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Physical activity and quality of life among long-term colorectal cancer survivors

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

5-FU	5-Fluorouracil
5YFU	Five-year follow-up
95% CI	95% confidence interval
ACS	American Cancer Society
ACSM	American College of Sports Medicine
BMI	Body mass index
CHAMPS	Community Healthy Activities Model Program for Seniors
CIS	Checklist Individual Strength
CRC	Colorectal cancer
DACHS	Darmkrebs: Chancen der Verhütung durch Screening
EORTC	European Organization for Research and Treatment of Cancer
FACT-C	Functional Assessment of Cancer Therapy - Colorectal Cancer
FACT-G	Functional Assessment of Cancer Therapy - General
FAQ	Fatigue Assessment Questionnaire
GLTEQ	Godin Leisure-Time Exercise Questionnaire
HADS	Hospital Anxiety and Depression Scale
HHS	U.S. Department of Health and Human Services
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, 10th Revision
IPAQ	International Physical Activity Questionnaire
MET-h/wk	Metabolic equivalent hours per week
METs	Metabolic equivalent values
MMOXX1	Triaxial MOX activity monitor

NHP	Nottingham Health Profile
PA	Physical activity
PROMIS	Patient-Reported Outcomes Measurement Information System
PROQOL-HIV	Patient Reported Outcomes Quality of Life-HIV
PSORIQoL	Psoriasis Index of Quality of Life
Q	Quartile
QLACS	Quality of Life in Adult Cancer Survivors
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-CIPN20	Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy
QOL	Quality of life
SD	Standard deviation
SF-36	Short-Form Health Survey
SWLS	Satisfaction with Life Scale
UICC	Union for International Cancer Control
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule
WHOQOL	World Health Organization Quality of Life Questionnaire

1. INTRODUCTION

1.1. Colorectal cancer

1.1.1. Epidemiology

With over 1.8 million estimated incident cases and 881,000 estimated deaths in 2018, colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related death worldwide (Bray *et al.*, 2018). Colorectal cancer incidence rates are higher in men than in women (Bray *et al.*, 2018; Siegel *et al.*, 2017) and there is a strong increase of CRC incidence with age (DeSantis *et al.*, 2014). Overall, the global CRC incidence varies strongly with the highest incidence rates in transitioned countries such as Europe, Australia/New Zealand, Northern America, and Eastern Asia and the lowest rates in transitioning countries such as Africa and Southern Asia (Bray *et al.*, 2018).

In Germany, colon cancer is the fifth most common cancer and the fourth most common cause of cancer-related death, whereas rectal cancer is the ninth most common cancer and the seventh most common cause of cancer-related death. In 2018, it is estimated that 58,047 individuals are diagnosed with CRC and 26,758 will die from the disease (Ferlay *et al.*, 2018). Also, in Germany incidence rates are higher in men than in women with incident cases of 33,120 vs. 27,890 in 2014. Further, the risk of CRC also increases with age demonstrated by more than half of all CRC patients being diagnosed beyond age 70 and only 10% before age 50. The medium age of diagnosis in 2014 was 75 years for women and 72 years for men. Age-standardized incidence rates and mortality rates have been decreasing since 2003, with a decline in mortality by more than 20% within the last ten years (Robert Koch-Institut and die Gesellschaft der epidemiologischen Krebsregister in Deutschland, 2017).

1.1.1.1. Colorectal cancer survivors

Although age-standardized incidence and mortality rates have been declining (Robert Koch-Institut and die Gesellschaft der epidemiologischen Krebsregister in Deutschland, 2017), the number of cancer survivors is continuously rising. This is traced back to earlier detection and improvements in cancer treatment as well as the aging of the population (DeSantis *et al.*, 2014; Miller *et al.*, 2016). In Germany, the relative five-year CRC survival rate has risen from 52% in 1991 (Brenner *et al.*, 2005) up to 62% in the year 2014 (Robert Koch-Institut and die Gesellschaft der epidemiologischen Krebsregister in Deutschland, 2017). Tumor stage is a highly relevant determinant of CRC prognosis. Relative five-year survival rates of

90.3% are observed for CRC survivors with a localized stage, 70.4% for regional stage, and 12.5% for distant stage (DeSantis *et al.*, 2014).

According to the National Coalition for Cancer Survivorship, a cancer survivor is any individual with a cancer history from diagnosis throughout the rest of her or his life (Leigh and Logan, 1991). Although there is no official definition of long-term survivorship, the majority of pertinent studies define cancer patients who are still alive five years after their diagnosis as long-term survivors (Bloom *et al.*, 2007; Deimling *et al.*, 2006; Jansen *et al.*, 2010; Thong *et al.*, 2013). This definition was established because cancer survivors without a recurrence five years after diagnosis are considered to be cured as their chance of mortality is often comparable to the one of the general population (Dickman and Adami, 2006).

1.1.2. Treatment

In Germany, recommendations regarding CRC treatment are based on the S3-guideline “colorectal cancer”, developed by the Scientific Medical Professional Societies, the German Cancer Society, and the German Cancer Aid. This guideline aims to support physicians in giving evidence-based treatment advice to their patients and to safeguard the highest level of care (Schmiegel *et al.*, 2017).

If feasible, the resection of the tumor is the primary treatment option for CRC and is independent of tumor stage (Union for International Cancer Control [UICC]) and tumor site (colon or rectum), whereas recommendations on neoadjuvant and adjuvant therapy highly depend on tumor stage, tumor site, and specific risk factors (Schmiegel *et al.*, 2017).

As part of surgery, a stoma may need to be created in specific cases. If the tumor is located in the colon or in the upper or medium third of the rectum, a stoma is usually not necessary. In case of a tumor in the lower third of the rectum and a distance of less than 1-2 cm between the tumor and the anus, a stoma is required. If the sphincter muscle can be preserved, but the seam is located closely to the anus, a stoma will be necessary for a short period of time to improve wound healing. In cases where the tumor is located too closely to or is growing into the sphincter muscle a permanent stoma is necessary (Schmiegel *et al.*, 2017).

