	0.52
	6	0	0	1	0.09	7	0.33
	7	0	0	1	0.09	4	0.19
Alcohol Intake per Day [g/day]	0 - <0.5	755	43.74	445	38.93	536	25.25
	0.5 - <6	531	30.76	375	32.81	727	34.24
	6 - <12	172	9.97	123	10.76	317	14.93
	≥12	268	15.53	200	17.50	543	25.58
Current Sport	No	648	37.54	352	30.80	684	32.22
	Yes	1078	62.46	791	69.20	1439	67.78
Transport Physical Activity	Insufficient	219	12.69	188	16.45	249	11.73
	Sufficient	1507	87.31	955	83.55	1874	88.27
Smoking Status	Never Smoker	932	54.00	607	53.11	1102	51.91
	Ex-Smoker	637	36.91	440	38.50	835	39.33
	Current Smoker	157	9.10	96	8.40	186	8.76
Packs of Cigarettes	*n*	1726		1143		2123	
	mean	0.34		0.27		0.26	

*All information of cases at FU1 and FU2 were used, and not just cases present in both time-points.

**Information collected at diagnosis.

Retrospective Health-Related Quality of Life. The global health status before diagnosis, QoL post-operation, QoL during radiotherapy, and QoL during chemotherapy were just asked retrospectively to cases at FU1. Before diagnosis, patients had a global health status average of 76.89 points. The QoL post-operation was equal to 57.71 points, while the QoL

during radiography was equal to 49.87 points. The lowest QoL was observed during chemotherapy with an average of 32 points (Tab.2).

Health-Related Quality of Life. On average, cases had a global health status of 67.90 points at FU1 and 64.50 points at FU2, meaning that the QoL of the cases decreased from FU1 to FU2. Controls had a global health status of 67.15 points at FU2. Comparing the QoL of cases and controls at FU2, the control group had a higher QoL than cases (Tab.2).

Functional Scale. For every functional scale, the QoL of the cases was always higher at FU2 than FU1, while at FU2, controls had a higher QoL than cases. The scale with the highest average point was the social functioning with an average of 80.67 points for cases at FU1, 85.31 points for cases at FU2, and 86.90 points for controls at FU2. The scale with the lowest average point among the functional scales was role functioning for the cases at FU1 (72.19 points), and emotional functioning for both cases and controls at FU2 (72.86 for cases and 78.45 for controls) (Tab.2).

Tab. 2: Mean of the quality of life, and functional scales for cases at FU1 and FU2, and controls at FU2.

	Cases FU1 (partial*)		Cases FU2 (partial*)		Controls FU2	
	n	**mean**	***n***	**mean**	***n***	**mean**
Global Health Status before Diagnosis**	1711	76.89	-	-	-	-
Quality of Life post Operation**	1707	57.71	-	-	-	-
Quality of Life during Radiotherapy**	1371	49.87	-	-	-	-
Quality of Life during Chemotherapy**	702	32.00	-	-	-	-
Global Health Status	1726	67.90	1143	64.50	2123	67.15
Cognitive Functioning	1724	77.05	1140	78.55	2119	85.66
Emotional Functioning	1725	67.85	1140	72.86	2116	78.45
Physical Functioning	1724	77.73	1141	79.93	2121	82.31
Role Functioning	1723	72.19	1139	78.94	2113	82.60
Social Functioning	1725	80.67	1138	85.31	2115	86.90

*All information of cases at FU1 and FU2 were used, and not just cases present in both time-points.

**Retrospective HRQoL was asked just to cases at FU1.

5.2 Model 1 - Generalized Linear Mixed Model with Random Effect

To investigate the effect of LSFs on HRQoL of cases at different time-points, a generalized linear mixed model with the sample population as random effect variable was created. Here, the effects of LSFs on the global health status and the functional scales at FU1 and FU2 were studied. The model was adjusted with important confounders, such as age group, occupation status, BMI, and CCI.

Global Health Status. The number of packs of cigarettes smoked per year had a significant influence on the global health status (*p*-value=0.04), which was not related to the time-point. If the number of packs of cigarettes smoked increased by 1, then the QoL decreased by 1.23 points, meaning that the more a participant smoked, the worse their QoL was (Tab.3).

Tab. 3: Association between packs of cigarettes per year and Global Health Status.

Main Effect of Packs of Cigarettes per Year*		
Effect	**Beta**	***p*-value**
Packs per Year	-1.23	0.04

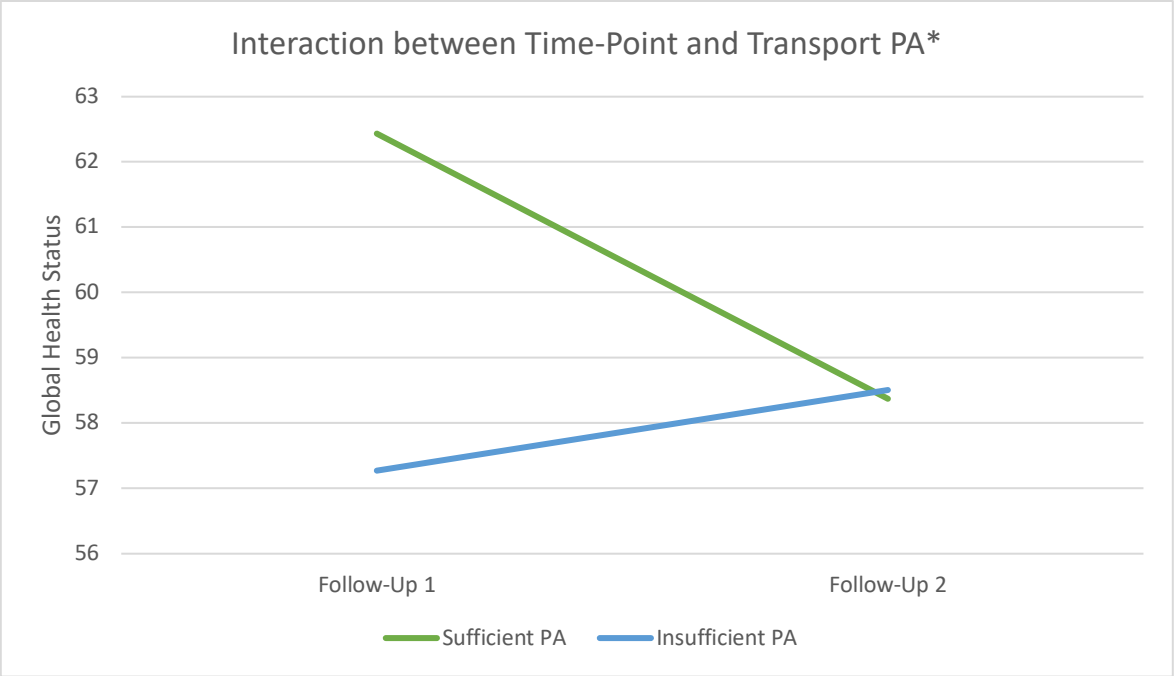
*Adjusted with age group, occupation status, BMI, and CCI.

Furthermore, a significant interaction between the transport PA and the time-point was observed (*p*-value=0.02), meaning that the transport PA had a different effect on the QoL depending on the time. At FU1, patients reporting sufficient transport PA had a higher global health status than those insufficiently cycling or walking as a measure of transport. At FU2, transport PA was not significantly related to the global health status, meaning that transport PA lost its effect (Tab.4 and Fig.3).

Tab. 4: Interaction between time-point and transport PA for Global Health Status.

