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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The association between muscle fiber typing and physical performance in cachectic and non-cachectic colorectal cancer patients compared to healthy individuals

Amber Louwies
Nathalie Minnekens

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :

Prof. dr. Kenneth VERBOVEN

BEGELEIDER :

Mevrouw Britt VAN DE HATERD

2024
2025

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Acknowledgments

This master's thesis was conducted within the REVAL research group at the Faculty of Rehabilitation Sciences, Hasselt University, as part of the doctoral research project of Dra. Britt van de Haterd. We sincerely thank Dra. Britt van de Haterd for her continuous support, expertise, and guidance throughout this research project. Her constructive feedback and critical insights proved invaluable at every phase of this thesis. We also express our appreciation to our promoter, Prof. Dr. Kenneth Verboven, for his valuable feedback and scientific contributions throughout the research process. The guidance and knowledge they provided were essential in shaping the scientific and academic dimensions of this work.

Furthermore, we extend our gratitude to Prof. Dr. Frank Vandenabeele and the medical staff at Jessa Hospital, specifically the Departments of Medical Oncology and Abdominal Surgery, for their collaboration and assistance during the muscle biopsies and clinical assessments.

Special thanks to all participants for their willingness and trust in contributing to this study.

Lastly, we acknowledge the use of infrastructure and laboratory facilities at REVAL and Jessa Hospital, which provided the necessary resources to complete this project.

Sint-Katelijne-Waver 2860, 2025 N.M.

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Preface

This master's thesis examines skeletal muscle alterations in cancer-related cachexia, which falls within the research domain of muscle, organ, and cell physiology. This cross-sectional study aims to explore the biological and functional consequences of changes in muscle fiber composition in colorectal cancer patients, with or without cachexia, compared to healthy individuals.

Cancer cachexia is a multifactorial syndrome that affects approximately 50% of colorectal cancer patients and is characterized by involuntary weight loss, muscle wasting, and impaired physical performance. This condition has significant implications for treatment outcomes, quality of life, and overall prognosis. Although clinical manifestations are well recognized, the underlying muscle physiology, particularly the role of specific muscle fiber types in physical performance, remains poorly understood.

This research aims to elucidate how disease-induced changes at muscular level translate into functional limitations and how early identification of these changes can inform more effective rehabilitation strategies. The findings are particularly relevant for developing (p)rehabilitation and exercise interventions to preserve muscle mass and function in cancer patients.

This thesis forms part of Dra. Britt van de Haterd's doctoral research, entitled "Tackling cachexia in colorectal cancer patients by unraveling the underlying mechanisms responsible for the loss of skeletal muscle tissue and fat tissue." The study was conducted within the REVAL research group (Faculty of Rehabilitation Sciences, Hasselt University) in collaboration with clinical partners at Jessa Hospital, Hasselt (Medical Oncology and Abdominal Surgery departments). Ethical approval for the study was granted on 15/04/2022, by the Ethical Review Committee of the Jessa Hospital, Hasselt, and the Committee for Medical Ethics of the University of Hasselt (protocol number: 2021/148; clinical trial registration: NCT06780423).

This master's thesis was conducted as a collaborative project by Amber Louwies and Nathalie Minnekens, second-year master's students of Rehabilitation Sciences and Physiotherapy. The research question and the study design were developed in consultation with promoter Prof.

Dr. Kenneth Verboven and Dra. Britt van de Haterd. The literature review and introduction were collaboratively developed by both authors. The methods section was prepared through mutual contributions, with statistical analyses conducted jointly. Nathalie Minnekens took the lead in drafting the results section, which encompassed data visualization, as well as the discussion, conclusion, and abstract paragraphs of the manuscript. All experimental procedures, including participant testing, muscle biopsies, and immunohistochemical analyses, were performed under supervision and in collaboration with the REVAL research team and medical staff at Jessa Hospital.

AI-based language tools were used to assist in refining grammar and clarity. The authors retain full responsibility for all content-related decisions and final formulations.

Abstract

Background: Colorectal Cancer (CRC) is a prevalent condition. Up to 50% of patients develop cancer cachexia (CC), a complex syndrome characterized by muscle wasting and impaired physical function. Cachexia affects skeletal muscle fiber composition, potentially impairing physical performance.

Aim: To examine the relationship between muscle fiber type distribution and physical performance in cachectic and non-cachectic CRC patients, compared to healthy individuals.

Methods: This cross-sectional study involved 62 participants divided into three groups: Cach (n=12), Non-Cach (n=25), and HC (n=25). Physical performance was evaluated using the JAMAR handgrip strength test and the Short Physical Performance Battery (SPPB). Quality of life and physical activity were assessed using the SF-36 questionnaire and the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD). Utilizing immunohistochemistry, muscle biopsies from the m. erector spinae and the m. vastus lateralis were analyzed for fiber type distribution, Cross-Sectional Area (CSA), and Relative Cross-Sectional Area (RCSA).

Results: Cachectic and non-cachectic patients showed significantly lower handgrip strength and SPPB scores compared to HC. Both CRC groups exhibited a higher proportion and RCSA of type II fibers in both muscles compared to HC. SF-36 scores were lower in CRC patients regardless of cachexia status, while PASIPD scores showed no significant group differences.

Conclusion: CRC-related cachexia is associated with impaired physical performance and a shift toward more type II muscle fibers. These findings highlight the importance of early assessment and (p)rehabilitation interventions to counteract muscle wasting and preserve physical functioning.

Keywords: Colorectal cancer, cachexia, physical performance, muscle fiber type, skeletal muscle.

Table of contents

1. Introduction

CRC accounts for 10% of all cancer cases worldwide, making it one of the leading causes of death worldwide (Mattiuzzi & Lippi, 2019). CRC prevalence increases with age, but recently, a notable rise in diagnosis has been observed among individuals under the age of 50. Mortality rates are higher in men than in women, partly due to a lower incidence of CRC among women (Dekker et al., 2019). Multiple risk factors are associated with an increased likelihood of developing CRC, including genetic predisposition, smoking, excessive alcohol consumption, high body weight, red meat consumption, type 2 diabetes, and insufficient intake of vegetables and fruits, as recently reviewed by Dekker et al. (2019). In contrast, physical activity plays a vital role in the prevention and management of various health conditions, including cancer. Regular moderate-intensity activity (30–60 minutes per day) has been shown to significantly reduce the risk of developing CRC (Warburton et al., 2006).

According to Fearon et al. (2011), cancer cachexia (CC) is a complicated illness characterized by a progressive loss of skeletal muscle mass, either alone or in conjunction with fat loss. This poses a significant challenge faced by approximately 50% of CRC patients (Shibata et al., 2020). More specifically, CC is defined as either a weight loss of more than 5% within the last six months or a weight loss of 2%-5% combined with a body mass index (BMI) of <20 kg/m² or decreased muscle mass (Roeland et al., 2020). However, there is no universally accepted diagnostic criterion, as definitions and thresholds may differ between clinical and research settings. Moreover, conventional nutritional therapy has been demonstrated to be insufficient to address the comprehensive reversal of cachexia syndrome, resulting in a spectrum of functional impairments (Fearon et al., 2011). These impairments, at least partly result from muscle mass loss and diminished skeletal muscle function (Mangano et al., 2022), include reduced overall body strength, restricted mobility, and diminished physical activity levels. Furthermore, decreased strength and increased fatigability of the respiratory and limb muscles are characteristics of cancer-associated cachexia. Impaired oxygen uptake, decreased total energy expenditure, and decreased carbohydrate oxidation, all of which are linked to higher rates of fat oxidation, all contribute to this dysfunction (Murphy et al., 2012).

Skeletal muscle tissue consists of three types of muscle fibers besides myofibrils (actin and myosin filaments), sarcolemma and sarcoplasm: type I (slow oxidative) fibers, characterized

by long contraction times and fatigue-resistant motor units important for endurance and postural control; type IIa (fast oxidative glycolytic) fibers, which have more fatigue-resistant motor units; and type IIb (fast glycolytic) fibers, known for short contraction times and quickly fatigued motor units (Bottinelli & Reggiani, 2000; Martin & Freyssenet, 2021). Previous research in patients with diverse types of cancer, such as lung, breast, gastrointestinal, and head-neck cancer, has shown a shift in the distribution of muscle fiber types with a higher proportion of type II fibers compared to healthy controls. Additionally, both patients with and without weight loss show a significant decrease (~20%) in the cross-sectional area (CSA) of both type I (slow) and type IIA (fast) muscle fibers (Toth et al., 2016). Type II (fast) muscle fibers are more prone to atrophy than type I (slow) fibers in cancer-related cachexia, as confirmed by studies in both humans and animals (Martin & Freyssenet, 2021). Indeed, preclinical models using colon cancer cell injections further demonstrated that type I fibers exhibit greater resilience under fasting conditions compared to type II fibers. This differential response underscores the impact of cachexia, which is associated with pronounced atrophy in type II muscle fibers (Song et al., 2024). Interestingly, investigations conducted among individuals with cachexia diagnosed with upper gastrointestinal and pancreatic cancers showed no evidence of selective muscle fiber atrophy (Johns et al., 2014), indicating the existence of inconclusive results in current CC literature. For individuals suffering from CC, the preservation of physical activity emerges as a fundamental strategy to prevent further muscle atrophy and to support the maintenance of muscle tissue composition and function. In this respect, both aerobic exercise and resistance training are essential components of rehabilitation programs designed to counteract muscle wasting in cancer patients (RANJBAR et al., 2019; Stene et al., 2013). Evidence demonstrates that physical exercise during treatment not only helps preserve muscle mass and strength but, in some cases, can even lead to functional improvements (Argilés et al., 2016; Libramento et al., 2025).