For patients with stage I colon cancer, no adjuvant therapy is indicated. So far, study results regarding benefits of adjuvant chemotherapy for patients with stage II colon cancer have been inconclusive. Therefore, possible benefits and risks of chemotherapy should be discussed with the patient. In case of microsatellite instability, no adjuvant therapy is recommended for stage II colon cancer patients. Those stage II colon cancer patients with prognostically unfavorable risk factors such as a T4 tumor, a tumor perforation/tears, an

emergency operation, or an insufficient number of lymph nodes examined, might benefit from adjuvant chemotherapy and it should therefore be considered. If chemotherapy is administered, a monotherapy with fluoropyrimidines is recommended. For patients with stage III colon cancer, adjuvant chemotherapy treatment including oxaliplatin (FOLFOX scheme) is recommended. If there is a contraindication to oxaliplatin, a monotherapy with fluoropyrimidines such as 5-Fluorouracil (5-FU) and folinic acid can be administered. Treatment of stage IV colon cancer patients highly depends on the general health condition of the patient, the metastasis spread, and specific tumor characteristics, therefore no universal recommendations are given. If surgery is not possible or if the tumor and/or metastases cannot be fully resected, treatment primarily with chemotherapy can be administered to prolong life and mitigate symptoms (Schmiegel *et al.*, 2017).

In general, there is no age limitation regarding chemotherapy treatment. Contraindications for adjuvant chemotherapy of colon cancers include poor health status, an uncontrolled infection, cirrhosis of the liver (Child-Pugh Score B and C), severe coronary heart disease or cardiac insufficiency, kidney insufficiency (preterminal and terminal), confined bone marrow functioning, other life expectancy affecting comorbidities, and the inability to participate in regular control check-ups (Schmiegel *et al.*, 2017).

In stage I rectal cancer patients, no neoadjuvant or adjuvant therapy is administered. Recommendations for stage II and III rectal cancer include neoadjuvant radiotherapy or neoadjuvant radiochemotherapy containing either oral capecitabin or 5-FU by infusion. A resection of cT1/2 and cT3a/b tumors prior to treatment should be considered in case of specific tumor characteristics. For stage II and III rectal cancer patients who did not receive neoadjuvant treatment, adjuvant radiochemotherapy or adjuvant chemotherapy should be administered following recommendations for colon cancer. Since studies showed adjuvant radiochemotherapy to be less effective and associated with more side effects compared to neoadjuvant radiochemotherapy, it should only be administered in stage II and III rectal cancer patients with histopathologic confirmed risk factors. Study results regarding benefits of adjuvant chemotherapy after neoadjuvant radiochemotherapy in rectal cancer patients have been inconclusive and therefore no universal recommendation is available. For stage IV rectal cancer patients, treatment is applied as recommended for stage IV colon cancer patients (Schmiegel *et al.*, 2017).

In general, if the tumor is located in the upper third of the rectum and there is no risk constellation for a local recurrence, therapy should be administered as recommended for colon cancer (Schmiegel *et al.*, 2017).

1.1.2.1. Side effects of colorectal cancer treatment

Colorectal cancer survivors experience treatment side effects during treatment, following treatment (long-term effects), and some effects can even occur several years later (late effects) (American Cancer Society, 2017). However, problems are reported to be most prominent during the first three years (Denlinger and Barsevick, 2009).

Side effects from surgery can include urogenital or sexual dysfunction and fatigue, which might be present for a long period of time. Especially for rectal cancer patients, side effects such as a change in bowel movements, diarrhoea, constipation, gas or bloating are common (American Cancer Society, 2017). Patients with a stoma may experience complications such as a para-stomal hernia, leakage, dermatitis, obstruction, prolapse, retraction, or anastomotic leakage after stoma closure (Kuipers *et al.*, 2015).

Chemotherapy can lead to side effects such as fatigue, mental deficits (American Cancer Society, 2017) including oxaliplatin induced peripheral neuropathy (Denlinger and Barsevick, 2009), nausea and vomiting, hair loss, loss of appetite, mouth scores, swelling and rashes, a higher risk of infection due to low white blood cells, or numbness, tingling, or blistering of the hands and feet which most commonly occur after treatment including oxaliplatin (American Cancer Society, 2017). While some of the side effects go away after treatment, others such as numbness of hand and feet (American Cancer Society, 2017) or neuropathy (Denlinger and Barsevick, 2009) may persist.

After radiation, side effects such as nausea, diarrhoea, fatigue, skin irritation, or sexual problems can occur. Symptoms like rectal irritation, rectal inflammation, or bladder irritation can lead to the urgency of frequent defecation and urination as well as pain. After treatment completion most of these side effects go away but some such as rectal or bladder irritation or sexual problems may persist permanently (American Cancer Society, 2017). Possible late effects of radiation include bowel dysfunction (Denlinger and Barsevick, 2009) like intestinal obstruction, bone fractures at the base of the spine, or infertility. Radiation also increases the risk of second cancers (American Cancer Society, 2017).

1.2. Health-related quality of life

Research on quality of life (QOL) exists since the 1960s (Schuessler and Fisher, 1985). Since its introduction in research, there has been growing awareness of the concept of QOL in several disciplines such as sociology, politics, psychology, economics (Schuessler and Fisher, 1985), philosophy, and medicine (Daig and Lehmann, 2007). In medicine, the concept of QOL was integrated in the 1970/80s (Elkinton, 1966; Spitzer, 1987) and has played an important role in this field ever since (Bullinger, 2014). Also in oncology it has become clear that objective measures such as survival should not be the only endpoints of interest but also the QOL of cancer patients should be considered in treatment decisions (Jacobsen and Jim, 2011; Spitzer *et al.*, 1981; Ware, 1995). The first QOL instruments were applied in research in the 1990s. Todays´ challenge is to integrate study findings into health care (Bullinger, 2014) which is emphasized by more than 300,000 search results for “quality of life” in Pubmed.

1.2.1. Definition

Although several definitions of QOL exist, there is not one universally accepted definition (Daig and Lehmann, 2007). The World Health Organization (WHO) defines QOL as an “individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (World Health Organization, 1995). In QOL research, an operational definition which defines QOL as a multidimensional concept, is widely spread. Multidimensional QOL mostly comprises physical, emotional, social (Bullinger, 2014; Fayers and Machin, 2000), mental, and role aspects (Bullinger, 2014). In medical research, the concept of health-related QOL (HRQOL) is well accepted (Bullinger, 2000). It was introduced in clinical research to differentiate aspects of QOL which affect health, from overall QOL which includes a broader sense of well-being (e.g. happiness, satisfaction with life) that is subjective and therefore challenging to measure (Centers for Disease Control and Prevention, 2000). However, HRQOL, health, and QOL are often used interchangeably and definitions often fail to differentiate HRQOL from health and QOL (Karimi and Brazier, 2016). Therefore, Karimi et al. suggest “a clearer use of HRQOL would be to use it only to signify empirical studies of how health affects QOL or to signify the utility associated with a health state” (Karimi and Brazier, 2016). Throughout this dissertation QOL is always considered in the context of HRQOL.