Interaction between Time-Point and Transport PA*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Insufficient vs. Sufficient	-5.16 (-8.30, -2.02)	0.01
At FU2	Insufficient vs. Sufficient	0.13 (-3.24, 3.51)	0.94
Insufficient PA	FU1 vs. FU2	-1.23 (-5.42, 2.95)	0.56
Sufficient PA	FU1 vs. FU2	4.06 (2.45, 5.68)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

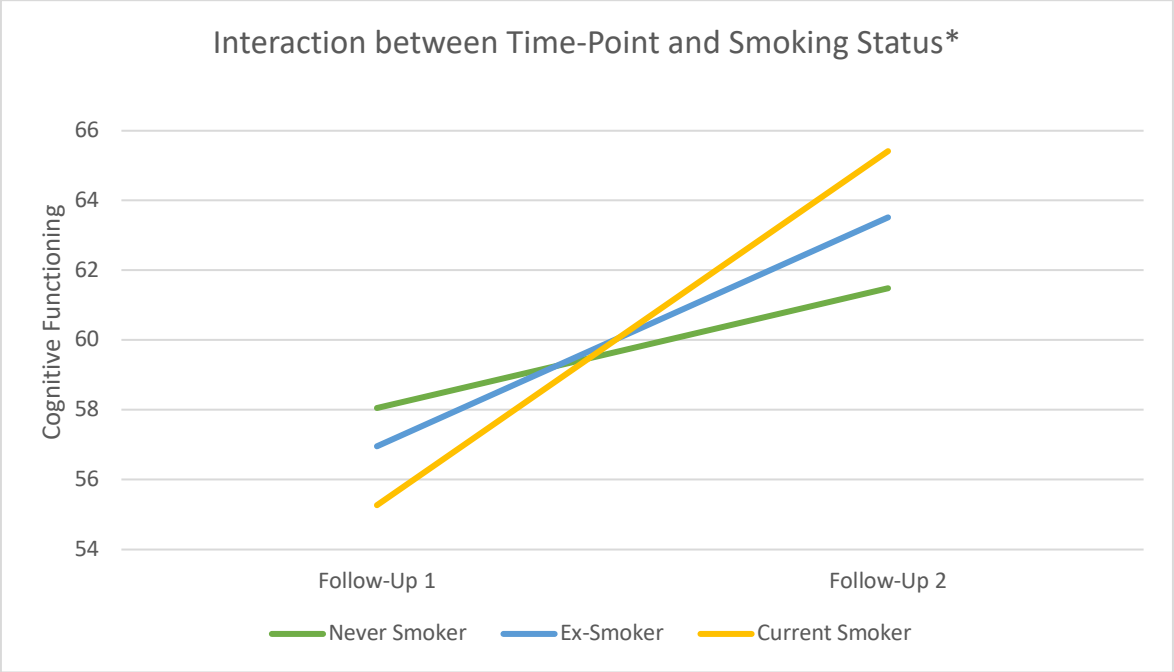
Fig. 3: Interaction between time-point and transport PA for Global Health Status.

Cognitive Functioning. For the cognitive functioning scale, there was a significant interaction between time-point and smoking status (*p*-value=0.01). At both FU1 and FU2, there wasn't a significant difference in cognitive functioning between the smoking status groups. Nevertheless, this functional scale significantly improved from FU1 to FU2 for all three smoking categories (Tab.5 and Fig.4).

Tab. 5: Interaction between time-point and smoking status for Cognitive Functioning.

Interaction between Time-Point and Smoking Status*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Never Smoker vs. Ex-Smoker	1.10 (-1.33, 3.52)	0.38
At FU1	Never Smoker vs. Current Smoker	2.67 (-2.45, 8.02)	0.30
At FU1	Ex-Smoker vs. Current Smoker	1.69 (-3.42, 6.79)	0.52
At FU2	Never Smoker vs. Ex-Smoker	-2.03 (-4.81, 0.75)	0.15
At FU2	Never Smoker vs. Current Smoker	-3.93 (-9.56, 1.71)	0.17
At FU2	Ex-Smoker vs. Current Smoker	-1.90 (-7.46, 3.66)	0.50
Never Smoker	FU1 vs. FU2	-3.43 (-5.78, -1.08)	<0.01
Ex-Smoker	FU1 vs. FU2	-6.59 (-9.22, -3.90)	<.0001
Current Smoker	FU1 vs. FU2	-10.15 (-15.00, -5.30)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

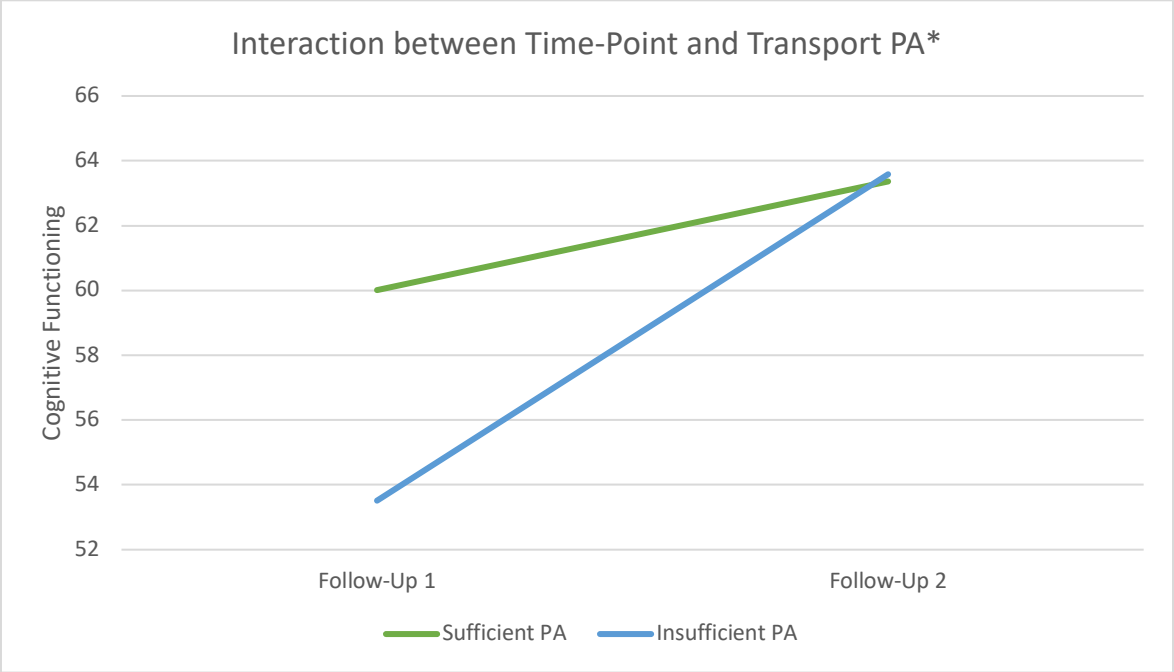
Fig. 4: Interaction between time-point and smoking status for Cognitive Functioning.

Another significant interaction for the cognitive functioning was found between the time-point and transport PA (p-value<0.01). At FU1, the cognitive functioning of the 2 groups was significantly different, but at FU2, this LSF lost its effect, and no significant difference was observed. The cognitive functioning for both transport PA groups significantly increased from FU1 to FU2 (Tab.6 and Fig.5).

Tab. 6: Interaction between time-point and transport PA for Cognitive Functioning.

Interaction between Time-Point and Transport PA*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Insufficient vs. Sufficient	-6.50 (-9.59, -3.41)	<.0001
At FU2	Insufficient vs. Sufficient	0.22 (-2.93, 3.37)	0.89
Insufficient PA	FU1 vs. FU2	-10.07 (-14.21, -5.94)	<.0001
Sufficient PA	FU1 vs. FU2	-3.35 (-5.23, -1.48)	<0.01

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

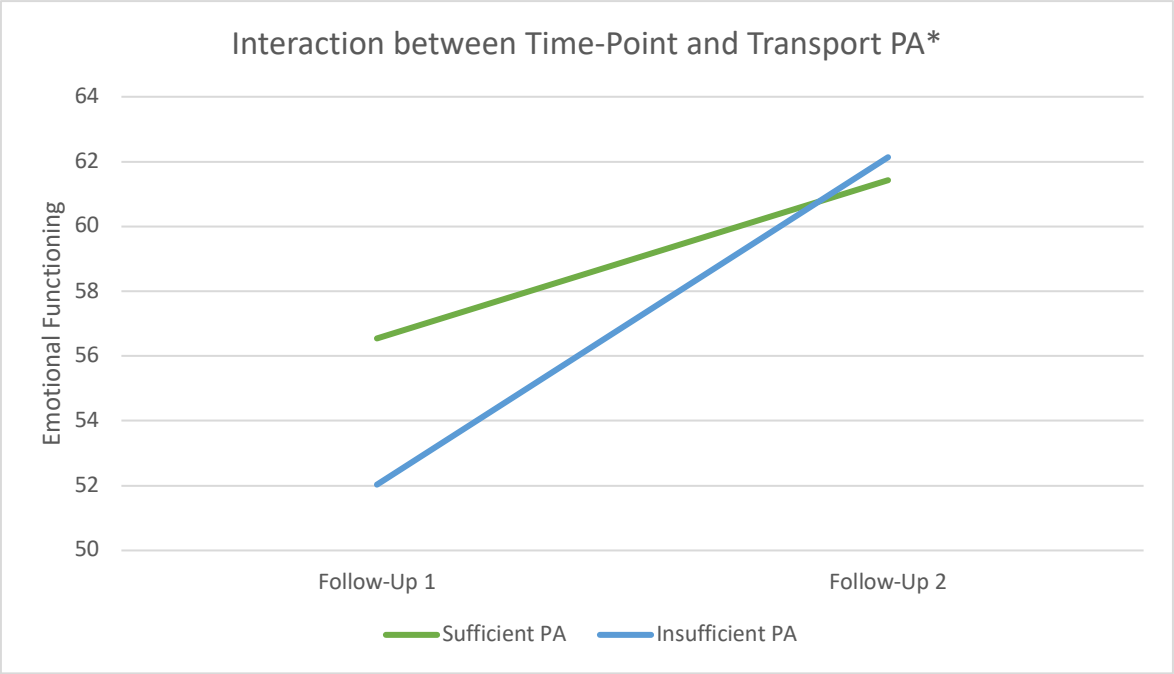
Fig. 5: Interaction between time-point and transport PA for Cognitive Functioning.