The intricate relationship between muscle fiber composition and physical performance remains underexplored, particularly in the context of cachectic versus non-cachectic patients with CRC, when compared to healthy controls. This study seeks to bridge this critical gap in the literature by systematically investigating the influence of variations in muscle fiber typing on physical performance across these distinct populations.

2. Methods

The research question for this study is: “Is muscle fiber typing associated with physical performance in cachectic and non-cachectic colorectal cancer patients compared to healthy individuals?”

2.1. Participants

The participants for the healthy control (HC) group were recruited by researchers from Hasselt University through social media and/or email. Participants had to meet the following inclusion criteria: men and women at least 18 years old, and a body mass index (BMI) between 18 and 30 kg/m². CRC patients were recruited through the Department of Medical Oncology/Limburg Oncology Center and the Department of Abdominal Surgery (Jessa Hospital). The cachectic CRC patients, men and women at least 18 years old, unintentional weight loss of ≥5% in the last six months or unintentional weight loss ≥2% in combination with BMI <20kg/m2 or unintentional weight loss ≥2% and sarcopenia, and a Cachexia Staging Score (CSS) between 5 and 12, were included. The CSS is a screening tool used to assess cachexia in colorectal cancer patients, it’s composed of five components: weight loss over the past six months (score: 0–3), the SARC-F questionnaire on muscle function (score: 0–3), ECOG performance status (score: 0–3), reduced appetite (score: 0–2), and abnormal biochemistry (score: 0–2), with a maximum score of 13. Based on the total score, patients are classified into four stages: non-cachexia (0–2), pre-cachexia (3–4), cachexia (5–8), and refractory cachexia (9–12). The CSS screening tool is added in the appendix (Appendix 1). The non-cachectic CRC patients, men and women at least 18 years old, unintentional weight loss <2% or unintentional weight loss 2-5% but BMI >20kg/m2 and no sarcopenia, and a Cachexia Staging Score (CSS) between 0 and 2, were included. Both CRC patients and HC participants were excluded if they had a severe mental or psychiatric disorder, insufficient proficiency in the Dutch language, neuromuscular disorders affecting the spine and lower extremities, or bedridden status.

The study included 25 healthy participants, 12 cachectic, and 25 non-cachectic patients.

2.2. Procedure

The healthy participants were recruited by researchers from Hasselt University through professional social media and/or email. They were invited to attend a single testing session at the REVAL research center (Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek).

Participants were instructed to avoid engaging in intense physical activities for three days before the procedure. The inclusion and exclusion criteria were re-evaluated upon arrival, and informed consent was obtained.

Next, the HC participants' physical performance was assessed using the Short Physical Performance Battery (SPPB) and the handgrip strength test (JAMAR). Following this, the physician arrived to perform the biopsy procedure on the m. Erector Spinae (ES) and m. Vastus Lateralis (VL). Finally, participants completed the questionnaires, including the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) and the Short Form-36 (SF-36). This session, lasting approximately one hour, involved the collection of various measurements, which are further detailed in the following sections.

The recruitment of CRC patients was conducted through the Department of Medical Oncology, the Limburg Oncology Center (Jessa Hospital), and the Department of Abdominal Surgery (Jessa Hospital). Medical doctors from both the Department of Oncology and the Department of Abdominal Surgery at Jessa Hospital provided potential participants with detailed information about the study, along with the informed consent form. Patients who were interested in participating were contacted by the principal investigator, Dra. Britt van de Haterd, a researcher from Hasselt University. These patients were invited for a screening appointment to review the inclusion and exclusion criteria. During this appointment, participants also received an information brochure and had the opportunity to ask questions. Patients who signed and returned the informed consent form within seven working days were enrolled in the study. Dra. Britt van de Haterd collected the signed consent forms regularly. Participants retained the right to withdraw from the study at any time. The physical performance of CRC patients was assessed using the Short Physical Performance Battery (SPPB) and the handgrip strength test (JAMAR). Muscle biopsies for the non-cachectic CRC patients were obtained by an abdominal surgeon in the operating room at Jessa Hospital

under general anesthesia. For patients with cachexia-related CRC, the muscle biopsy procedure was conducted at the REVAL research center. Additionally, participants completed the questionnaires, including the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) and the Short Form-36 (SF-36).

2.2.1. Short Physical Performance Battery (SPPB)

This test assesses individuals' physical performance (Beaudart et al., 2019) and consists of three subcomponents: balance, gait speed, and lower limb strength. The balance assessment requires participants to maintain three progressively challenging stances for 10 seconds each: feet together, one foot partially forward, and one foot fully forward. Gait speed is measured by timing a four-meter walk at a normal pace, with the best time from two trials recorded. Lower limb strength is evaluated using a sit-to-stand test, where participants cross their arms over their chest and rise from a seated position to stand as quickly as possible, repeating the movement five times. If the patient is unable to rise from a seated to a standing position once successfully, this part of the assessment is discontinued. Each subcomponent is scored individually, and the total score, ranging from 0 to 12, is calculated by summing these individual scores. Based on the total score, individuals are classified into one of three risk categories: severe limitations (0–3), high risk (4–9), and low risk (10–12). The SPPB protocol is added in the appendix (Appendix 2).

2.2.2. Muscle biopsy

Participants were prone for the biopsy of the ES. Before performing the biopsy sampling, the puncture site was determined for each subject using ultrasound guidance to identify the correct spinal level, measure the distance from the spinous process to the puncture site (intramuscular septum), and assess the thickness of the skin and subcutaneous tissue (depth to the fascia) based on anatomical landmarks. Following this step, the biopsies were conducted without continuous ultrasound guidance. The skin and surrounding area were anesthetized subcutaneously with 5 mL of 1% xylocaine (5cc superficial and 1cc deep) after applying povidone-iodine to the skin and fascia of the participant’s back. Participants were then asked to wait for ten minutes to allow the anesthesia to take full effect. A tiny cut, about 2-3 mm long, was made where the coaxial biopsy needle would enter the body. The thoracolumbar fascia (TLF) was then penetrated by inserting the coaxial needle through the

incision perpendicularly. By acting as a steady guide for the biopsy needle, this needle made it possible to take muscle samples from the ES without making additional skin punctures.

For the biopsy procedure, the 'Bard Mission®' biopsy needle (14G, 100mm) with serial number B243201941492 was used. The biopsy needle was inserted into the biopsy device and guided through the coaxial needle. To obtain a sample from the ES muscle, the needle was angled laterally at 35° from the perpendicular position, and the trigger mechanism was activated to extract the tissue. The biopsy was repeated three times while maintaining the coaxial needle in its original position.

For the VL procedure, the patient was positioned in supine with a knee roll placed under the knees. The puncture site was determined using palpation. The rest of the procedure, which included anesthetizing the muscle, inserting the biopsy needles, and collecting the sample, matched with the procedure of the ES.

After the biopsies were completed, the coaxial needle was removed, and the puncture site was treated with steri strips and a post-operative bandage for the ES. They used sterile strips, a post-operative bandage, and a compression bandage for the VL. To stop intramuscular bleeding, the area was subjected to firm pressure for five minutes. If the biopsy is performed at REVAL, participants are asked to wait for 30 minutes after the procedure to avoid potential side effects that may arise from the local anesthesia. A sterile needle was used to carefully remove the extracted muscle samples from the biopsy needle, they were then mounted on cork for orientation. After being embedded in a compound known as "tissue-tek®," which has an ideal cutting temperature, they were instantly frozen in isopentane that had been cooled in liquid nitrogen. Before being prepared for analysis, the frozen samples were kept at -80°C. Immediately after the biopsy and one day afterward, the pain was assessed using the VAS score. This scale ranging from 0-10 represents the degree of pain. Zero means no pain, while ten means the worst pain you can imagine (Agten et al., 2018).

2.2.3. Immunohistochemistry

After the muscle biopsies were collected from the patients and the samples were frozen at -80°C, they were further analyzed using muscle staining. The samples are retrieved from the -80°C freezer and air-dried at room temperature for 30 minutes. Subsequently, the slides are fixed in acetone for 5 minutes using a designated container filled with acetone, in which the slides are placed into the provided slots. After fixation, the slides are air-dried again at room temperature for 15 minutes. The biopsies on the slides are then encircled with a DAKO pen. Thereafter, the slides are incubated with CD31 in a 0.1% Tw/PBS solution for 45 minutes. Following this incubation, the slides are rinsed three times for 5 minutes with PBS using a designated container filled with PBS, ensuring proper placement of the slides in the slots. Subsequently, the slides are incubated with HAM biotin in 0.1% Tw/PBS for 45 minutes, followed by another three rinses with PBS, each lasting 5 minutes. The slides are then incubated with avidin Texas Red, BA-F8, and anti-laminin in 0.1% Tw/PBS for 45 minutes, after which they are rinsed three times for 5 minutes with PBS. Afterward, the slides are incubated with DAPI, GAMIgG2b 488, and GARIgG 647 in 0.1% Tw/PBS for 30 minutes, followed by a final rinsing step, in which the slides are washed three times for 5 minutes with PBS. Finally, the slides are mounted.

The following dilution factors were applied when preparing the solutions: CD31 1:50, BA-F8 1:50, Anti-laminin 1:50, HAM Biotin mouse 1:200, Avidin Texas Red 1:400, Alexa Fluor 488 1:400, Alexa Fluor 647 1:400, and DAPI 1:333. To prepare the solution 0.1% Tw/PBS, 1 ml of Tween-20 is dissolved in 800 ml of 1× PBS and mixed thoroughly by gently tilting the container, after which the volume is adjusted to 1 L with 1× PBS. Since Tween-20 is highly viscous, it should be pipetted slowly to ensure accurate measurement. A total of 60µl of liquid (solution) was pipetted onto each biopsy.

Following the immunohistochemical analysis, muscle fibers were analyzed using the Smash program, a software platform designed for the quantitative assessment of several key metrics, including Cross-Sectional Area (CSA), Relative Cross-Sectional Area (RCSA), and the muscle fiber distribution of Type I and Type II muscle fibers.