1.2.2. Assessment of quality of life

In medical research, QOL is usually assessed by self-report (Kohlmann, 2014). Since studies found that cancer patients´ reported QOL often differed from the perceptions of external observers (e.g. nurses, physicians, family) (Horton, 2002; Jones *et al.*, 2011; Sneeuw *et al.*, 1999), external QOL assessments should only be used if an individual is unable to communicate. Although several computer-based QOL applications have been developed in the last years such as the *Patient-Reported Outcomes Measurement Information System* (PROMIS) which provides applications including computerized adaptive testing (Cella *et al.*, 2007), standardized paper-pencil measures are still frequently used. Quality of life measures can be classified in generic and disease-specific measures. Generic measures assess the QOL of individuals, independent of the existence of a disease, whereas, disease-specific measures additionally assess the patients´ QOL depending on possible detriments as a result of specific diseases (Kohlmann, 2014). Generic measures allow comparisons of patients´ QOL with patients of other diseases as well as with the general population, however, they lack the sensitivity of assessing specific symptoms patients may suffer from (Jacobsen and Jim, 2011).

1.2.2.1. Generic measures

Examples for generic measures are the *Short-Form Health Survey* (SF-36) (Ware and Sherbourne, 1992), the *Nottingham Health Profile* (NHP) (Hunt and McEwen, 1980; Hunt *et al.*, 1981), and the *World Health Organization Quality of Life Questionnaire* (WHOQOL) (World Health Organization, 1995). One of the generic measures mostly used is the SF-36 (Bullinger, 2014), which has been translated into more than 40 languages (Daig and Lehmann, 2007). The SF-36 was developed within the Medical Outcome Study to assess the health status within clinical practice, research, health policy evaluations as well as in general population surveys. It consists of 36 items which measure the health status on eight scales: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. The eight scales can be classified into two main dimensions: the physical and the mental health component score (Ware and Sherbourne, 1992). In addition, short forms such as the SF-12 are available (Ware *et al.*, 1996).

1.2.2.2. Disease-specific measures

Disease-specific measures cover a wide range of diseases such as cancer, HIV, or skin disorders. Examples are the *Quality of Life Questionnaire-Core 30* (QLQ-C30) of the European Organization for Research and Treatment of Cancer (EORTC) *(Aaronson et al., 1993)*, the *Functional Assessment of Cancer Therapy-General* (FACT-G) (Cella *et al.*, 1993; Webster *et al.*, 2003), the *Patient Reported Outcomes Quality of Life-HIV* (PROQOL-HIV) (Duracinsky *et al.*, 2012), and the *Psoriasis Index of Quality of Life* (PSORIQoL) (McKenna *et al.*, 2003). The QLQ-C30 is a measure widely used and well accepted to assess the disease-specific QOL in cancer patients (Bullinger *et al.*, 2006; Deutschinoff *et al.*, 2005). The core instrument QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QOL scale. Also, six single items which include further symptoms and problems (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) are available (Aaronson *et al.*, 1993). The EORTC study group also provides cancer site-specific modules such as the QLQ-CR38 (Sprangers *et al.*, 1999) for CRC and its updated version QLQ-CR29 (Gujral *et al.*, 2007; Whistance *et al.*, 2009).

Cancer-specific measures were mostly designed to assess QOL in cancer patients shortly after diagnosis or treatment and thus might assess aspects that are no longer relevant for cancer survivors such as nausea and vomiting (van Leeuwen *et al.*, 2018). Further, those measures might lack problems which are relevant to cancer survivors specifically in the years after diagnosis for example fear of recurrence or return to work (van Leeuwen *et al.*, 2018). Therefore, measures have been developed or are currently being developed which specifically assess issues relevant to cancer survivors.

The *Quality of Life in Adult Cancer Survivors* (QLACS) was designed to assess QOL in long-term cancer survivors. The QLACS comprises 47 items of which 28 items assess generic domains and 19 items cancer-specific domains. The generic domains include positive and negative feelings, cognitive and sexual problems, physical pain, fatigue, and social avoidance, whereas the cancer-specific domains comprise appearance concerns, financial problems, distress over recurrence, family-related distress, and benefits of cancer (Avis *et al.*, 2005).

Currently the EORTC is developing a QOL questionnaire for cancer survivors who have been disease free for at least one year after treatment. The aim is to additionally provide a survivorship questionnaire assessing not only psychosocial aspects of QOL in cancer survivors, but also more detriments in QOL caused by chronic physical side effects of

cancer and its treatment. A core questionnaire as well as three modules for specific cancer sites are currently being tested (van Leeuwen *et al.*, 2018).

1.2.3. Quality of life in long-term colorectal cancer survivors

As already mentioned, the number of cancer survivors is steadily increasing due to aging of the population and improvements in early detection and treatment (DeSantis *et al.*, 2014; Miller *et al.*, 2016). Thus, the QOL of this growing population is a highly relevant issue. Many cancer survivors suffer from symptom burden and detriments in QOL not only during or right after determining treatment, but also long into survivorship (Arndt *et al.*, 2017; Arndt *et al.*, 2006; Wu and Harden, 2015).

In CRC survivors, detriments in QOL were found up to 15 years after diagnosis (Caravati-Jouvenceaux *et al.*, 2011). Although the overall QOL among long-term CRC survivors was reported to be comparable to the QOL of the general population (Caravati-Jouvenceaux *et al.*, 2011; Jansen *et al.*, 2010; Trentham-Dietz *et al.*, 2003), the sequelae of cancer and its treatment can affect especially symptom-related QOL even years after diagnosis. Detriments were reported for long-term CRC survivors regarding social functioning (Caravati-Jouvenceaux *et al.*, 2011; Jansen *et al.*, 2011a), physical QOL (Jansen *et al.*, 2010), depression, distress related to cancer (Jansen *et al.*, 2010), anxiety, body image, sexual function, impotence (Bailey *et al.*, 2015), bowel problems (Jansen *et al.*, 2010) such as diarrhoea (Caravati-Jouvenceaux *et al.*, 2011; Jansen *et al.*, 2011a) or embarrassment by bowel movements, and micturition problems (Bailey *et al.*, 2015).