Emotional Functioning. For the emotional functioning scale, there was a significant interaction between time-point and transport PA (*p*-value=0.02). At FU1, patients doing sufficient transport PA had a significantly higher score than patients who didn't, while at FU2, this LSF lost its effect and the difference between the 2 groups was no longer significant. The emotional functioning significantly increased from FU1 to FU2 for both groups (Tab.7 and Fig.6).

Tab. 7: Interaction between time-point and transport PA for Emotional Functioning.

Interaction between Time-Point and Transport PA*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Insufficient vs. Sufficient	-4.51 (-7.75, -1.27)	<0.01
At FU2	Insufficient vs. Sufficient	0.70 (-2.59, 4.01)	0.67
Insufficient PA	FU1 vs. FU2	-10.10 (-14.26, -5.95)	<.0001
Sufficient PA	FU1 vs. FU2	-4.88 (-6.38, -3.38)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

Fig. 6: Interaction between time-point and transport PA for Emotional Functioning.

Physical Functioning. A significant main effect on physical functioning was packs of cigarettes smoked per year (*p*-value=0.01). By the increase of 1 pack of cigarettes smoked, the physical functioning of the patient decreased by 1.20 points, meaning that the increase in smoking was associated with a lower physical functioning (Tab.8). Another main effect was current sport status (*p*-value<0.01). Patients who didn't practise any kind of sports had 2.40 points less than patients practising sports (Tab.8).

Tab. 8: Association between LSFs (packs of cigarettes per year and current sport status) and Physical Functioning.

Main Effect of Packs of Cigarettes per Year and Current Sport Status*			
Effect	**Group**	**Beta**	***p*-value|**
Packs per Year		-1.20	0.01
Current Sport	Insufficient	-2.40	<0.01
Current Sport	Sufficient	0	.

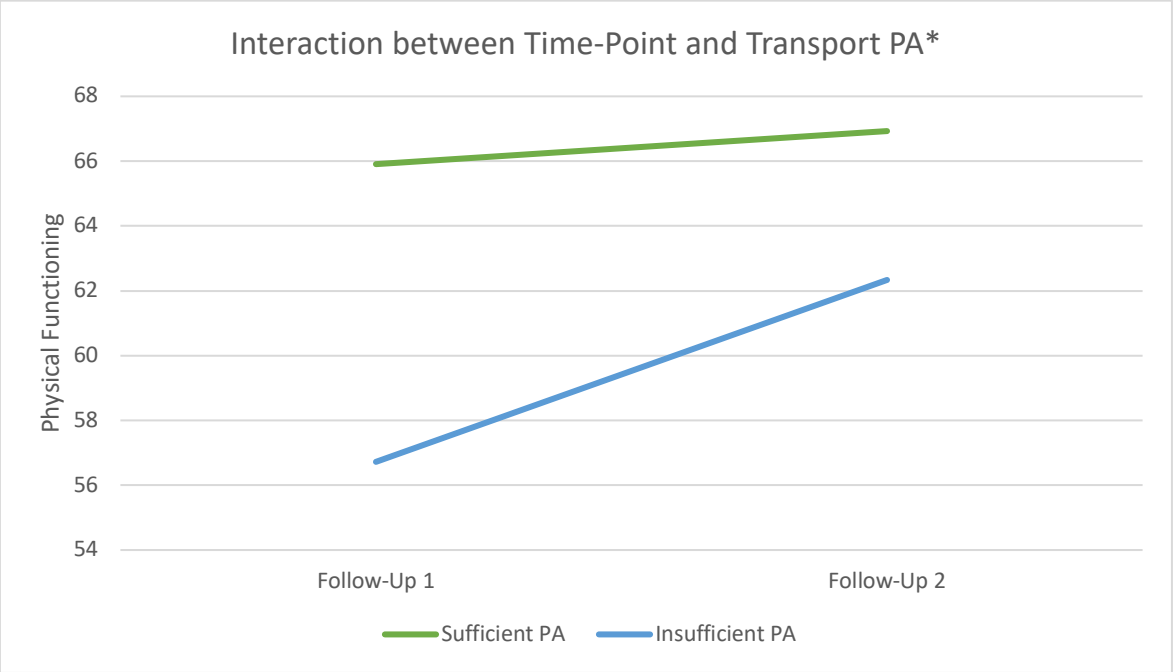
*Adjusted with age group, occupation status, BMI, and CCI.

A significant interaction was observed between time-point and transport PA (*p*-value=0.01). At both FU1 and FU2, patients reporting sufficient transport PA had a higher physical functioning than those insufficiently cycling or walking as a measure of transport. Furthermore, the physical functioning of patients doing insufficient transport PA increased significantly from FU1 to FU2, while this increase was not significant for the other group (Tab.9 and Fig.7).

Tab. 9: Interaction between time-point and transport PA for Physical Functioning.

Interaction between Time-Point and Transport PA*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Insufficient vs. Sufficient	-9.19 (-11.48, -6.89)	<.0001
At FU2	Insufficient vs. Sufficient	-4.59 (-6.94, -2.45)	<0.01
Insufficient PA	FU1 vs. FU2	-5.61 (-8.56-2.66)	<0.01
Sufficient PA	FU1 vs. FU2	-1.02 (-2.09, -0.05)	0.06

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

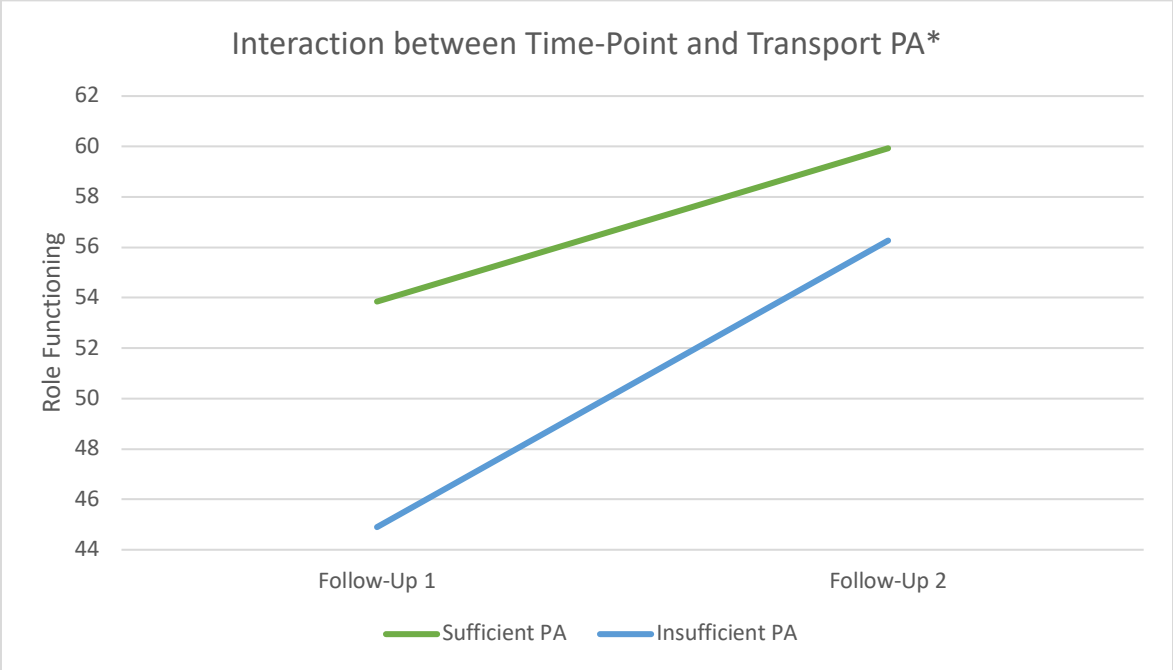
Fig. 7: Interaction between time-point and transport PA for Physical Functioning.

Role Functioning. The only significant interaction for role functioning was between time-point and transport PA (*p*-value=0.04). At FU1, patients doing sufficient PA had a significantly higher score than patients doing insufficient PA. This difference was not seen at FU2. Nevertheless, the role functioning significantly increased from FU1 to FU2 for both groups (Tab.10 and Fig.8).