2.2.4. Hand dynamometry JAMAR

This device is used to assess the isometric muscle strength of various muscle groups. The patient is told to hold the device in their preferred hand while sitting in a straight-backed chair with their feet flat on the floor, their elbow flexed at a 90° angle, their shoulder adducted and neutrally rotated, and their forearm and wrist in a neutral position supported on a table. The patient is instructed to exert maximum force by squeezing the device for three seconds. The patients were all verbally encouraged. The test is performed three times, and the highest recorded value (expressed in kilograms) is compared to established normative data (Roberts et al., 2011).

2.2.5. SF-36 Health Condition Questionnaire

This questionnaire evaluates the patient's self-perceived health status, providing insight into their ability to perform daily activities. It comprises 36 items, organized into the following subcategories: Physical Functioning (10 items), Role Limitations due to Physical Problems (4 items), Role Limitations due to Emotional Problems (3 items), Energy/Fatigue (4 items), Emotional well-being (5 items), Social Functioning (2 items), Pain (2 items), General Health Perception (5 items), and Health Change (1 item). The item responses are aggregated into subscale scores and subsequently transformed into a standardized 100-point scale. Better perceived health status is indicated by higher scores (Brazier et al., 1992). The questionnaire is added to the appendix (Appendix 3).

2.2.6. Physical Activity Scale for Individuals with Physical Disabilities Questionnaire (PASIPD)

Participants' weekly frequency (number of days per week) and duration (hours per day) of work, home, and leisure activities are evaluated by the questionnaire. A 4-point Likert scale, with 1 denoting never and 4 denoting frequently, is used to rate responses about frequency. A scale from 1 (less than one hour per day) to 4 (more than four hours per day) is used to measure duration. The average number of hours per day for each item is multiplied by a metabolic equivalent (MET) value that corresponds to the activity's intensity, the results are added together to create the score. The scores range from 0 (no activity) to >100 METS hours per day (very high). The questionnaire is added to the appendix (Appendix 4).

2.3. Data analysis

The statistical analysis was conducted using SAS JMP Pro version 17 software. Given the presence of continuous data with more than two groups (HC, Cachectic, Non-cachectic) and one X-variable with more than two levels, the normality of each group was assessed using the Shapiro-Wilk test, while homoscedasticity was evaluated through the Brown-Forsythe test. For the SPPB, PASIPD, and the SF-36 (which includes the subscales: Physical Functioning, Role Limitations Due to Physical Health, Role Limitations Due to Emotional Problems, Emotional Well-Being, Social Functioning, Pain, Health Change, and Total), the data were not normally distributed, but the homoscedasticity was confirmed. To analyze the differences between paired observations, a non-parametric test, specifically the Wilcoxon each-pair test, was conducted.

If the data were normally distributed and homoscedasticity was confirmed, one-way ANOVA was used. To determine the specific groups between which significant differences exist, the Student's t-test is employed as a post hoc analysis. This was the case for the following tests: Jamar and SF-36 (which includes the subscales: Energy/fatigue and General health).

For muscle biopsy data (VL and ES), which involved continuous data with more than two groups and two X-variables (group and muscle fiber type), the normality of each group was assessed using the Shapiro-Wilk test, while homoscedasticity was evaluated through the Brown-Forsythe test. The results indicated that both assumptions of normality and homoscedasticity were satisfactorily met. Consequently, a two-way mixed ANOVA was conducted to investigate the effects of the independent variables on the dependent variable under consideration. In our study, we conducted distinct analyses for each dependent variable (CSA, RCSA, and percentage) to evaluate the effects of group, fiber type, and their interaction. This method effectively controls potential cross-reactivity among the groups and acknowledges that both fiber types (type I and type II) are derived from the same patient, thus permitting a more nuanced understanding of the underlying biological interactions. Following this, we employed a multiple comparison analysis, with cross-reactivity treated as the primary effect of interest. To comprehensively assess the differences, all pairwise comparisons were executed utilizing Student's t-tests, ensuring a robust statistical framework for our findings.

The significance level was established at 5% ($p \leq .05$), and a confidence interval of 95% for all statistical analyses conducted in this study. Figure 1 illustrates the Decision flowchart for Statistical Analysis of Data.

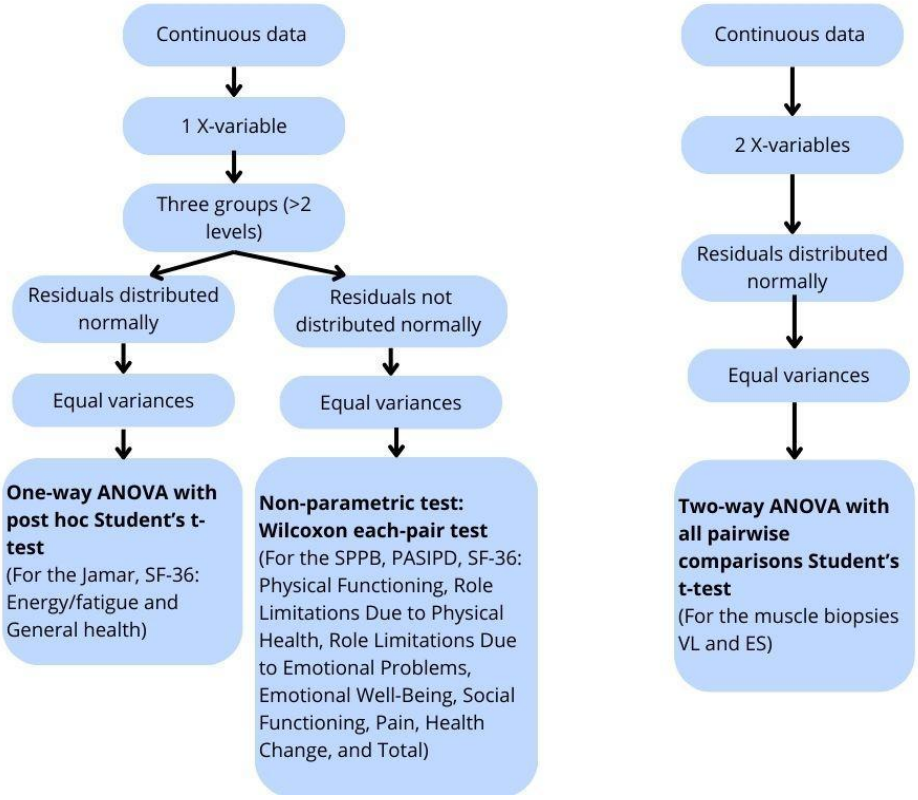

Figure 1: Decision flowchart for Statistical Analysis of Data. SF-36; SF-36 Health Condition Questionnaire, SPPB: Short Physical Performance Battery; PASIPD, Physical Activity Scale for Individuals with Physical Disabilities; VL, Vastus Lateralis; ES, Erector Spinae.

3. Results

3.1 Patient characteristics

Table 1 shows the overall characteristics of the study patients, comprising 25 HC, 12 CRC with CC (Cachectic (Cach) group), and 25 CRC without CC (Non-Cachectic (Non-Cach) group). The majority of participants in each group were male (HC: 72%, Cach: 41,7%, and Non-Cach: 72%). All three groups had a similar age and BMI (Table 1). An overview of detailed, individual patient characteristics is added in the appendix (Appendix 5).

Table 1

Patient characteristics

Table 1: Anthropometric data. Values are presented as mean ± SD or number only.

	Cachectic (n= 12)	Non-Cachectic (n= 25)	Healthy controls (n= 25)	P_{anova}
Age (years)	66 ± 15	66 ± 13	66 ±10	0.9879
Gender (male: female)	5:7	18:7	18:7	0.1416
Weight (kg)	75.6 ± 16.1	82.7 ± 15.2	78.8 ± 11.5	0.3213
Length (m)	1.71 ± 0.07	1.76 ± 0.08	1.73 ± 0.07	0.1041
Body mass index (kg/m2)	25.9 ± 5.1	26.5 ± 3.5	26.2 ± 2.6	0.8873
Cachexia staging score	6 ± 1	1 ± 1	/	<.0001

Note. Kg; kilogram, m; meter; m^2, square meters.

3.2 Functional tests

3.2.1. JAMAR

Handgrip strength (isometric muscle strength) was significantly decreased for Cach compared to HC (p=0.008) and Non-Cach (p=0.011). However, no significant difference in isometric handgrip strength was observed between HC and Non-Cach (p=0.885) (Figure 2).

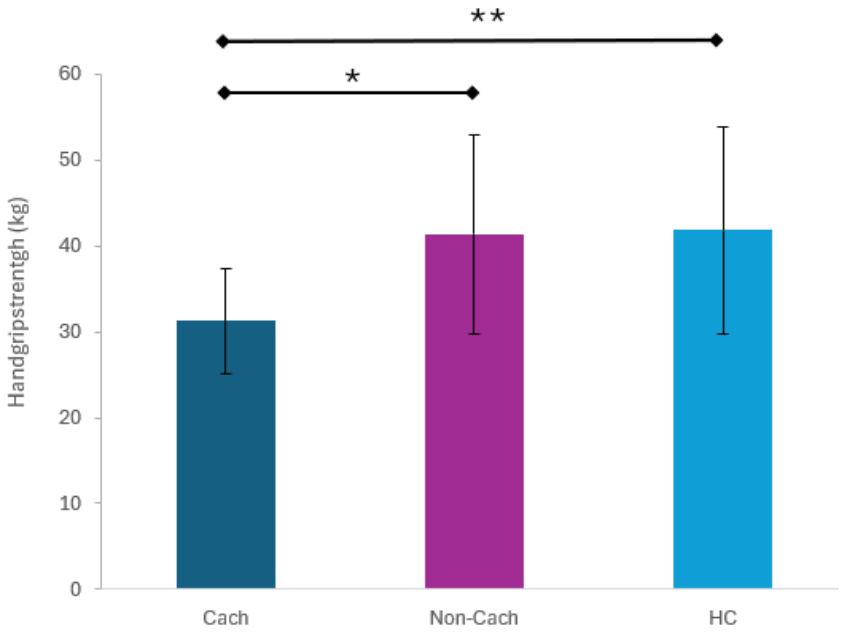

Figure 2: Handgrip strength (kg) measured by JAMAR hand dynamometry across three groups: cachectic CRC patients (Cach, n=12), non-cachectic CRC patients (Non-Cach, n=24), and healthy controls (HC, n=24). The graph shows group means ± SD. *p<0.05, **p<0.01. Kg, Kilogram; Cach, Cachexia; Non-Cach, Non-Cachexia; HC, Healthy Control; SD, standard deviation.