Comparing younger and older long-term CRC survivors, younger survivors reported worse mental QOL (Adams *et al.*, 2016), anxiety, and a lower body image (Bailey *et al.*, 2015), whereas older survivors scored significantly lower on physical QOL (Adams *et al.*, 2016) and sexual function (Bailey *et al.*, 2015). Lower QOL was reported among long-term CRC survivors having one or more comorbidities (Adams *et al.*, 2016; Caravati-Jouvenceaux *et al.*, 2011; Ramsey *et al.*, 2002; Sapp *et al.*, 2003), a lower income (Caravati-Jouvenceaux *et al.*, 2011; Lundy *et al.*, 2009; Ramsey *et al.*, 2000; Ramsey *et al.*, 2002), being physically inactive (Lynch *et al.*, 2016; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013), a smoker, or obese (Adams *et al.*, 2016). Further, rectal cancer survivors with a permanent stoma were reported to have a QOL inferior to rectal cancer patients without a stoma (Fucini *et al.*, 2008; Krouse *et al.*, 2009; Näsvall *et al.*, 2017). Inconsistent results have been reported regarding stage and QOL in long-term CRC survivors (Adams *et al.*, 2016; Aminisani *et al.*, 2017; Pucciarelli *et al.*, 2008; Ramsey *et al.*, 2002).

The experience of cancer can also have positive consequences on the lives of survivors including phenomena such as post-traumatic growth or benefit finding (Chambers *et al.*, 2012a; Jansen *et al.*, 2011b).

1.2.4. Fatigue

Fatigue is the most common and distressing symptom experienced by cancer patients during and after treatment (Ryan *et al.*, 2007) and is still frequently reported by cancer survivors (Denlinger and Barsevick, 2009; Minton and Stone, 2009; Wu and Harden, 2015), even ten years post-diagnosis (Thong *et al.*, 2013). Cancer patients suffering from fatigue are often not able to perform activities of everyday life, which can negatively affect their social relationships (Hofman *et al.*, 2007; Scott *et al.*, 2011) and QOL (Butt *et al.*, 2008; Cheng and Lee, 2011; Hofman *et al.*, 2007; Ness *et al.*, 2013).

Fatigue is also prevalent among CRC survivors (Jensen *et al.*, 2011; Pucciarelli *et al.*, 2011; Wang *et al.*, 2012). Although fatigue is commonly reported in the general population, the fatigue experience of short- as well as long-term CRC survivors is described to be more severe (Caravati-Jouvenceaux *et al.*, 2011; Jansen *et al.*, 2011a; Thong *et al.*, 2013).

Although fatigue has been associated with cancer, its treatment, symptoms such as depression or poor sleep as well as with lifestyle factors (Brown and Kroenke, 2009; George *et al.*, 2014; Grimmett *et al.*, 2011; Roscoe *et al.*, 2007; Schmidt *et al.*, 2015; Wang and Woodruff, 2015), the underlying causal mechanisms of fatigue are still not fully understood (Barsevick *et al.*, 2013; Saligan *et al.*, 2015; Wang and Woodruff, 2015). There have been diverse conceptual and operational definitions of fatigue and there is no consensus on how it should be measured (e.g. unidimensional vs. multidimensional). The variability of study outcomes has hampered comparisons of study findings and thus their generalizability for clinical practice (Barsevick *et al.*, 2013; Minton and Stone, 2009).

Although there is not one universally accepted definition of cancer-related fatigue (Minton and Stone, 2009), the following definition of the National Comprehensive Cancer Network is widely used: “cancer-related fatigue is a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (Berger *et al.*, 2010).

Self-report measures that are often used to assess fatigue, mostly incorporate one or more aspects of this definition. Apart from the physical, cognitive, and affective domains, other domains such as motivation, energy or vitality, or diurnal variation have been measured (Barsevick *et al.*, 2010). Unidimensional scales only assess the physical aspect, whereas

multidimensional scales cover different aspects of fatigue (Minton and Stone, 2009). An example of a unidimensional assessment of fatigue is included in the QLQ-C30. The EORTC has further developed a multidimensional fatigue module, the QLQ-FA12 which assesses physical, cognitive, and emotional fatigue (Weis *et al.*, 2017). The *Fatigue Assessment Questionnaire* (FAQ) also multidimensionally assesses physical, cognitive, and affective fatigue (Glaus and Muller, 2001).

Although the multidimensional concept of fatigue is widely accepted (de Raaf *et al.*, 2013), some studies have suggested that the different fatigue dimensions might not be expressions of one symptom but rather expressions of independent symptoms (multiple-symptom concept) (de Raaf, 2013). A recent review article found that physical and mental fatigue behaved differently in some studies and therefore concludes that further research on the multiple-symptom concept should be performed to clarify the concept of fatigue (de Raaf *et al.*, 2013).

Interventions to reduce fatigue mostly supported in the literature include the treatment of additional medical conditions (e.g. anemia) or symptoms (e.g. depression, insomnia, pain), psychosocial interventions such as fatigue self-care or coping techniques, and exercise (Pachman *et al.*, 2012).

1.3. Physical activity

Industrial progress and technological innovation have contributed to a collectively sedentary lifestyle of individuals, not only in the Western world (Hills *et al.*, 2015). However, the human body is designed for being physically active (Booth *et al.*, 2008) and there is strong evidence that physical inactivity is associated with an increase of several non-communicable diseases. According to the WHO, physical inactivity is the fourth leading risk factor for mortality worldwide (World Health Organization, 2009). Therefore, being physically active is a highly relevant issue.

1.3.1. Definition

A frequently cited definition of physical activity (PA) is the one of Caspersen et al. which describes PA “as any bodily movement produced by skeletal muscles that results in energy expenditure” (Caspersen *et al.*, 1985). Physical activity comprises all activities carried out in daily life including leisure time, occupation, transportation, household chores, or planned exercise (World Health Organization, 2010). The terms PA and exercise should not be confused since “exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness” (Caspersen *et al.*, 1985).