Tab. 10: Interaction between time-point and transport PA for Role Functioning.

Interaction between Time-Point and Transport PA*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Insufficient vs. Sufficient	-8.95 (-12.49, -5.41)	<.0001
At FU2	Insufficient vs. Sufficient	-3.66 (-7.37, 0.05)	0.06
Insufficient PA	FU1 vs. FU2	-11.37 (-16.00, -6.74)	<.0001
Sufficient PA	FU1 vs. FU2	-6.08 (-7.81, -4.35)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

Fig. 8: Interaction between time-point and transport PA for Role Functioning.

Social Functioning. The grams of alcohol consumed per day was not time-related, but it influenced the social functioning (*p*-value=0.04). Patients consuming 0g-0.5g of alcohol per day had a significantly lower score compared to patients consuming more than 12g of alcohol per day. Although the other groups didn't show a significant difference in social functioning compared to the group of patients consuming more than 12g, a pattern could still be seen: the more a patient drinks, the better the functioning scale was (Tab.11).

Tab. 11: Association between alcohol consumption and Social Functioning.

Main Effect of Alcohol Consumption*			
Effect	**Group**	**Beta**	***p*-value**
Alcohol Consumption	0g -<0.5g	-3.75	0.01
Alcohol Consumption	0.5g - <6g	-2.29	0.09
Alcohol Consumption	6g - <12g	-1.38	0.40
Alcohol Consumption	≥12g	0	.

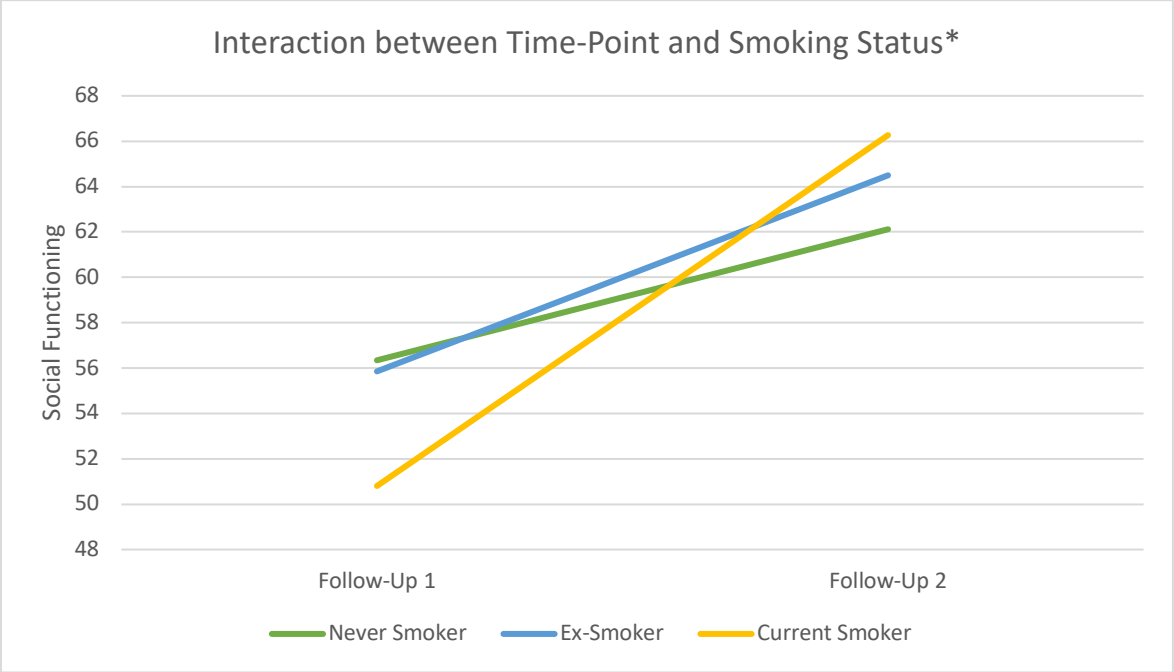
*Adjusted with age group, occupation status, BMI, and CCI.

For the social functioning, there was a significant interaction between time-point and smoking status (*p*-value<0.01). At FU1, never smokers had a significantly higher social functioning than current smokers, while at FU2 there were no significant differences between the smoking groups. Nevertheless, the social functioning significantly increased from FU1 to FU2 for all three smoking groups (Tab.12 and Fig.9).

Tab. 12: Interaction between time-point and smoking status for Social Functioning.

Interaction between Time-Point and Smoking Status*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Never Smoker vs. Ex-Smoker	0.49 (-1.99, 2.97)	0.70
At FU1	Never Smoker vs. Current Smoker	5.54 (0.09, 10.99)	0.05
At FU1	Ex-Smoker vs. Current Smoker	5.05 (-0.29, 10.39)	0.06
At FU2	Never Smoker vs. Ex-Smoker	-2.38 (-5.26, 0.50)	0.11
At FU2	Never Smoker vs. Current Smoker	-4.15 (-10.04, 1.74)	0.17
At FU2	Ex-Smoker vs. Current Smoker	-1.77 (-7.61, 4.07)	0.55
Never Smoker	FU1 vs. FU2	-5.78 (-8.33, -3.22)	<.0001
Ex-Smoker	FU1 vs. FU2	-8.64 (-11.57, -5.71)	<.0001
Current Smoker	FU1 vs. FU2	-15.47 (-20.68, -10.24)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

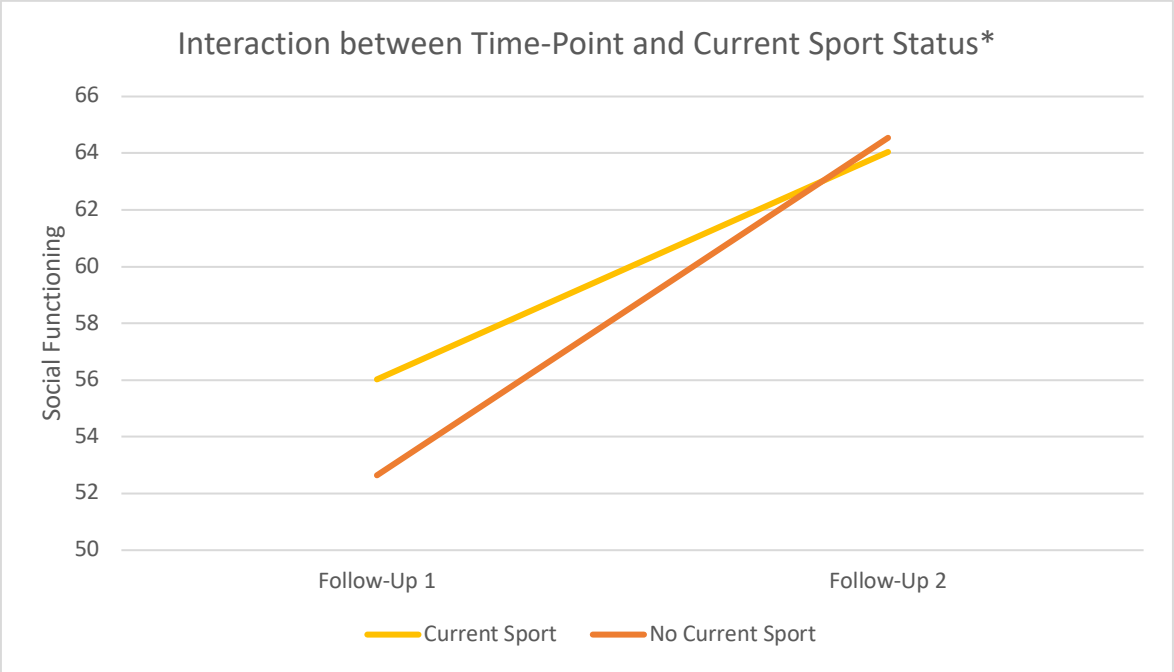
Fig. 9: Interaction between time-point and smoking status for Social Functioning.

Another significant interaction was between time-point and current sport status (*p*-value=0.02). At FU1, patients doing sports reported significantly better social functioning than patients who didn't practise any sport, but this LSF lost its effect as the difference was no longer significant at FU2. The social functioning improved from FU1 to FU2 for both groups (Tab.13 and Fig.10).

Tab. 13: Interaction between time-point and current sport for Social Functioning.