3.2.2. SPPB

Findings from the SPPB demonstrate that HC achieved a significantly higher score compared to Cach (p=0.0007) and Non-Cach (p=0.014), the latter two not differing in SPPB score (p=0.126) (Figure 3).

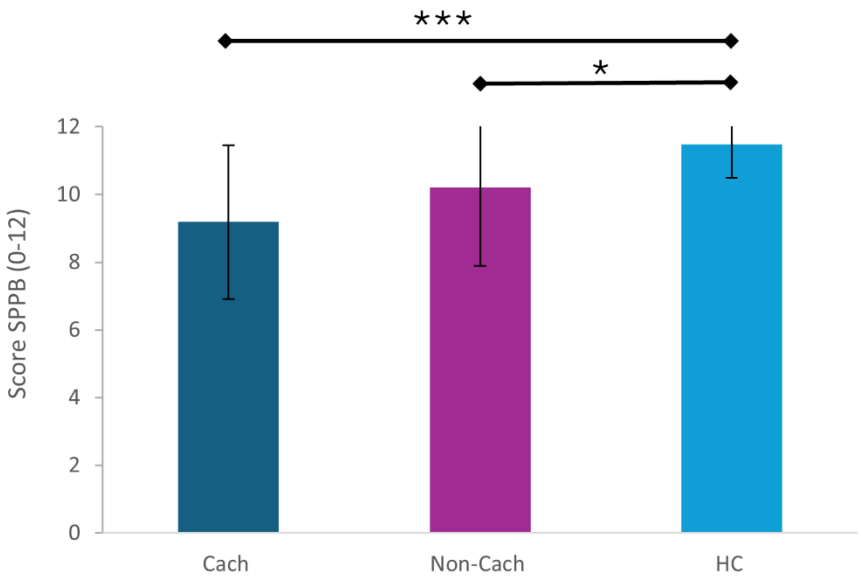

Figure 3: Assessment of physical performance using the total SPPB score (0-12) across three groups: cachectic CRC patients (Cach, n=11), non-cachectic CRC patients (Non-Cach, n=25), and healthy controls (HC, n=21). The graph shows group means ± SD. *p<0.05, ***p<0.001. SPPB, Short Physical Performance Battery; Cach, Cachexia; Non-Cach, Non-Cachexia; HC, Healthy Control; SD, Standard deviation.

3.3 Microscopic skeletal muscle characteristics

3.3.1. Erector Spinae

The analysis for the CSA reveals no statistically significant differences in the mean CSA (µm²) among the three groups when assessed for each muscle fiber type (Fig. 4A). Further statistical analysis of muscle fiber distribution indicates a significantly higher proportion of type I muscle fibers in HC compared to Cach (p=0.007) and Non-Cach (p=0.0003). Conversely, muscle fiber distribution of type II muscle fibers was significantly lower in HC compared to Cach (p=0.007) and Non-Cach (p=0.0003) (Fig. 4B). Moreover, the analysis of RCSA illustrates a statistically significant difference in the RCSA of type I muscle fibers, with HC exhibiting a higher RCSA compared to Cach (p=0.011) and Non-Cach (p=0.0006). Additionally, a significant difference is noted in the RCSA of type II muscle fibers, where HC demonstrates a significantly lower RCSA relative to both Cach (p=0.011) and Non-Cach (p=0.0006) (Fig. 4C).

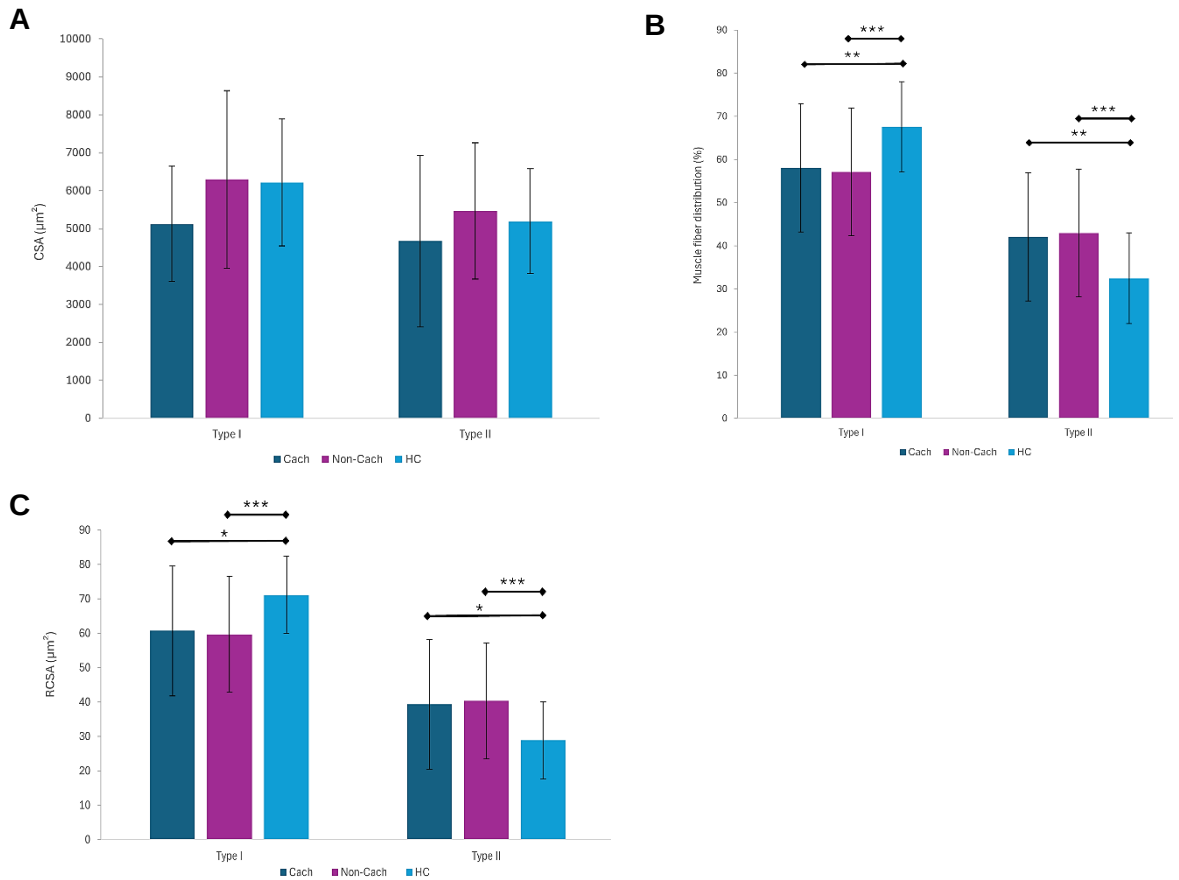

Figure 4: Microscopic skeletal muscle characteristics in the m. erector spinae. The panels describe: CSA **(A),** muscle fiber distribution **(B),** and RCSA **(C)** across three groups: cachectic CRC patients (Cach, n=10), non-cachectic CRC patients (Non-Cach, n=20), and healthy controls (HC, n=24). The graph shows group means ± SD. *p<0.05, **p<0.01, ***p<0.001. CSA, Cross-Sectional Area; RCSA, Relative Cross-Sectional Area; Cach, Cachexia; Non-Cach, Non-Cachexia; HC, Healthy Control; SD, standard deviation.

3.3.2. Vastus Lateralis

With respect to vastus lateralis muscle, it was observed that the type II specific CSA in Cach is significantly reduced when compared to both Non-Cach (p=0.02) and HC (p=0.0007). No statistically significant differences were detected among the groups for type I muscle fibers (Fig. 5A). Furthermore, a significant increase in the muscle fiber distribution towards more type I muscle fibers was observed in HC when compared to both Cach (p=0.006) and Non-Cach (p=0.005). Conversely, the muscle fiber distribution also showed a decrease in type II muscle fibers in HC relative to Cach (p=0.006) and Non-Cach (p=0.005) (Fig. 5B). Regarding RCSA, the analysis indicated a significant increase in RCSA for type I muscle fibers within the HC compared to Non-Cach (p=0.008). Conversely, type II muscle fibers demonstrate a markedly lower RCSA within HC relative to Non-Cach (p=0.008). Notably, the data reveals no significant differences in the RCSA for the Cach group compared to the other two groups (Fig. 5C).