1.3.2. Operationalization of physical activity

Physical activity can be categorized into four dimensions including the type, frequency, duration, and intensity of activities. The type describes the specific activity performed, the frequency describes the number of bouts per day or week, the duration describes the amount of minutes or hours spent, and the intensity describes the energy expenditure of activities (Strath *et al.*, 2013). The intensity of PA can be measured in kilocalories, oxygen consumption, joules, or metabolic equivalent values (METs) which are frequently used in research (Physical Activity Guidelines Advisory Committee, 2018). One MET is defined as the energy consumed while sitting quietly (resting metabolic rate), which is comparable with an oxygen consumption of 3.5 milliliters per kilogram per minute. The energy expenditure of activities is expressed as multiples of the resting metabolic rate (Ainsworth *et al.*, 1993), for example 7.5 METs for bicycling, general; 7.0 METs for jogging, general; 4.8 METs for golfing, general; 2.5 METs for slow walking (Ainsworth *et al.*, 2011). The dose of PA can be derived by multiplying the dimensions of frequency, duration, and intensity whereas the volume of PA is the quantification of the dose over a specific period of time (Physical Activity Guidelines Advisory Committee, 2018; Strath *et al.*, 2013) and is commonly expressed in MET hours or MET minutes per week or day (Physical Activity Guidelines Advisory

Committee, 2018). Four categories of PA intensities have been commonly used: vigorous PA, moderate PA, light PA, and sedentary time. Vigorous PA includes energy costs of ≥6 METs (e.g. jogging), moderate PA of 3.0-5.9 METs (e.g. golfing), and light PA of 1.1-2.9 METs (e.g. slow walking) (U.S. Department of Health and Human Services, 2008). Sedentary behavior comprises energy costs of 1.0-1.5 METs (e.g. watching television) (Ainsworth *et al.*, 2011; Garber *et al.*, 2011), whereas physical inactivity is defined as not being physically active beyond activities which are needed in everyday life (U.S. Department of Health and Human Services, 2008).

The first studies on PA and coronary heart disease, only assessed occupational PA (Dishman *et al.*, 2012, p. 37-70), however, since the decline of occupations requiring hard PA, research has focused more and more on leisure time PA (Lamb and Brodie, 1990; Morris *et al.*, 1980). Nowadays, the PA domains mostly assessed include occupational and leisure time PA as well as domains such as transportation and household PA (Physical Activity Guidelines Advisory Committee, 2018; Strath *et al.*, 2013).

1.3.3. Health benefits

There is strong evidence that individuals engaging in regular PA have several physical and mental health benefits (Hills *et al.*, 2015) which include health conditions such as coronary heart disease (Kyu *et al.*, 2016; Sattelmair *et al.*, 2011; Sofi *et al.*, 2008), hypertension (Huai *et al.*, 2013), stroke (Kyu *et al.*, 2016; Lee *et al.*, 2003; Wendel-Vos *et al.*, 2004), diabetes (Aune *et al.*, 2015; Kyu *et al.*, 2016), obesity (Shaikh *et al.*, 2015), musculoskeletal health (Bolam *et al.*, 2013; Marques *et al.*, 2012), psychological health (Gill *et al.*, 2013; Martinsen, 2008; Rosenbaum *et al.*, 2014), functionality, balance (Chou *et al.*, 2012), and all-cause and cardiovascular mortality (Woodcock *et al.*, 2011; Wu *et al.*, 2015).

Furthermore, associations have been found between PA and numerous cancers (Behrens *et al.*, 2018; Kyu *et al.*, 2016; Robsahm *et al.*, 2013). There is strong evidence that increased PA decreases the risk of colon, breast (Physical Activity Guidelines Advisory Committee, 2018; Steindorf, 2013), bladder, endometrium, esophagus, kidney, stomach, and lung cancer. Moreover, a dose-response relationship between PA and lower risk of breast and colon cancer exists (Physical Activity Guidelines Advisory Committee, 2018).

In general, there is evidence of a dose-response relationship not only for PA and cancer but also for several health outcomes. This implies that higher levels of PA are most beneficial for health, whereas a lower level is better than inactivity (Garber *et al.*, 2011). However, the exact shape of the dose-response curve is not entirely understood and may be dependent on the starting level of PA and the specific health outcomes (Haskell *et al.*, 2007). For example it has been reported that the greatest benefits on health was for sedentary people

becoming more physically active (Hills *et al.*, 2015). The minimum level of PA that is beneficial for health has not been extensively explored (Hills *et al.*, 2015) and without considering the minimum PA levels, most research has concentrated on moderate to vigorous PA. However, due to improvements in objective PA measures such as accelerometers, the contribution of light PA independently of moderate to vigorous PA is nowadays accurately measurable. Therefore, the associations between light PA and health benefits are reported more and more (LaMonte *et al.*, 2017; Powell *et al.*, 2011).

In addition to the accumulating evidence of the beneficial health effects of PA, a recent report summarizing systematic reviews found strong evidence for the association between sedentary behavior and all-cause mortality, cardiovascular disease, type 2 diabetes, and metabolic syndrome. Moderate evidence was reported for the association between sedentary behavior and ovarian, endometrial, and colon cancer. The report also concluded that sedentary behavior might be associated with health, independent of PA (de Rezende *et al.*, 2014). Furthermore, two meta-analyses reported that the increased risk of all-cause mortality associated with sedentary behavior may be attenuated but not eliminated by higher levels of PA (Biswas *et al.*, 2015; Ekelund *et al.*, 2016).

Several biological mechanisms have been suggested to be responsible for the health benefits of PA on chronic diseases. Physical activity has been shown to reduce abdominal adiposity and help maintain a healthy weight, improve lipoprotein profiles (e.g. by increasing high density lipoprotein cholesterol), glucose homeostasis, and insulin sensitivity as well as endothelial function, decrease blood pressure, and systemic inflammation. Cancer-specific effects of PA relate to decreases in fat stores, changes in immune function, insulin and insulin-like growth factors, levels of sex hormones, and production of free-radicals (Warburton *et al.*, 2006). According to a recent review, the health benefits of PA for chronic stress- and inflammatory-related diseases include the improved communication, activation, and recovery of the neuroendocrine, inflammatory, and metabolic stress response pathways (Silverman and Deuster, 2014).

1.3.4. Physical activity recommendations

Due to the positive health effects of PA, the first PA recommendations were published by the Centers for Disease Control and Prevention, and the American College of Sports Medicine (ACSM) in 1995 (Pate *et al.*, 1995). Since then, several qualified organizations such as the American Cancer Society (ACS) (Kushi *et al.*, 2012) and government agencies such as the Department of Health and Human Services (HHS) (U.S. Department of Health and Human Services, 2008) have developed PA recommendations, for example the HHS´ 2008 Physical Activity Guidelines for Americans. The first PA recommendations from 1995

were updated by the ACSM together with the American Heart Association in 2007 (Haskell *et al.*, 2007). Recently, the HHS published an updated PA report, which will be used to develop the second version of the Physical Activity Guidelines for Americans (Physical Activity Guidelines Advisory Committee, 2018).