Interaction between Time-Point and Current Sport Status*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	No Current Sport vs. Current Sport	-3.38 (-5.65, -1.12)	<0.01
At FU2	No Current Sport vs. Current Sport	0.50 (-2.27, 3.27)	0.72
No Current Sport	FU1 vs. FU2	-11.90 (-15.15, -8.66)	<.0001
Current Sport	FU1 vs. FU2	-8.02 (-10.83, -5.21)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

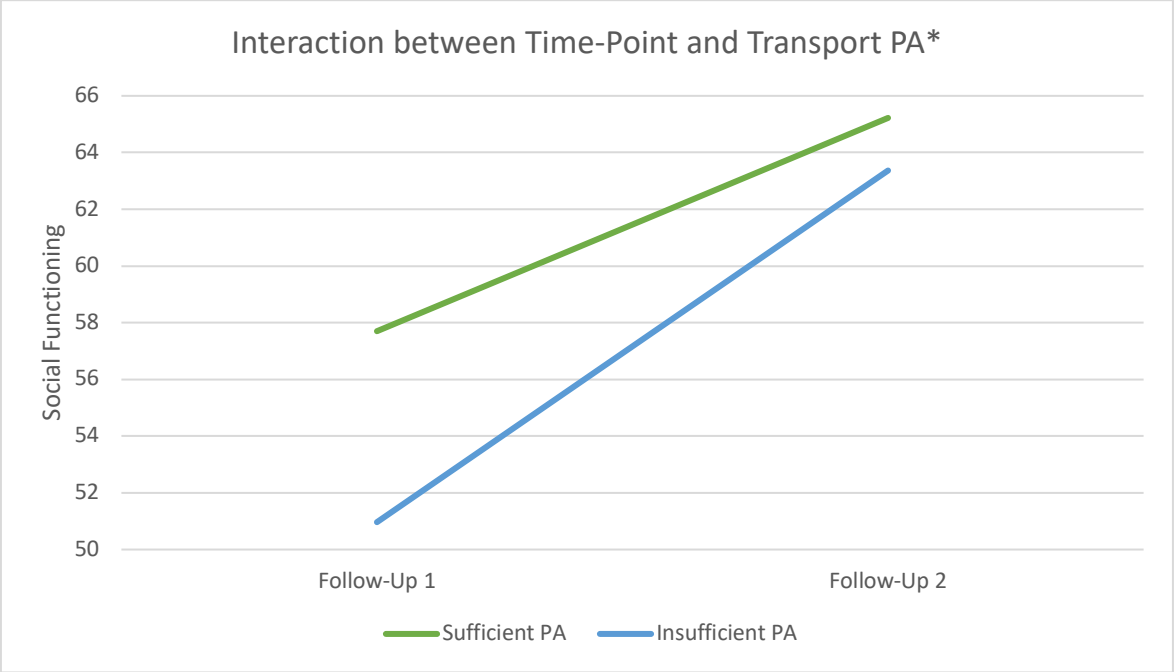
Fig. 10: Interaction between time-point and current sport status for Social Functioning.

The third significant interaction was between time-point and transport PA (*p*-value=0.04). As shown in the table and figure below, at FU1, patients doing sufficient transport PA had a better social functioning at both FU1 compared to patients who didn't. Nevertheless, the score increased for both groups at FU2 (Tab.14 and Fig.11).

Tab. 14: Interaction between time-point and transport PA for Social Functioning.

Interaction between Time-Point and Transport PA*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
At FU1	Insufficient vs. Sufficient	-6.74 (-9.97, -3.50)	<.0001
At FU2	Insufficient vs. Sufficient	-1.85 (-5.22, 1.51)	0.28
Insufficient PA	FU1 vs. FU2	-12.40 (-16.80, -8.00)	<.0001
Sufficient PA	FU1 vs. FU2	-7.52 (-9.62, -5.43)	<.0001

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

Fig. 11: Interaction between time-point and transport PA for Social Functioning.

5.3 Model 2 - Linear Regression with Interaction

To investigate the effect of LSFs on the HRQoL at FU2, a linear regression with interaction with the case-control status was created. In this model, the effect of LSFs on the global health status and the functioning scales of the cases and controls at FU2 were analysed. The model was adjusted with important confounders, such as age group, occupation status, BMI, and CCI.

Global Health Status. At FU2, just alcohol consumption influenced the global health status in general (p-value<0.01), meaning that this LSF didn't influence the QoL of the cases and controls differently. Participants consuming 0g-0.5g of alcohol per day reported a lower global health status compared to participants consuming more than 12g of alcohol per day. Although other groups didn't show a significant difference in the QoL compared to the group of participants consuming more than 12g, a pattern could still be seen as the QoL improved as the quantity of alcohol consumed increased (Tab.15).

Tab. 15: Association between alcohol consumption and Global Health Status.

Main Effect of Alcohol Consumption*			
Effect	**Group**	**Beta**	***p*-value**
Alcohol Consumption	0g -<0.5g	-3.79	<0.01
Alcohol Consumption	0.5g - <6g	-1.69	0.15
Alcohol Consumption	6g - <12g	0.64	0.66
Alcohol Consumption	≥12g	0	.

*Adjusted with age group, occupation status, BMI, and CCI.

Cognitive Functioning. The influence of current sport status on the cognitive functioning was not associated with the case-control status, but it was still significant (*p*-value=0.04). Participants who didn't do sports had a better score than participants who did sport (Tab.16). Transport PA also had a significant effect on the cognitive functioning (*p*-value<0.01). Participants reporting sufficient transport PA had a better score than participants who didn't (Tab.16).

Tab. 16: Association between LSFs (current sport status and transport PA) and Cognitive Functioning.

Main Effect of Current Sport Status and Transport PA*			
Effect	**Group**	**Beta**	***p*-value**
Current Sport	No	1.65	0.04
Current Sport	Yes	0	.
Transport PA	Insufficient	-3.43	<0.01
Transport PA	Sufficient	0	.

*Adjusted with age group, occupation status, BMI, and CCI.

Emotional Functioning. At FU2, there was a significant interaction between case-control status and the number of packs of cigarettes smoked per year (*p*-value=0.02). As shown in Table 17, the number of packs of cigarettes smoked influenced just the emotional functioning of controls and not cases (Tab.17).

Tab. 17: Association between packs of cigarettes per year and Emotional Functioning.

Main Effect of Packs of Cigarettes per Year*			
Effect	**Group**	**Beta**	***p*-value**
Packs per Year	Controls	-2.36	0.01
Packs per Year	Cases	1.00	0.35

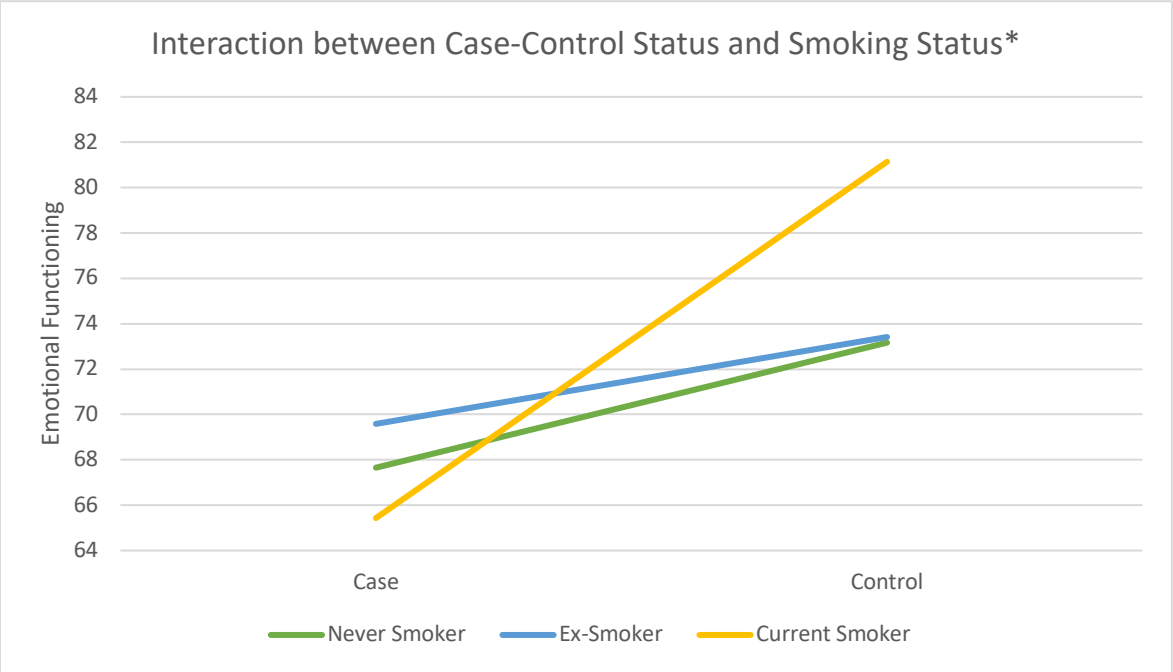
*Adjusted with age group, occupation status, BMI, and CCI.