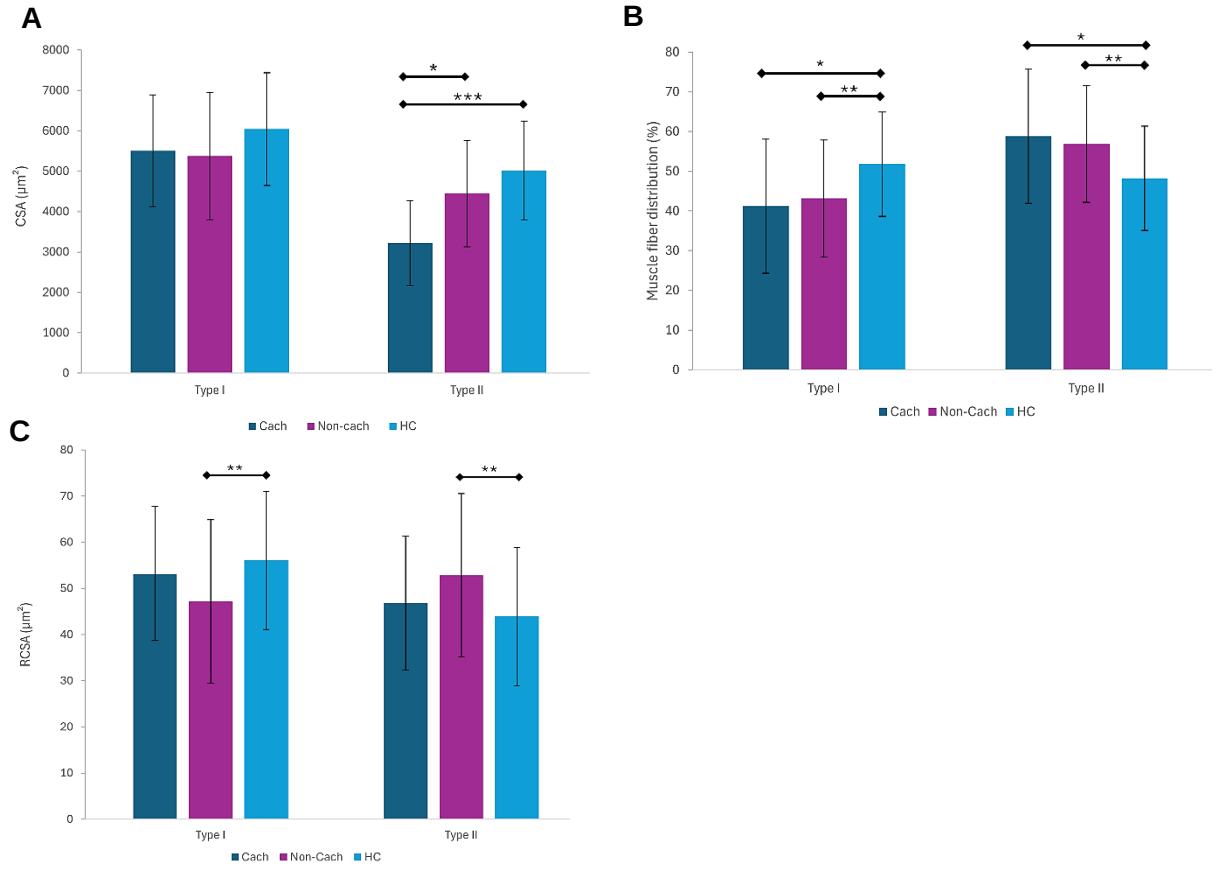

Figure 5: Microscopic skeletal muscle characteristics in the m. vastus lateralis. The panels describe: CSA **(A),** muscle fiber distribution **(B),** and RCSA **(C)** across three groups: cachectic CRC patients (Cach, n=10), non-cachectic CRC patients (Non-Cach, n=22), and healthy controls (HC, n=25). The graph shows group means ± SD. *p<0.05, **p<0.01, ***p<0.001. CSA, Cross-Sectional Area; RCSA, Relative Cross-Sectional Area; Cach, Cachexia; Non-Cach, Non-Cachexia; HC, Healthy Control; SD, standard deviation.

3.4 Questionnaires

3.4.1. SF-36

The total SF-36 score was significantly higher for HC when compared to both Cach (p=0.003) and Non-Cach (p=0.013) (Fig. 6A). Furthermore, Cach scored significantly lower on "Physical functioning" (p=0.035), "Role limitations due to physical health" (p=0.007), "Role limitations due to emotional problems" (p=0.006), "Energy/fatigue" (p=0.033), "Health change" (p=0.0004) subscores compared to HC. Conversely, no significant differences between the groups were detected in the domains "Emotional well-being," "Social functioning," "Pain," and "General health" (Fig. 6B).

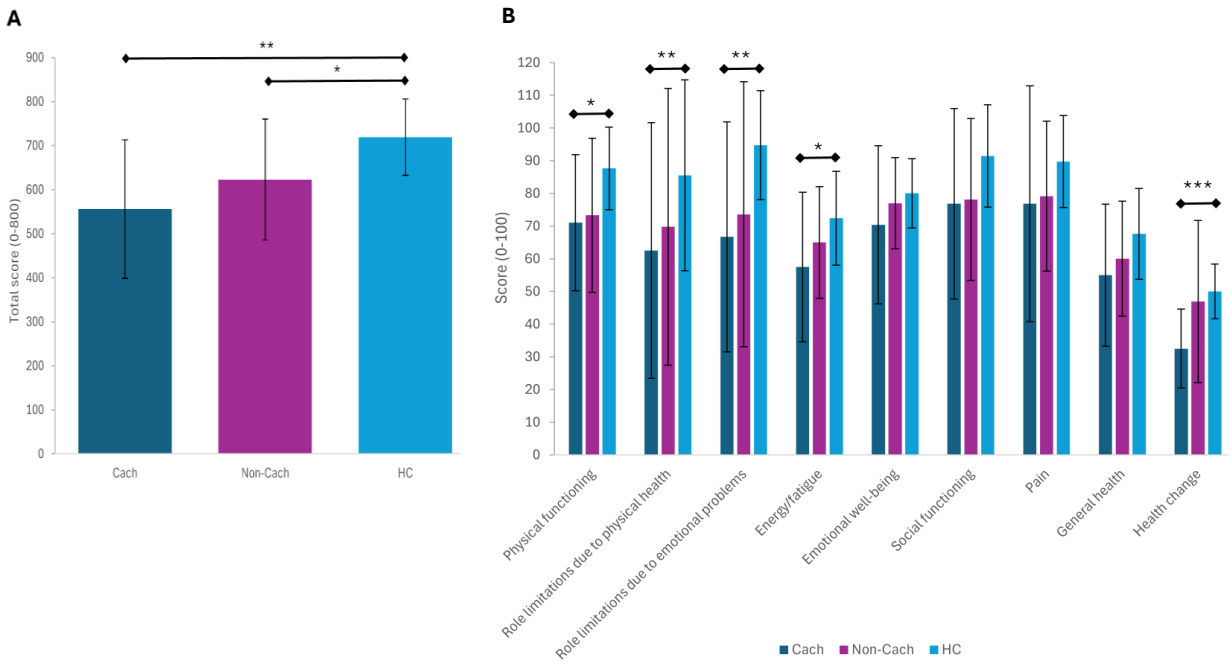

Figure 6: Assessment of health-related quality of life using SF-36. The panels describe: Total score **(A)** and score for each subcategory **(B)** across three groups: cachectic CRC patients (Cach, n=10), non-cachectic CRC patients (Non-Cach, n=24), and healthy controls (HC, n=19). The graph shows group means ± SD. *p<0.05, **p<0.01, ***p<0.001. Cach, Cachexia; Non-Cach, Non-Cachexia; HC, Healthy Control; SD, standard deviation.

3.4.2. PASIPD

The analysis from the PASIPD questionnaire indicated no significant differences in the levels of physical activity among the three groups (Figure 7).

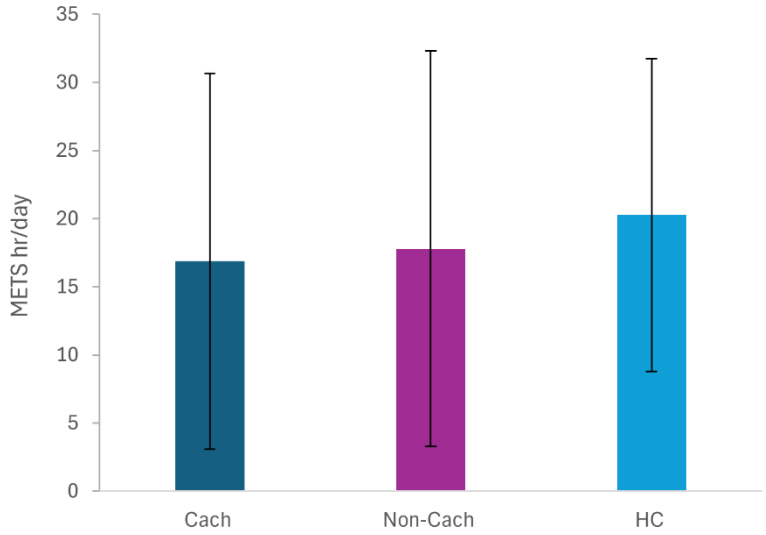

Figure 7: Comparison of physical activity level (METs-hours/day) across three groups: cachectic CRC patients (Cach, n=12), non-cachectic CRC patients (Non-Cach, n=24), and healthy controls (HC, n=25). The graph shows group means ± SD. PASIPD, Physical Activity Scale for Individuals with Physical Disabilities; METs, Metabolic equivalents; Cach, Cachexia; Non-Cach, Non-Cachexia; HC, Healthy Control; SD, standard deviation.

4. Discussion

The study's findings support the initial hypothesis positing that CC is associated with impaired physical performance and microscopic alterations in muscle morphology in patients with CRC. Specifically, cachectic CRC patients had significantly lower isometric muscle strength when compared to both HC and Non-Cach CRC patients. This observation aligns with the loss of skeletal muscle mass observed in cancer cachexia, as described in the literature (Fearon et al., 2011; Setiawan et al., 2023). Interestingly, this study found no significant difference in handgrip strength between the Cach and Non-Cach patients, however, a statistically significant difference was observed between cancer patients and healthy controls (Murphy et al., 2012). This contrasts with previous studies that identified reduced grip strength as a hallmark of cachexia, reporting a 7% to 31% lower handgrip force in cachectic cancer patients compared to non-cachectic individuals (Martin & Freyssenet, 2021). Moreover, the observed decline in physical performance was corroborated by the SPPB scores, where Cach patients scored significantly lower than HC patients, while no significant difference was observed between Cach and Non-Cach patients. These findings suggest that cancer patients, regardless of cachexia status, exhibit impairments in various aspects, such as impairments in balance, gait speed, and lower limb strength compared to healthy individuals, underscoring the overall impact of cancer on physical performance.