According to the Physical Activity Guidelines for Americans, adults aged 18 years or older should engage in at least 150 minutes of moderate intensity aerobic PA or 75 minutes of aerobic vigorous intensity PA, or an equivalent combination of both activities throughout the week (U.S. Department of Health and Human Services, 2008). An increase up to 300 minutes of moderate and 150 minutes of vigorous PA per week or an equivalent combination of both go along with additional health benefits. Activities should be performed for at least 10 minutes, and muscle strengthening should be performed at least twice per week. Adults aged 65 years and older with mobility problems should carry out activities improving balance to prevent falls. In general, older adults should orient their PA on their conditions and abilities (U.S. Department of Health and Human Services, 2008). According to the ACSM and the ACS, cancer survivors should engage in the same amounts of PA recommended for the general population during and after treatment receiving assistance (Rock *et al.*, 2012; Schmitz *et al.*, 2010).

1.3.5. Assessment of physical activity

There are several strategies to assess PA such as questionnaires including diaries, recall questionnaires, or interviews, direct observation, measures of energy expenditure, physiological markers, and motion sensors (Strath *et al.*, 2013; Westerterp, 2009).

Subjective measures such as questionnaires or interviews based on self-report are a common and practical method to assess PA in epidemiologic studies (Dishman *et al.*, 2012, p. 37-70). Recall questionnaires frequently assess specific activity types or PA intensities, mostly moderate to vigorous PA. Often, questionnaires also include questions regarding sedentary time (Physical Activity Guidelines Advisory Committee, 2018), frequently assessed by the time watching television (Lynch *et al.*, 2016). Examples for PA questionnaires that are frequently used in research are the *International Physical Activity Questionnaire* (IPAQ) (Craig *et al.*, 2003), the *Godin Leisure-Time Exercise Questionnaire* (GLTEQ) (Godin and Shephard, 1985), or the *Community Healthy Activities Model Program for Seniors* (CHAMPS) (Stewart *et al.*, 2001). The IPAQ asks for the number of days and minutes per week during which vigorous (8 METs) and moderate PA (4 METs), walking (3.3 METs), and also sitting (1 MET) was performed. The IPAQ assesses time spent in activities across domains including occupation, leisure time, self-powered transport, household, and yard/garden. The short version contains nine items and the long version 31 items.

Objective PA measures include different approaches such as the doubly labeled water technique, calorimetry, heart rate monitoring, or motion sensors such as pedometers or accelerometers (Hills *et al.*, 2014). Although the doubly labeled water technique is the gold standard due to its accurate and unobtrusive assessment of the energy expenditure, its application is not practical in most settings (Dishman *et al.*, 2012, p. 37-70). However, the measurement of accelerometers has become more accurate assessing upper and lower body movements and its application is getting easier since devices are available in wrist watches and smart phone apps (Physical Activity Guidelines Advisory Committee, 2018). Some of these measures have been successfully paired, for example, accelerometers and heart rate monitoring (Brage *et al.*, 2004; Haskell *et al.*, 1993) and also multi-sensor systems exist which include a diversity of sensors and technologies (Physical Activity Guidelines Advisory Committee, 2018).

Both, subjective as well as objective PA measures have advantages as well as disadvantages (Hills *et al.*, 2014). The assessment of PA using questionnaires is time and cost efficient and enables the evaluation of rich descriptive data (Hills *et al.*, 2014) among large populations (Dishman *et al.*, 2012, p. 37-70). Further, it is adequate for ranking participants PA from low to high (Physical Activity Guidelines Advisory Committee, 2018). Shortcomings include that they rely on the recall ability of participants (Hills *et al.*, 2014) and that they often miss out on the accuracy of the PA volume performed (Physical Activity Guidelines Advisory Committee, 2018). The accuracy of objective measures such as accelerometers in assessing physical movement is steadily increasing and the devices are getting more affordable, therefore, in epidemiological studies devices are more and more preferred over PA questionnaires (Physical Activity Guidelines Advisory Committee, 2018). However, some objective measures including accelerometers can only be used for specific activities such as walking and running (Hills *et al.*, 2014).

1.3.6. Physical activity in long-term colorectal cancer survivors

The beneficial effects of PA for the primary prevention of cancer were described in section 1.3.3. Moreover, evidence has accumulated that PA is also prognostically relevant for CRC patients. Physically active CRC survivors were reported to have significantly improved recurrence-free (Meyerhardt *et al.*, 2006b; Walter *et al.*, 2017) and overall survival (Baade *et al.*, 2011; Meyerhardt *et al.*, 2006a; Meyerhardt *et al.*, 2006b; Walter *et al.*, 2017).

Aside from a better prognosis for physically active CRC survivors, studies reported PA to be positively associated with physical and psychological health. Survivors participating in prehabilitation programs including PA reported improvements in health outcomes after treatment such as fitness capacity (Gillis *et al.*, 2014; Li *et al.*, 2013; West *et al.*, 2015).

Studies investigating PA after treatment showed that patients who were more physically active tended to report better overall QOL, better functioning (Grimmett *et al.*, 2011; Husson *et al.*, 2015; Mols *et al.*, 2015; Rodriguez *et al.*, 2015), less pain, insomnia (Mols *et al.*, 2015), and fatigue (Grimmett *et al.*, 2011; Mols *et al.*, 2015; Peddle *et al.*, 2008; Vallance *et al.*, 2014). Although a recent review article by Lynch et al. reported that observational studies unanimously observed associations between PA and QOL, the evidence is much weaker from intervention studies (Lynch *et al.*, 2016). Also, a recent meta-analysis failed to show a significant association between PA and fatigue in randomized controlled trials, although in all studies PA was accompanied by reduced levels of fatigue (Brandenbarg *et al.*, 2018).

So far, most studies investigating the association between PA and QOL or fatigue have focused on short-term CRC survivors (less than five years post-diagnosis). However, as described in section 1.2.3, CRC survivors still experience detriments in QOL long into survivorship, therefore, it is of interest if PA is also beneficial for the QOL of long-term CRC survivors. Moreover, most studies cross-sectionally assessed the association between PA and QOL or fatigue after CRC diagnosis. However, it is also relevant to investigate if pre-diagnosis PA has the potential to buffer detriments in QOL even years after diagnosis or if only ongoing PA after diagnosis is beneficial for long-term CRC survivors to improve QOL and decrease fatigue.