There was also a significant interaction between the case-control status and smoking status (*p*-value=0.05). For cases, the smoking status didn't influence the emotional functioning, but for controls, current smokers reported a significantly higher emotional functioning than ex-smokers and never smokers. In all three smoking groups, controls had a better emotional functioning compared to cases (Tab.18 and Fig.12)

Tab. 18: Interaction between case-control status and smoking status for Emotional Functioning.

Interaction between Case-Control Status and Smoking Status*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
Controls	Never Smoker vs. Ex-Smoker	-0.25 (-2.29, 1.80)	0.81
Controls	Never Smoker vs. Current Smoker	-7.97 (-14.28, -1.67)	0.01
Controls	Ex-Smoker vs. Current Smoker	-7.73 (-13.99, -1.46)	0.03
Cases	Never Smoker vs. Ex-Smoker	-1.93 (-4.70, 0.84)	0.17
Cases	Never Smoker vs. Current Smoker	2.22 (-5.31, 9.75)	0.56
Cases	Ex-Smoker vs. Current Smoker	4.15 (-3.28, 11.59)	0.27
Never Smoker	Controls vs. Cases	5.51 (3.17, 7.86)	<.0001
Ex-Smoker	Controls vs. Cases	3.83 (1.19, 6.47)	<0.01
Current Smoker	Controls vs. Cases	15.71 (6.78, 24.64)	<0.01

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

Fig. 12: Interaction between case-control status and smoking status for Emotional Functioning.

Physical Functioning. At FU2, alcohol consumption influenced the physical functioning in general (*p*-value<0.01). Participants consuming 0g-0.5g of alcohol per day had on average a lower functional score compared to participants consuming more than 12g of alcohol per day. Furthermore, current sport status (*p*-value<.0001), and transport PA (*p*-value<.0001) influenced the physical functioning. Participants who didn't practise any sports or did insufficient transport PA had a significantly lower physical functioning than the other group (Tab.19).

Tab. 19: Association between LSFs (alcohol consumption, current sport status, and transport PA) and Physical Functioning.

Main Effect of Alcohol Consumption, Current Sport Status, and Transport PA*			
Effect	**Group**	**Beta**	***p*-value**
Alcohol Consumption	0g -<0.5g	-3.05	<0.01
Alcohol Consumption	0.5g - <6g	-0.89	0.26
Alcohol Consumption	6g - <12g	-0.19	0.85
Alcohol Consumption	≥12g	0	.
Current Sport	No	-2.93	<.0001
Current Sport	Yes	0	.
Transport PA	Insufficient	-5.72	<.0001
Transport PA	Sufficient	0	.

*Adjusted with age group, occupation status, BMI, and CCI.

For physical functioning, there was a significant interaction between case-control status and packs of cigarettes smoked per year (*p*-value<0.01), but the increase of the number of cigarettes smoked decreased just the physical functioning of the control group. This LFS didn't influence cases (Tab.20).

Tab. 20: Interaction between case-control status and packs of cigarettes per year for Physical Functioning.

Interaction between Case-Control Status and Packs of Cigarettes per Year*			
Effect	**Group**	**Beta**	***p*-value**
Case-Control*Packs per Year	Controls	-2.80	<.0001
Case-Control*Packs per Year	Cases	-0.20	0.80

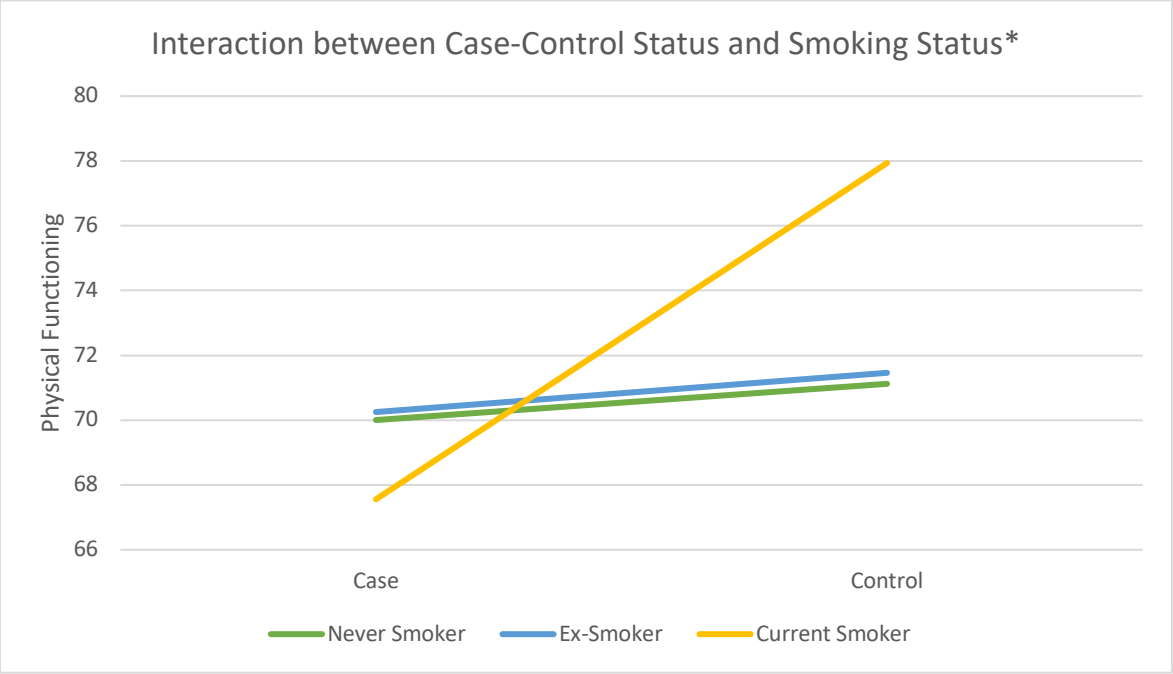
*Adjusted with age group, occupation status, BMI, and CCI.

Another interaction was between case-control status and smoking status (*p*-value=0.04). For cases, the smoking status didn't significantly influence the physical functioning, meaning that the score of this scale was not significantly different from status to status. For controls instead, the current smokers had a higher score than ex-smokers and never smokers. Furthermore, the current smokers of the control group reported a significantly higher score than the current smoker in the case group (Tab.21 and Fig.13).

Tab. 21: Interaction between case-control status and smoking status for Physical Functioning.

Interaction between Case-Control Status and Smoking Status*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
Controls	Never Smoker vs. Ex-Smoker	-0.34 (-1.84, 1.16)	0.66
Controls	Never Smoker vs. Current Smoker	-6.81 (-11.45, -2.18)	<0.01
Controls	Ex-Smoker vs. Current Smoker	-6.47 (-11.08, -1.87)	<0.01
Cases	Never Smoker vs. Ex-Smoker	-0.25 (-2.28, 1.79)	0.81
Cases	Never Smoker vs. Current Smoker	2.45 (-3.13, 8.02)	0.39
Cases	Ex-Smoker vs. Current Smoker	2.69 (-2.81, 8.20)	0.34
Never Smoker	Controls vs. Cases	1.12 (-0.61, 2.84)	0.20
Ex-Smoker	Controls vs. Cases	1.21 (-0.73, 3.16)	0.22
Current Smoker	Controls vs. Cases	10.37 (3.78, 16.97)	<0.01

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

Fig. 13: Interaction between case-control status and smoking status for Physical Functioning.

Role Functioning. Alcohol consumption had a general influence on the role functioning (*p*-value<0.01). Participants consuming less than 0.5g of alcohol per day had a worse role functioning compared to participants consuming more than 12g of alcohol per day. For current sport status (*p*-value=0.01) and transport PA (*p*-value<.0001), participants who didn't practise any sport or didn't do enough transport PA reported a lower role functioning compared to the other group (Tab.22).

Tab. 22: Association between LSFs (alcohol consumption, current sport status, and transport PA) and Role Functioning.

Main Effect of Alcohol Consumption, Current Sport Status, and Transport PA*			
Effect	**Group**	**Beta**	***p*-value**
Alcohol Consumption	0g -<0.5g	-4.42	<0.01
Alcohol Consumption	0.5g - <6g	-2.04	0.08
Alcohol Consumption	6g - <12g	-2.44	0.09
Alcohol Consumption	≥12g	0	.
Current Sport	No	-2.38	0.01
Current Sport	Yes	0	.
Transport PA	Insufficient	-4.93	<.0001
Transport PA	Sufficient	0	.

*Adjusted with age group, occupation status, BMI, and CCI.

A significant interaction was observed between case-control status and the number of packs of cigarettes smoked per year (*p*-value=0.02), but this was relevant and influenced just the role functioning of the control group (Tab.23).