Muscle biopsy analysis of the ES and VL muscles revealed that cachectic CRC patients exhibited an altered muscle fiber distribution, corresponding to a lower type I muscle fiber number compared to the HC group. This observable shift toward a predominance of type II muscle fibers in individuals experiencing cachexia may be associated with diminished muscle endurance and overall functional capacity, as outlined by Bottinelli & Reggiani (2000). Furthermore, a significant reduction in the CSA of type II muscle fibers was observed in the VL muscle of cachectic individuals, indicating muscle fiber atrophy. This finding aligns with the established understanding that CC leads to muscle mass degradation affecting both type I and type II muscle fibers, with type II muscle fibers often being more susceptible to atrophy (Fearon et al., 2011; Martin & Freyssenet, 2021; Toth et al., 2016).

Moreover, results derived from the SF-36 health questionnaire indicate that Cach patients exhibited significantly lower scores across several domains. Notably, both Cach and Non-Cach

patients exhibited significantly lower total SF-36 scores compared to HC. This can indicate that cancer itself, irrespective of cachexia status, adversely affects their ability to perform daily activities (Murphy et al., 2012). The absence of significant differences in PASIPD scores, which are based on subjective self-reports, contrasts with the objectively measured impairments observed in the SPPB and JAMAR tests. This discrepancy is in line with previous studies that have noted a lack of agreement between self-reported and objectively measured physical activity in adults (Prince et al., 2008). This may be attributed to the limitations inherent in self-reported physical activity measures, which are subjective outcome measures prone to recall bias and overestimation (Douma et al., 2020; Teh et al., 2023).

The results of this study suggest meaningful implications for clinical practice. It emphasizes the importance of early identification of muscle strength and physical performance as clinical parameters. Tests, such as histological fiber analysis and dynamic strength assessments, may offer added value in evaluating cachexia and physical vulnerability. These findings also support the clinical potential of targeted exercise interventions, particularly strength training. Structured physical training programs have been demonstrated to improve physical function, enhance quality of life, and lessen cancer-related fatigue in the context of cancer rehabilitation, both during and after treatment (Schmitz et al., 2010). Additionally, prehabilitation before starting cancer treatment may be a valuable approach to minimize complications, support better physical and psychological outcomes, and expand treatment options (Silver & Baima, 2013). The observed relationship between physical performance and muscle fiber type suggests that clinicians should consider the shift toward more fatigable and less efficient type II muscle fibers within cachectic CRC patients when developing therapeutic interventions, by adapting training intensity and duration to prevent early exhaustion and promote muscular endurance. In this context, exercise represents a strong potential as a non-pharmacological intervention for managing conditions that cause muscle wasting (Hardee et al., 2019).

This study possesses several strengths that improve the scientific integrity of its findings. One of the primary strengths is the inclusion of three distinct comparison groups: Cach, Non-Cach, and HC. This allows for a more thorough comparison and a better interpretation of the differences between these conditions. The study benefits from using various assessment

methods, integrating objective physical performance tests (such as the SPPB, JAMAR and histological analysis of muscle biopsies) with self-report questionnaires like the SF-36 and PASIPD. This approach allows for a more comprehensive evaluation of functioning. All measurement tools utilized in this study are well-established instruments recognized for their proven reliability and validity in both clinical and research settings (Beaudart et al., 2019; Brazier et al., 1992; van der Ploeg et al., 2007; Ward & Adams, 2007).

There are a few biases that can have influenced the results of this study. First, HC patients were recruited through researchers from Hasselt University. These participants were contacted through email and social media. This recruitment may have favored individuals who are more health-conscious or physically active, potentially contributing to an overestimation of the differences in physical performance between the HC group and CRC patients. Consequently, the observed performance gap, particularly in SPPB and JAMAR scores, may reflect baseline fitness differences rather than disease-related changes alone. Second, information and measurement bias could have compromised the reliability of the data. Self-reported measures such as the SF-36 and PASIPD are sensitive to recall bias and social desirability, especially in older or chronically ill populations (Teh et al., 2023). This could have led to either an overestimation or an underestimation of perceived physical functioning and activity levels. Third, residual confounding factors could not be entirely controlled within the study design. Factors such as pre-diagnosis levels of physical activity, medication use, comorbidities, nutritional status, and ongoing or past chemotherapy may have substantially affected muscle fiber composition and overall physical performance (Staxen et al., 2024). Moreover, the overall sample size, particularly in the cachectic group (n = 12), was relatively small, which reduces the statistical power and raises the possibility of type II error. Additionally, the variability in the number of participants across different tests and outcome measures may lead to inconsistencies in comparison and increase interpretive bias. Another factor to consider is the age of the participants. With an average age ranging from 65 to 70 years, this group is relatively older, which suggests that age-related changes in muscle could influence fiber composition and physical performance assessments (Lexell, 1995; Tieland et al., 2018). Lastly, the sample included an overrepresentation of male participants across all groups, ranging from 58% to 68%. This disparity may impact the observed muscle characteristics and functional outcomes, which could limit the generalizability of the findings

to female CRC patients. Research indicates that there is a difference in muscle fiber distribution between men and women in healthy individuals. Specifically, women tend to have a higher amount of type I muscle fibers, while men usually possess more type II fibers (Haizlip et al., 2015). Furthermore, the analysis focused exclusively on morphological characteristics in two muscles: the m. erector spinae and the m. vastus lateralis. It did not include assessments of muscle quality or metabolic function. It is important to note that these muscles have significantly different functions. The m. erector spinae primarily serve to maintain posture and stability in the trunk, while the m. vastus lateralis is involved in dynamic movements of the lower limbs, such as walking and rising from a chair (Vandenabeele & Agten, 2020).

Future research should replicate these findings using larger and more varied clinical samples while ensuring sufficient clinical homogeneity for meaningful interpretation. To gain a better understanding of the progression and underlying mechanisms, longitudinal studies are necessary to monitor changes in muscle fiber type and functional decline over time, especially in relation to disease progression or exercise interventions. Since the current study's cross-sectional design does not allow for causal conclusions, such longitudinal studies are essential to determine whether changes in fiber type lead to reduced performance, if reduced performance influences fiber type, or if both are affected by an unmeasured third factor. Additionally, randomized controlled trials could explore the effectiveness of personalized (p)rehabilitation programs in improving muscle structure and enhancing the quality of life in this population.

5. Conclusion

This study shows that CC in CRC is characterized by a change in the composition of muscle fibers, specifically a decrease in type I muscle fibers and an increase in type II muscle fibers, which leads to a reduction in physical performance. Both Cach and Non-Cach CRC patients exhibit lower functional test scores, and self-reported health outcomes compared to HC, reflecting the adverse effects of cancer on physical performance. The significance of muscular weakness and the need for customized exercise interventions are highlighted by these observations. Incorporating a combination of aerobic and resistance training within cancer prehabilitation programs is essential to prevent muscle loss and enhance physical performance in this patient population.

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7. Appendices

Appendix 1: CSS staging tool

Screening colorectale kankerpatiënten

Structurele karakteristieken van de romp en beenspieren bij colorectale kankerpatiënten met cachexie

In opdracht van Universiteit Hasselt, Martelarenlaan 42, 3500 Hasselt

REVAL - Rehabilitation en research center, Agoralaan gebouw A, 3590 Diepenbeek
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Ethische Toetsingscommissie Jessa Ziekenhuis
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Lokale hoofdonderzoeker (Jessa Ziekenhuis):
Prof. dr. Jeroen Mebis

Lokale onderzoekers (UHasselt) dra. Britt van de Haterd dr. Anouk Agten Prof. dr. Kenneth Verboven

Scoringstabel

Screening van de colorectale kankerpatiënten om deel te nemen aan de studie gebeurd door de lokale onderzoeker aan de hand van de 'cachexia staging score' (CSS). De totale score hiervan moet tussen de vijf en acht zijn om deel te nemen aan de studie.