Despite reported benefits of PA on CRC survivors´ health, a great number of CRC survivors do not meet recommended amounts of PA. In one study only one third of CRC survivors met PA recommendations and half of all survivors were totally inactive (Speed-Andrews *et al.*, 2012). Moreover, CRC survivors were reported to have lower PA levels compared to other cancer survivors (Bellizzi *et al.*, 2005) and one study reported that less than one quarter of CRC survivors participated in a sport last month (McGowan *et al.*, 2013). Also, in two studies around 50-70% of long-term CRC survivors did not meet PA recommendations (Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013).

Therefore, it is also of great importance to investigate the potential determinants which keep CRC survivors from being physically active. More than half of all CRC patients are diagnosed beyond 70 years of age (Robert Koch-Institut and die Gesellschaft der epidemiologischen Krebsregister in Deutschland, 2017), thus, many CRC survivors may not be capable to engage in recommended levels of PA. Apart from age (Fisher *et al.*, 2016; van Putten *et al.*, 2016), other factors exist which have been shown to be associated with physical inactivity in CRC survivors such as disease-specific (Lynch *et al.*, 2010) or treatment side effects (Courneya *et al.*, 2005; van Putten *et al.*, 2016), fatigue (Chambers *et al.*, 2009; Courneya *et al.*, 2005; Fisher *et al.*, 2016; van Putten *et al.*, 2016), pain,

psychological barriers such as anxiety and depressive symptoms (van Putten *et al.*, 2016), and factors such as smoking or obesity (Chambers *et al.*, 2009). Further, personal attributes such as lack of time (Courneya *et al.*, 2005), fear of injury, or lack of enjoyment (Lynch *et al.*, 2010; McGowan *et al.*, 2013) have also been associated with physical inactivity.

Although some studies have already investigated risk factors of physical inactivity in CRC survivors, in both cross-sectional (Fisher *et al.*, 2016; McGowan *et al.*, 2013) and longitudinal studies (Chambers *et al.*, 2009; Courneya *et al.*, 2005; Lynch *et al.*, 2010; van Putten *et al.*, 2016), none of these studies investigated physical inactivity specifically in long-term CRC survivors. However, it has been reported that also long-term CRC survivors are not sufficiently active. Therefore, understanding potential determinants of physical inactivity in long-term CRC survivors has strong clinical and population health relevance.

1.4. Aims of the dissertation

The aim of this dissertation was to investigate if PA is positively associated with QOL and fatigue among long-term CRC survivors and to explore the potential determinants of physical inactivity among this population. Further, it was of interest to investigate at what point in time PA is most effective for improving the QOL and fatigue of long-term CRC survivors. The following objectives were addressed:

- To review and summarize the literature on the association between PA and QOL in long-term CRC survivors.

- To investigate the association of pre-diagnosis and post-diagnosis PA with QOL in long-term CRC survivors.

- To investigate the association of pre-diagnosis and post-diagnosis PA with fatigue in long-term CRC survivors.

- To investigate the potential determinants of physical inactivity in long-term CRC survivors.

2. MATERIAL AND METHODS

2.1. Systematic review of the association between physical activity and quality of life in long-term colorectal cancer survivors

2.1.1. Literature search

The literature search was carried out in August 2016 and was repeated in January 2017 to guarantee inclusion of all relevant publications. The databases PubMed, Web of Science, PsychINFO, and CINAHL were searched for relevant articles. The exact combinations of search terms are listed in Appendix I. Cross-referencing was performed to identify additional articles which were not identified by the database search.

2.1.2. Inclusion criteria

To be included in the review, studies had to assess QOL in CRC patients five and more years post-diagnosis and PA within the time span of diagnosis to QOL assessment. Results of studies which investigated short-term as well as long-term survivors were also eligible if specific results for long-term survivors were provided. Studies comprising survivors with a mean of ≥5 years since diagnosis were also included. All types of CRC and all types of PA were eligible. However, QOL had to be assessed by more than one scale as it is a multidimensional concept. When studies investigated several cancer types, only the specific results for CRC survivors were included. Furthermore, PA had to be the independent variable and QOL the outcome variable. All types of quantitative original studies, published in English or German, were included. Conference abstracts, study protocols, editorials, commentaries, qualitative studies, theses, reviews, and meta-analyses were not considered. There was no restriction regarding the publication date.

2.1.3. Data extraction

Titles and abstracts of all identified articles were screened by myself. Subsequently the full texts of the selected articles were checked for eligibility. The study characteristics of the eligible studies (e.g. first author, year, journal, sample size, country, sex, age, tumor site, cancer stage, cancer treatment, sampling, study design, comorbidities, inclusion and exclusion criteria, baseline response rate, timing/type of PA assessment, timing/type of QOL assessment, confounders/adjustment, statistical methods, results) were independently extracted by myself and a second reviewer. Discrepancies were discussed and if they could not be solved, a third reviewer was involved.

2.1.4. Statistical significance and clinical relevance

All statistically significant results mentioned in this review refer to a p-value <0.05. If studies reported clinical relevance using either the QLQ-C30 or the SF-36, the reported clinical relevance was adopted. For those studies using the QLQ-C30 and not reporting clinical relevance, clinical relevance was determined by using a medium clinical relevance, which is defined by Osoba et al. as a mean difference of ≥10 score points (Osoba *et al.*, 1998).

2.1.5. Combining the results of different quality of life instruments

As the included studies used various QOL instruments with different notation for the embedded scales, results pertaining different QOL scales of different questionnaires were combined as shown in Table 1.

Table 1 Combining the results of different quality of life instruments

	Questionnaire	Scale
Global QOL	QLQ-C30 (Aaronson *et al.*, 1993)	Overall QOL/ global health
	SF-36 (Gandek *et al.*, 2004)	General health and global health composite score
	EQ-5D (Revicki *et al.*, 2009)	Overall HRQOL
Physical functioning	QLQ-C30	Physical functioning
	SF-36	Physical functioning and physical health composite score
	FACT-C (Sprangers, 1999)	Physical well-being
	PROMIS (Hays *et al.*, 2009)	Physical HRQOL
Role functioning	QLQ-C30	Role functioning
	SF-36	Role physical
	FACT-C	Functional well-being
Social functioning	QLQ-C30	Social functioning
	SF-36	Social functioning
	FACT-C	Social well-being
Emotional functioning	QLQ-C30	Emotional functioning
	SF-36	Mental health
	FACT-C	Emotional well-being

QOL: quality of life; **HRQOL:** health-related QOL; **QLQ-C30:** Quality of Life Questionnaire-Core 30; **SF-36:** The Short Form Health Survey; **EQ-5D:** EuroQol five dimensions questionnaire; **FACT-C:** Functional Assessment of Cancer Therapy-Colorectal Cancer; **PROMIS:** Patient-Reported Outcomes Measurement Information System