Tab. 23: Interaction between case-control status and packs of cigarettes per year for Role Functioning.

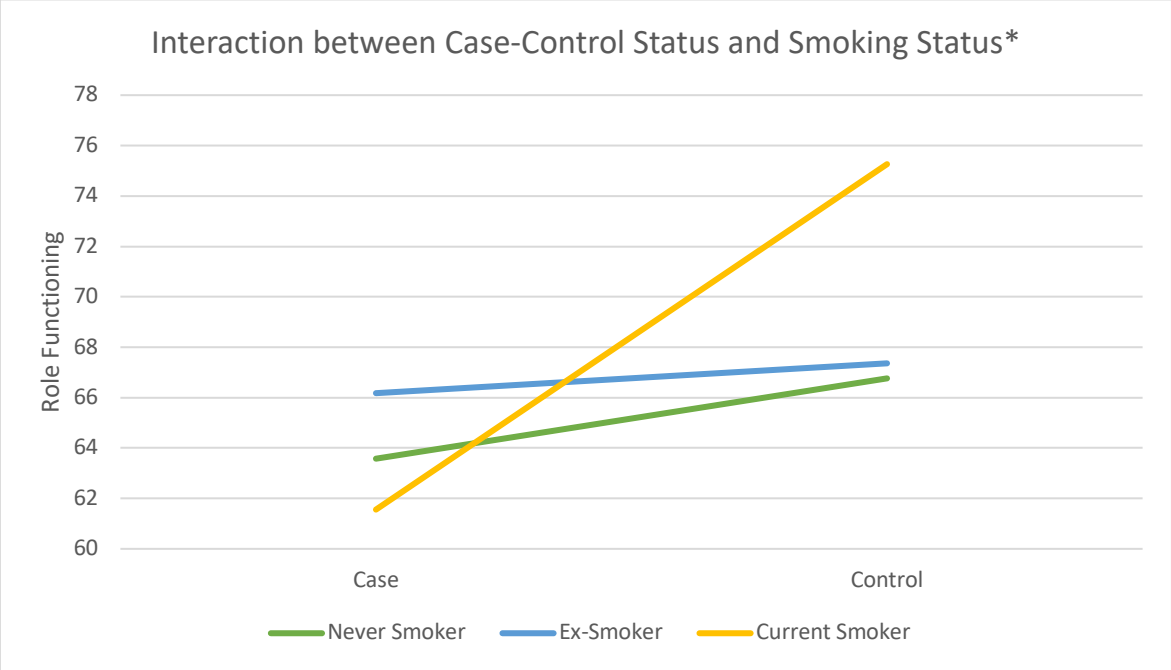
Interaction between Case-Control Status and Packs of Cigarettes per Year*			
Effect	**Group**	**Beta**	***p*-value**
Case-Control*Packs per Year	Control	-3.03	<0.01
Case-Control*Packs per Year	Cases	0.62	0.59

Another significant interaction was observed between case-control status and smoking status (*p*-value=0.05). For cases, none of the smoking statuses was significantly different from another, while for controls, current smokers had a better role functioning than ex-smokers and never smokers. The role functioning of never smokers and current smokers was significantly higher in participants in the control group than participants in the case group (Tab.24 and Fig.14).

Tab. 24: Interaction between case-control status and smoking status for Role Functioning.

Interaction between Case-Control Status and Smoking Status*			
Group	**Comparison**	**Mean Δ (95% CI)**	***p*-value**
Controls	Never Smoker vs. Ex-Smoker	-0.60 (-2.80, 1.60)	0.60
Controls	Never Smoker vs. Current Smoker	-8.50 (-15.27, -1.73)	0.01
Controls	Ex-Smoker vs. Current Smoker	-7.90 (-14.63, -1.18)	0.02
Cases	Never Smoker vs. Ex-Smoker	-2.60 (-5.58, 0.38)	0.09
Cases	Never Smoker vs. Current Smoker	2.02 (-6.08, 10.12)	0.62
Cases	Ex-Smoker vs. Current Smoker	4.62 (-3.37, 12.61)	0.26
Never Smoker	Controls vs. Cases	3.19 (0.66, 5.71)	0.01
Ex-Smoker	Controls vs. Cases	1.18 (-1.66, 4.03)	0.41
Current Smoker	Controls vs. Cases	13.71 (4.12, 23.29)	<0.01

*Adjusted with age group, occupation status, BMI, and CCI.



*Adjusted with age group, occupation status, BMI, and CCI.

Fig. 14: Interaction between case-control status and smoking status for Role Functioning.

Social Functioning. LSFs which influenced the social functioning were alcohol consumption (p-value<0.01) and transport PA (p-value=0.03). In general, participants consuming less than 6g reported a lower score than participants consuming more than 12g of alcohol per day, while participants who didn't do sufficient transport PA reported a lower score than the other group (Tab.25).

Tab. 25: Association between LSFs (alcohol consumption and transport PA) and Social Functioning.

Main Effect of Alcohol Consumption, and Transport PA*			
Effect	**Group**	**Beta**	***p*-value**
Alcohol Consumption	0g -<0.5g	-4.19	<0.01
Alcohol Consumption	0.5g - <6g	-2.73	0.01
Alcohol Consumption	6g - <12g	-1.23	0.36
Alcohol Consumption	≥12g	0	.
Transport PA	Insufficient	-2.54	0.03
Transport PA	Sufficient	0	.

*Adjusted with age group, occupation status, BMI, and CCI.

6. Discussion

6.1 Methodology Discussion

Methods. Information collected at BL such as another tumour before BC diagnosis, and tumour stage at diagnosis were excluded identically for both datasets of cases at FU1 and FU2, but variables such as metastatic, recurrent, and secondary tumour were used to exclude cases just at that specific time-point, e.g. a participant who developed a secondary tumour at FU2 was not removed from the dataset at FU1, while a patient who developed a secondary tumour at FU1 remained in the FU2 dataset, because it was assumed that after 5 years, this event wouldn't have an impact on the QoL.

The instrument used to measure the HRQoL in the MARIE study was the EORTC QLQ-C30 questionnaire, which was designed specifically for cancer patients, but it was still valid to be used in a healthy population. Therefore, in order to be able to compare the HRQoL of cases at FU1 to the cases and controls at FU2, the same questionnaire was also distributed to the control group.

Analysis. To investigate the LSFs as determinants on the HRQoL, two statistical models were created. Model 1 included cases at FU1 and FU2 and was a generalized linear mixed model with interaction between time-point assessment and LSFs using the participant

number as a random effect variable. In this model, the same patients were followed through the FU1 and FU2, therefore, each of them had 2 lines with information of both time-points. Model 2 included cases and controls at FU2 and was a simple linear regression with interaction between the case-control status and LSFs. As this model investigated the LSFs as determinants of HRQoL at just one time-point, the number of the participant as random effect variable was not needed.

As SAS excluded from the analysis every participant with any missing value, these were removed at the beginning while creating the datasets in order to report the same number of participants in the descriptive and analysis.

6.2 Discussion of the Results

Previous studies showed differences in QoL of BCPs overtime and that 10 years after diagnosis, the HRQoL of BCSs was still not completely compared to that of controls [6,26], therefore, in order to explain those differences, finding adjustable factors such as lifestyle LSFs as determinant on the HRQoL over time and comparing them to a control group was relevant.

Results of this thesis showed that the effect of transport PA was time-related and positively influenced the most subscales of HRQoL such as global health status, and cognitive, physical, role, and social functioning at FU1, while this lost importance over time. At FU2, this determined the cognitive, physical, role, and social functioning independently by the case-control status. Cases currently practising sports reported a better social functioning at FU1 but not at FU2, and a better physical functioning independently by the time, while at FU2 participants practising sports had a better physical and role functioning, but a worse cognitive functioning independently by the case-control status.

Alcohol consumption was the LSF with the least influence on the HRQoL of cases. BCPs consuming more grams of alcohol per day reported a higher social functioning independently by the time, while at FU2, a higher alcohol consumption improved the global health status, physical, role, and social functioning in general in the population sample.

Furthermore, differences in the effect of smoking status on the QoL of cases was observed over time. At FU1, never smokers reported a better social functioning compared to current smokers, while this effect was no longer observed at FU2. Nevertheless, the social and cognitive functioning of all smoking groups significantly improved after 10 years post-diagnosis, independently of the smoking status. At FU2, current smokers of the control group reported a better emotional, physical, and role functioning compared to that of cases. Ex-

smokers of the control group had a better emotional functioning, while never smokers of the control group had a better emotional and role functioning.
Another measure of smoking behaviour was the number of packs of cigarettes smoked per year. This was not time-dependent and decreased the global health status and physical functioning of the cases in general. At FU2, a difference between cases and controls were reported in emotional, physical, and role functioning, as this influenced just the QoL of controls.
Transport PA was the LSF that influenced the most subscale of HRQoL and alcohol consumption influenced the least subscale. Most of the LSFs had a strong influence on the QoL of cases at 5 years post-diagnosis and lost their effect at ≥10 years post-diagnosis. At FU2, just LSFs related to smoking behaviour determined differently the QoL of cases and controls, while other LSFs influenced it in general.
Physical functioning was the HRQoL's subscale that was the most influenced by LSFs, while emotional functioning was the least affected.