Metingen	Waarde	Score
Gewichtsverlies in 6 maanden	Gewicht stabiel of gewicht vermeerderd	0
	Gewichtsverlies ≤5%	1
	Gewichtsverlies ≥5% en ≤15%	2
	Gewichtsverlies ≥15%	3
SARC-F	0	0
	1-3	1
	4-6	2
	7-10	3
ECOG PS	0	0
	1-2	1
	3-4	2
Verminderde eetlust	0-3	0
	4-6	1
	7-10	2
Abnormale biochemie (WBC>$10*10^9$/L; Alb < 35 g/L; Hb < 120/110 g/L)	Allemaal abnormaal	0
	Eén van de drie abnormaal	1
	Meer dan één abnormaal	2

Alb, albumine, ECOG PS, 'Eastern cooperative oncology group performance status'; Hb, hemoglobine; WBC, witte bloedcellen;

Totale score

- 0-2: niet cachectic
- 3-4: pré cachectic
- 5-8: cachectic
- 9-12: hardnekkig cachectic

1. Gewichtsverlies in 6 maanden

Duidt aan wat past:

Gewicht stabiel of gewicht vermeerderd	0
Gewichtsverlies ≤5%	1
Gewichtsverlies ≥5% en ≤15%	2
Gewichtsverlies ≥15%	3

2. SARC-F vragenlijst

Duidt aan wat past:

Sterkte: Hoe moeilijk heeft u het om een zak van 5kg omhoog te tillen, en rond te dragen?
a. Gemakkelijk = 0
b. Beetje moeilijk = 1
c. Heel moeilijk of is onmogelijk = 2

Hulp bij wandelen: Hoe moeilijk heeft u het om door een lokaal te wandelen?
a. Gemakkelijk = 0
b. Beetje moeilijk = 1
c. Heel moeilijk of is onmogelijk = 2

Opstaan uit een stoel: Hoe moeilijk heeft u het om te verplaatsen uit een stoel of bed?
a. Gemakkelijk = 0
b. Beetje moeilijk = 1
c. Heel moeilijk of is onmogelijk = 2

Trappenlopen: Hoe moeilijk heeft u het om tien trappen te doen?
a. Gemakkelijk = 0
b. Beetje moeilijk = 1
c. Heel moeilijk of is onmogelijk = 2

Vallen: Hoe vaak bent u gevallen in het laatste jaar?
a: Niet = 0
b. 1-3 keer = 1
c. 4 keer of meer = 2

Totale score

0	0
1-3	1
4-6	2
7-10	3

3. ECOG PS

Duidt aan wat past:

0 = volledig actief, nog in staat om al de activiteiten te voltooien zoals voor de ziekte

1 = beperkt in fysiek inspannende activiteiten, maar ambulant en in staat om licht of zittend werk uit te voeren bijv. licht huishoudelijk werk, kantoorwerk

2 = Ambulant en in staat tot alle zelf zorg maar niet in staat enige werkzaamheden uit te voeren; ongeveer meer dan 50% van de wakkere uren

3 = in staat tot slechts beperkte zelfzorg; meer dan 50% van de wakkere uren aan bed of stoel gekluisterd

4 = kan geen zelfzorg uitvoeren; volledig beperkt tot bed of stoel

0	0
1-2	1
3-4	2

4. Verminderde eetlust

Duidt aan wat past:

Score van 0-10
0 = geen verminderde eetlust
10 = helemaal geen eetlust

0-3	0
4-6	1
7-10	2

5. Abnormale biochemie

Duidt aan wat past:

- Witte bloedcellen > $10*10^9$/L
- Albumine < 35 g/L
- Hemoglobine < 120/110 g/L

Allemaal normaal	0
Eén van de drie abnormaal	1
Meer dan één abnormaal	2

Totale score van de 5 categorieën

- 0-2: niet cachectic
- 3-4: pré cachectic
- 5-8: cachectic
- 9-12: hardnekkig cachectic

Appendix 2: SPPB protocol

Short Physical Performance Battery (SPPB)

Test benodigdheden:

- stopwatch
- tape van 4 meter lang
- stoel (en eventueel antislipmat)

De test uitvoer

1) De balans test

Bij deze test dient de patiënt minimaal 10 seconden stil te staan in 3 progressief moeilijker wordende houdingen. Hierbij wordt het volgende systeem voor het toekennen van punten gebruikt.

a. Indien de patiënt 10 seconden met zijn/haar voeten naast elkaar en tegen elkaar aan kan staan, krijgt deze 1 punt en wordt de volgende positie getest. Indien de eerste test niet mogelijk is krijgt de patiënt een score 0 en kunnen de andere balanstesten worden overgeslagen.

b. Indien de patiënt 10 seconden met zijn/haar voeten in semi-tandem positie kan staan, krijgt deze nog 1 punt en wordt de volgende positie getest.

c. Indien de patiënt 10 seconden met zijn/haar voeten in tandem positie kan staan, krijgt deze nog 2 punt. Indien deze houding meer dan 3 seconden maar minder dan 9 seconden kan worden gehandhaafd krijgt de patiënt 1 punt.

2) De loopsnelheid over 4 meter:

De tijd van het afleggen van een afstand van 4 meter, gelopen op gebruikelijke snelheid, wordt gemeten. De beste tijd van 2 pogingen wordt gebruikt voor het toekennen van punten.

Tijdens de test is het gebruik van een hulpmiddel voor lopen toegestaan (dit levert geen strafpunten op). Voor het toekennen van de score wordt gebruik gemaakt van de volgende afkappunten:

Seconden	Afkappunten
< 4.82	**4**
4.82-6.20	**3**
6.21-8.70	**2**
8.70	**1**
Niet in staat	**0**

Indien er onvoldoende ruimte is om de test over 4 meter uit te voeren, kan de test ook worden afgenomen over 3 meter. Hierbij worden dan wel een ander scoringsformulier gebruikt.

Seconden	Afkappunten
< 3.62	**4**
3.62-4.65	**3**
4.66-6.52	**2**
6.52	**1**
Niet in staat	**0**

3) De herhaald opstaan uit een stoel test:

De tijd die een patiënt nodig heeft om 5 maal zo snel mogelijk op te staan uit een stoel (en weer gaat zitten) wordt gemeten. Tijdens de test worden de handen voor de borst gehouden. De uitgangspositie is zittend en bij de 5e keer dat de persoon rechtop staat wordt de tijd gestopt.

Seconden	Afkappunten
< 11.20	4
11.20-13.69	3
13.70-16.69	2
16.7-60	1
> 60 sec of niet in staat	0

Bronvermelding:

- Effectieve ouderenzorg: toolkit mobiliteit. Beschikbaar via: http://www.effectieveouderenzorg.nl/Portals/0/PDF/Toolkit/Toolkit%20Mobiliteit.pdf

Scoringsformulier

	score
Balans 0-1 pt	
Balans 0-1 pt	
Balans 0-2 pt	
Lopen 0-4 pt	
Opstaan 0-4 pt	
Totaal	

> 9	Nog niet in de gevaren zone.	Het gaat goed, ga zo door. Blijf bewegen dat is goed voor uw gezondheid.
4 - 9	Verhoogd risico op nieuwe beperkingen. Komen in aanmerking voor acties gericht op verbeteren van het functioneren.	Het gaat best goed en om dat te behouden is het belangrijk om actief te blijven. U kunt zelf veel doen door het uitvoeren van uw dagelijkse activiteiten. Ook kunt u meedoen aan beweegactiviteiten in de buurt.
< 4	Ervaren al veel beperkingen. Komen in aanmerking voor acties om functioneren te behouden en om te gaan met beperkingen.	Het gaat wat minder misschien is het goed om eens met de huisarts / een ouderenadviseur of een andere professional te praten.

Bronvermelding**:**

- Vroegsignalering Functionele achteruitgang. Nabij (kennisprogramma TNO). Beschikbaar via: http://nabij-vitalewijk.nl/wp-content/uploads/2014/12/SPPB-TEST.pdf

Appendix 3: SF-36 questionnaire

SF-36

Structurele karakteristieken van de romp en beenspieren bij colorectale kankerpatiënten met cachexie

In opdracht van Universiteit Hasselt, Martelarenlaan 42, 3500 Hasselt

REVAL - Rehabilitation en research center, Agoralaan gebouw A, 3590 Diepenbeek
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SF-36

In dit deel van de vragenlijst wordt naar uw gezondheid gevraagd. Wilt u elke vraag beantwoorden door het juiste hokje aan te kruisen. Wanneer u twijfelt over het antwoord op een vraag, probeer dan het antwoord te geven dat het meest van toepassing is.

1. Wat vindt u, over het algemeen genomen, van uw gezondheid ?

uitstekend	☐
zeer goed	☐
goed	☐
matig	☐
slecht	☐

2. *In vergelijking met een jaar geleden*, hoe zou u *nu* uw gezondheid in het algemeen beoordelen ?

veel beter dan een jaar geleden	☐
iets beter dan een jaar geleden	☐
ongeveer hetzelfde als een jaar geleden	☐
iets slechter dan een jaar geleden	☐
veel slechter dan een jaar geleden	☐

3. De volgende vragen gaan over dagelijks bezigheden. Wordt u door uw gezondheid *op dit moment* beperkt bij deze bezigheden ? Zo ja, in welke mate ?

	Ja, ernstig beperkt	*Ja, een beetje beperkt*	*Nee, helemaal niet beperkt*
Forse inspanning zoals hardlopen, zware voorwerpen tillen, inspannend sporten	☐	☐	☐
Matige inspanning zoals het verplaatsen van een tafel, stofzuigen, fietsen	☐	☐	☐

Tillen of boodschappen dragen	☐	☐	☐
Een paar trappen oplopen	☐	☐	☐
Eén trap oplopen	☐	☐	☐
Buigen, knielen of bukken	☐	☐	☐
Meer dan een kilometer lopen	☐	☐	☐
Een halve kilometer lopen	☐	☐	☐
Honderd meter lopen	☐	☐	☐
Uzelf wassen of aankleden	☐	☐	☐

4. Had u, ten gevolge van uw lichamelijke gezondheid, *de afgelopen 4 weken* één van de volgende problemen bij uw werk of andere dagelijkse bezigheden ?

	ja	*nee*
U heeft minder tijd kunnen besteden aan werk of andere bezigheden	☐	☐
U heeft minder bereikt dan u zou willen	☐	☐
U was beperkt in het soort werk of soort bezigheden	☐	☐
U had moeite met het werk of andere bezigheden (het kostte u bijvoorbeeld extra inspanning)	☐	☐

5. Had u, ten gevolge van een emotioneel probleem (bijvoorbeeld doordat u zich depressief of angstig voelde), *de afgelopen 4 weken* één van de volgende problemen bij uw werk of andere dagelijkse bezigheden ?

	ja	*nee*
U heeft minder tijd kunnen besteden aan werk of andere bezigheden	☐	☐
U heeft minder bereikt dan u zou willen	☐	☐
U heeft het werk of andere bezigheden niet zo zorgvuldig gedaan als u gewend bent	☐	☐

6. In hoeverre heeft uw lichamelijke gezondheid of hebben uw emotionele problemen u *de afgelopen 4 weken* belemmerd in uw normale sociale bezigheden met gezin, vrienden, buren of anderen ?

Helemaal niet ☐

Enigszins ☐

Nogal ☐

Veel ☐

Heel erg veel ☐

7. Hoeveel pijn had u *de afgelopen 4 weken* ?

Geen ☐

Heel licht ☐

Licht ☐

Nogal ☐

Ernstig ☐

Heel ernstig ☐

8. In welke mate heeft pijn u *de afgelopen vier weken* belemmerd bij uw normale werkzaamheden (zowel werk buitenshuis als huishoudelijk werk) ?

Helemaal niet	☐
Een klein beetje	☐
Nogal	☐
Veel	☐
Heel erg veel	☐

9. Deze vragen gaan over hoe u zich *de afgelopen 4 weken* heeft gevoeld. Wilt u bij elke vraag het antwoord aankruisen dat het beste aansluit bij hoe u zich heeft gevoeld.

Hoe vaak gedurende *de afgelopen 4 weken* :

	Voortdurend	*Meestal*	*Vaak*	*Soms*	*Zelden*	*Nooit*
Voelde u zich levenslustig?	☐	☐	☐	☐	☐	☐
Voelde u zich erg zenuwachtig?	☐	☐	☐	☐	☐	☐
Zat u zo erg in de put dat niets u kon opvrolijken?	☐	☐	☐	☐	☐	☐
Voelde u zich kalm en rustig?	☐	☐	☐	☐	☐	☐
Voelde u zich energiek?	☐	☐	☐	☐	☐	☐
Voelde u zich neerslachtig en somber?	☐	☐	☐	☐	☐	☐
Voelde u zich gelukkig?	☐	☐	☐	☐	☐	☐
Voelde u zich moe?	☐	☐	☐	☐	☐	☐

10. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen gedurende *de afgelopen 4 weken* uw sociale activiteiten (zoals bezoek aan vrienden of naaste familieleden) belemmerd ?

voortdurend	☐
meestal	☐
soms	☐
zelden	☐
nooit	☐

11. Wilt u het antwoord kiezen dat het beste weergeeft hoe juist of onjuist u elk van de volgende uitspraken voor uzelf vindt.

	Volkomen juist	*Grotendeels juist*	*weet ik niet*	*Grotendeels onjuist*	*Volkomen onjuist*
Ik lijk gemakkelijker ziek te worden dan andere mensen	☐	☐	☐	☐	☐
Ik ben net zo gezond als andere mensen die ik ken	☐	☐	☐	☐	☐
Ik verwacht dat mijn gezondheid achteruit zal gaan	☐	☐	☐	☐	☐
Mijn gezondheid is uitstekend	☐	☐	☐	☐	☐

Appendix 4: PASIPD questionnaire

Vragenlijst activiteitenniveau

Structurele karakteristieken van de romp en beenspieren bij colorectale kankerpatiënten met cachexie

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Physical Activity Scale for Individuals with Physical Disabilities (PASIPD)

Deze vragenlijst gaat over uw huidig niveau van fysieke activiteit. Hiermee willen wij enkel uw activiteitenniveau nagaan. Er zijn geen juiste of foute antwoorden.

Gelieve het antwoord te omcirkelen wat uw situatie het beste beschrijft.

Vrijetijdsbesteding

1. Hoe vaak heeft u zich de laatste 7 dagen beziggehouden met stationaire activiteiten zoals lezen, TV kijken, computerspelen, of handwerk doen?

1. Nooit (ga naar vraag #2)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Wat waren deze activiteiten?

Hoeveel uur spendeerde u gemiddeld per dag aan deze activiteiten?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

2. Hoe vaak bent u de laatste 7 dagen gaan wandelen buitenshuis *voor iets anders dan speciaal voor oefening*. Bijvoorbeeld, naar werk of de klas gaan, de hond uitlaten, winkelen, of voor andere klusjes?

1. Nooit (ga naar vraag #3)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag wandelend buitenhuis?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

3. Hoe vaak hebt u de laatste 7 dagen aan lichte sport of recreatieve activiteiten gedaan zoals bowling, golf met een kar, jagen of vissen, darts, biljart of poolen, therapeutische oefeningen (kinesitherapie of ergotherapie, stretching, gebruik van een statafel) of gelijkaardige activiteiten?

1. Nooit (ga naar vraag #4)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Wat waren deze activiteiten?

Hoeveel uur spendeerde u gemiddeld per dag aan deze lichte sport of activiteiten?

1. Minder dan 1u
2. 1-2u
3. 2-4u 4. Meer dan 4u

4. Hoe vaak hebt u de laatste 7 dagen aan matige sport of recreatieve activiteiten gedaan zoals dubbeltennis, softbal, golf zonder kar, stijldansen, voor plezier of gelijkaardige activiteiten?

1. Nooit (ga naar vraag #5)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Wat waren deze activiteiten?

Hoeveel uur spendeerde u gemiddeld per dag aan deze matige sport of activiteiten?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

5. Hoe vaak hebt u de laatste 7 dagen aan intensieve sport of recreatieve activiteiten gedaan zoals joggen, zwemmen, aerobic dansen, fietsen (arm of been), enkeltennis, rugby, basketbal, wandelen met krukken en braces, of gelijkaardige activiteiten?

1. Nooit (ga naar vraag #6)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Wat waren deze activiteiten?

Hoeveel uur spendeerde u gemiddeld per dag aan deze intensieve sport of activiteiten?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

6. Hoe vaak hebt u de laatste 7 dagen enige oefening gedaan, speciaal om spierkracht en spieruithouding te vergroten zoals gewichtheffen, push-ups, pull-ups, dips etc.?

1. Nooit (ga naar vraag #7)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Wat waren deze activiteiten?

Hoeveel uur spendeerde u gemiddeld per dag aan deze oefeningen om spierkracht en spieruithouding te vergroten?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

Huishoudactiviteiten

7. Hoe vaak hebt u de laatste 7 dagen enige lichte huistaken gedaan zoals afstoffen, de vloer vegen of de afwas doen?

1. Nooit (ga naar vraag #8)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag aan deze lichte huistaken?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

8. Hoe vaak hebt u de laatste 7 dagen enige zware huistaken gedaan zoals stofzuigen, de vloer schrobben, de ramen wassen etc.?

1. Nooit (ga naar vraag #9)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag aan deze zware huistaken?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

9. Hoe vaak hebt u de laatste 7 dagen thuisreparaties gedaan zoals tapijt leggen, schilderen, meubelen overlakken, elektrisch werk, etc.?

1. Nooit (ga naar vraag #10)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag aan thuisreparaties?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

10. Hoe vaak hebt u de laatste 7 dagen gazon- of tuinwerk gedaan zoals grasmaaien, blad- of sneeuwverwijdering, boom-of struik snoeien, houtkappen, etc.?

1. Nooit (ga naar vraag #11)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag aan gazon- of tuinwerk?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

11. Hoe vaak hebt u de laatste 7 dagen gezorgd voor een ander persoon, zoals kinderen, een afhankelijke echtgenoot, of een andere volwassene?

1. Nooit (ga naar vraag #12)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag aan zorgen voor een andere persoon?

1. Minder dan 1u
2. 1-2u
3. 2-4u
4. Meer dan 4u

Werk gerelateerde activiteit

12. Hoe vaak hebt u de laatste 7 dagen betaald gewerkt of als vrijwilliger? Uitgezonderd werk dat vooral zitten met lichte armbeweging inhoudt zoals kantoorwerk, computerwerk, licht bandwerk, een bus rijden, etc..

1. Nooit (ga naar EINDE)
2. Zelden (1-2d)
3. Soms (3-4d)
4. Vaak (5-7d)

Hoeveel uur spendeerde u gemiddeld per dag aan betaald of als vrijwilliger werken?

1. Minder dan 1u
2. 1-4u
3. 4-8u
4. Meer dan 8u

Appendix 5: patient characteristics

Cachexia (n=12)				**Non-cachexia** (n=25)				**Healthy Controls** (n=25)			
Gender	Age (years)	Weight (kg)	BMI (kg/m²)	Gender	Age (years)	Weight (kg)	BMI (kg/m²)	Gender	Age (years)	Weight (kg)	BMI (kg/m²)
M	63	83.8	26.45	M	61	94	27.47	M	73	78	26.99
F	69	105	35.91	M	67	72	24.06	F	72	69	26.62
F	65	65	23.03	F	42	61	21.61	M	55	77	25.73
F	51	85.5	32.18	M	77	92	31.1	F	58	65	24.46
F	43	84	28.39	F	39	56	19.38	M	78	93	31.44
F	64	70	28.04	M	70	69.8	21.78	F	62	79	29.37
F	53	45	17.58	F	86	65.5	24.01	F	74	64	25.00
M	88	79	26.09	M	48	75.5	24.37	M	63	85	27.76
M	85	85	25.11	M	64	82.1	27.12	F	68	65	24.18
F	52	66.2	22.38	M	65	93	29.35	M	66	65	23.31
M	85	55.3	19.13	M	61	112.7	31.22	F	68	72	25.21
M	78	83	26.79	M	81	92	27.47	M	48	82	26.47
				F	72	69	24.16	M	66	66	23.11
				F	82	55	20.96	M	51	81	25.28
				M	69	89	28.09	M	77	81	25.56
				M	50	105	31.35	M	62	113	34.11
				M	80	76	24.26	M	62	86	27.14
				M	64	80.4	25.38	M	68	72	24.06
				F	74	80	31.25	F	41	81	24.19
				M	52	99	28.97	M	81	83	26.20
				F	50	75	26.26	M	72	82	25.02
				M	69	100	30.86	M	79	77	26.03
				M	74	96	26.04	M	73	84	25.93
				M	78	88	27.16	M	59	71	22.41
				M	68	90	29.05	M	67	99	29.24