In previous studies, BCPs meeting the ACS and WHO recommendation, therefore practising enough PA, reported a positive influence on global health status, physical, social, role [11], cognitive and emotional functioning [10]. This last functional scale was not observed in this thesis. Another study used the FACT-B questionnaire and not the EORTC QLQ-C30, which made the comparison to the results of this thesis difficult. Nevertheless, they observed an improvement in emotional well-being, and social/family well-being [12], therefore the social functioning was the only similarity.
At FU2, this thesis observed a negative impact of currently practising sports on the cognitive functioning in general, but previous interventions showed that PA had a positive impact and improved this functioning scale [37,38].
A study on alcohol consumption in BCPs couldn't find any association between alcohol consumption and symptom severity [13], although another one observed a strong evidence between alcohol intake and role limitation due to emotional problems, and a weak evidence with role limitation due to physical health [14]. Both papers couldn't be completely compared to the results of this thesis as different instrument methods were used [13,14], and one of them investigated mainly on the symptom scales [13], which were not considered in this thesis.
Furthermore, previous studies showed that never smokers had a better global health status, physical functioning, and mental health compared to ex-smokers and current smokers [15],

while in this thesis it was observed a difference in social functioning between never smokers and current smokers at FU1, as never smokers reported a higher score. Other studies found an association between abstinence and smoking status with symptom scales such as fatigue, pain, and nausea [16,17], which were not investigated for this thesis.

Although previous studies reported similar results, these were not completely comparable to the results of this thesis because of different measure tools [12], or a different population sample, meaning that they didn't include exclusively BCPs but also other cancer patients [9,15,16].

6.3 Strength and Limitations

Strength. The strengths of this thesis included a large population sample, a longitudinal data with more than 10 years of follow-up. To the author's knowledge, this was one of the largest studies with a random age-matched control group, meaning that it was possible to compare the effect of LSFs on the HRQoL also to a healthy population and avoid interpretation mistakes.
Furthermore, this is the first study to look at multiple LSFs simultaneously including also smoking behaviour and alcohol consumption as determinants of HRQoL.

Limitation. The EORTC QLQ-C30 questionnaire wasn't distributed to the cases and controls at BL nor to controls at FU1, for this reason, the comparison between cases and controls at all time-points and a longitudinal approach were not possible. Furthermore, different questionnaires were used at different time-points, and between cases and controls, meaning that sometimes questions about LSFs were asked differently.
As the follow-ups of the MARIE study were taken in about every 5 years, it was assumed that this time period might be too long, and lifestyle could change over time. Therefore, a cross-sectional design was chosen, which could lead to the impossibility to have a longitudinal study and therefore, a clear cause-effect relationship between the LSFs and HRQoL. Another limitation was the impossibility to compare entirely the results of this thesis to previous studies, as often HRQoL were assessed with different tools.

7. Conclusion

Results from this thesis indicate that the LSFs can determine differently the HRQoL of cases at FU1 and FU2, and controls at FU2. For cases, the effects of LSFs were significant in the first 5 years post-diagnosis, while they lost importance after ≥10 years post-diagnosis. Furthermore, just smoking behaviour influenced differently some subgroups of the HRQoL of cases and controls at FU2, while other LSFs determined the QoL in general without a distinction in the case-control status.

The most important LSF found in this thesis is the transport PA, which influenced the most subscales of HRQoL. Therefore, BCPs should be advised to sufficiently walk and cycle, especially in the first 5 years post-diagnosis.

Although the results in this thesis were mostly comparable to findings of previous studies, further research is needed especially for smoking behaviour and alcohol consumption as the effects of these LSFs on the QoL of BCPs weren't sufficiently studied. Investigation on the symptom scales should also be carried out in order to have a better overview of LSFs as determinants on the entire spectrum of the HRQoL.
Furthermore, the same research method and design could be implemented for future research in other countries on a national or international level as this thesis considers just BCP in Germany, and different cultures could have different lifestyles. In fact, in Germany is very common to walk and ride a bike, while this LSF might not be relevant in other countries.

Researchers and clinicians should be aware of these findings and determinants of QoL in order to develop interventions to support the needs of long-term BCS.

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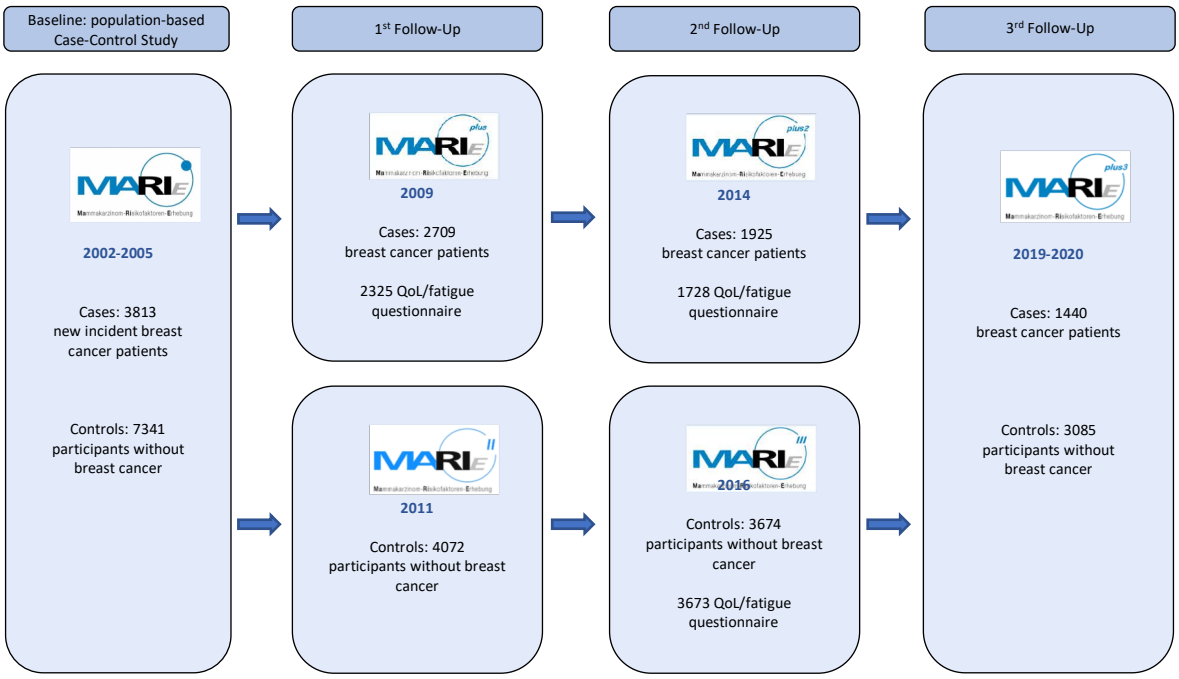
Declaration of Own Work

With my signature, I certify that this Master Thesis has been written by me using only the indicated resources and materials. Where I have presented data and results, the data and results are complete, genuine, and have been obtained by me unless otherwise acknowledged. I further confirm that this Master Thesis is being submitted for the completion of the **Health Sciences (M.Sc.)** study program at the **Hamburg University of Applied Sciences**. It has not been submitted, either in part or as a whole, for any other academic degree at this or another institution.

Place and Date:	Signature:
Milan, 06.12.2021	
	Lisa Ye

Appendix: Timeline of the MARIE Study



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After living 5 years in Germany, I moved back to Italy. I realised how grateful I am for all the people I met and all my experiences. I learned a new language, a new culture, I met many people who inspired me to do better and to become the best version of myself.

I am glad I chose this master study at the HAW Hamburg because here, I discovered my interest in epidemiology thanks to Prof. Dr. Reintjes and his passion for teaching this subject. In fact, some months after the start of my study in Hamburg, I decided to do my internship in the cancer epidemiology field at the UCCH (UKE). I am very happy about this decision because I could work with Prof. Dr. Jenny Chang-Claude and Tabea Maurer, which became my role models not only for being excellent scientists and mentors, but also for being very comprehensive, empathic, and patient with me while I was still learning. Thank you for giving me the opportunity to work and write my master thesis with you!
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