2.1.6. Quality assessment

The methodological quality of each included article was checked by two reviewers using items adapted from the checklist of Mols et al., with a more detailed emphasis on contents that are important to the specific study question of my review (Mols *et al.*, 2005). The following quality criteria were considered:

- Information bias:
    - Adequate assessment of exposure (i.e. valid PA instrument, assessment of all PA aspects, objective measure rather than self-report)
    - Adequate assessment of outcome (i.e. valid QOL instrument, assessment of all relevant QOL aspects)
    - Adequate description of data (socio-demographic and medical data is described e.g. age, tumor stage at diagnosis etc.; the process of data collection is described e.g. interview or self-report)
- Selection bias:
    - Inclusion and/or exclusion criteria are formulated
    - Healthy (survivor) participation bias (i.e. information about non-participants at baseline, information about drop-outs at follow-up, attrition bias)
- Study design:
    - Description of timing of PA/QOL assessment
    - Adequate information regarding time since diagnosis
    - Adequate sample size and power
    - Prospective study design rather than cross-sectional
- Correction of outcome measures for confounding (e.g. age, sex, comorbidities)

This systematic review was guided by the criteria, set out by the PRISMA guidelines (Stewart *et al.*, 2015).

2.2. The DACHS study

2.2.1. Study design

All empirical analyses of this dissertation are based on the study population of the DACHS (Darmkrebs: Chancen der Verhütung durch Screening) study. The DACHS study is an ongoing population-based case-control study with additional follow-up of CRC cases. The study is carried out in the southwest of Germany and currently includes over 6000 CRC patients and over 6000 controls, recruited since 2003. Eligible cases with a histologically confirmed diagnosis of primary CRC (International Classification of Diseases, 10th Revision [ICD-10] codes C18-C20) have to be older than 30 years at diagnosis, residents of the study region, German speaking, and physically and mentally able to participate in an interview of approximately one hour. The original study was designed to investigate the potentials of endoscopic screening for the reduction of CRC risk. Further details of the study have been described elsewhere (Brenner *et al.*, 2011; Hoffmeister *et al.*, 2015; Jansen *et al.*, 2014; Walter *et al.*, 2017). The DACHS study was approved by the ethics committees of the University of Heidelberg and the state medical boards of Baden-Wuerttemberg and Rhineland-Palatinate. All participants gave written informed consent.

2.2.2. Study population

In all analyses only CRC cases were included since no follow-up information for controls is available. For the analysis on determinants of physical inactivity, 1343 CRC survivors who were recruited between 2003 and 2008 and participated in the five-year follow-up (5YFU) between 2009 and 2014 were included. For the analyses on QOL and fatigue an updated dataset was available and therefore 1781 CRC survivors were included who had been recruited between 2003 and 2010 with a 5YFU participation date between 2009 and 2016.

2.2.3. Data collection

2.2.3.1. Assessment of baseline and follow-up information

Patients with newly diagnosed CRC were identified by their treating clinician during their hospital stay and were interviewed in the hospital or contacted by mail shortly after their discharge by clinicians or clinical cancer registries. At baseline, socio-demographic information, medical, and lifestyle history were obtained by trained interviewers using a standardized questionnaire. Three years after diagnosis detailed information about treatment, other diseases, and recurrence was collected from attending physicians, using a standardized questionnaire. In order to obtain follow-up data including changes in lifestyle, medical or recurrence history, QOL, and fatigue, CRC patients were sent a

questionnaire by mail five years after diagnosis. Information about recurrence, other diseases, and new cancers was verified by the patients´ physicians. Patients´ vital status was regularly checked through population registries.

2.2.3.2. Assessment of quality of life

At 5YFU, QOL was measured using the cancer-specific QOL questionnaire QLQ-C30 (Aaronson *et al.*, 1993). As mentioned earlier (1.2.2.2), the questionnaire contains five functional scales, three symptom scales, a global health and QOL scale (global QOL), and six single items. All QLQ-C30 scales were included in the analyses and scoring was performed according to the EORTC QLQ-C30 scoring manual (Fayers *et al.*, 2001). All scores were linearly transformed to a 0-100 point scale. Higher scores on global QOL and functioning scales imply better QOL, whereas higher scores on the symptom scales imply worse QOL. Differences of 10 points or more were considered as clinically meaningful (Osoba *et al.*, 1998).

2.2.3.3. Assessment of fatigue

At 5YFU, fatigue was measured using the FAQ developed by Glaus et al. (Glaus and Muller, 2001) and the QLQ-C30. The FAQ assesses the dimensions physical, cognitive, and affective fatigue. Since in the DACHS study, only the cognitive (3 items) and affective (5 items) questions of the FAQ were assessed, the fatigue scale of the QLQ-C30 (3 items) was included to additionally include the physical aspect of fatigue. Scoring was performed according to the FAQ and the QLQ-C30 scoring manuals (Fayers *et al.*, 2001; Glaus and Muller, 2001). Cognitive scores were linearly transformed to a 0-9 point scale, affective scores to a 0-15 point scale, and physical fatigue to a 0-100 point scale. Lower scores on cognitive, affective, and physical fatigue imply less fatigue.

2.2.3.4. Assessment of physical activity

At baseline, patients were asked for the hours per week they had engaged in different types of PA (hard work, light work, walking, cycling, sports). Information on PA was collected retrospectively at age 20, 30, 40, 50, 60, 70, and 80 years. At 5YFU, self-reported information on average PA during the last week was collected, using the short-form of the IPAQ (Craig *et al.*, 2003). The questionnaire asks for the number of days and minutes per week during which different activity types (vigorous PA e.g. jogging; moderate PA e.g. swimming; and walking) were performed (see section 1.3.5 for further details).

Based on activity-specific MET score values described by Craig et al. (Craig *et al.* 2003), MET hours per week (MET-h/wk) were calculated according to activities performed at baseline and at 5YFU (Table 2).

Table 2 Activity-specific MET-h/wk at baseline and at five-year follow-up

Baseline		Five-year follow up	
Activity	**MET-h/wk**	**Activity**	**MET-h/wk**
Hard work	8.0	Vigorous	8.0
Light work	2.5	Moderate	4.0
Walking	3.3	Walking	3.3
Cycling	6.0		
Sports	8.0		

MET-h/wk: Metabolic equivalent hours per week

Based on these values, for baseline PA the MET-h/wk spent at ages 20, 30, 40, 50, 60, 70, and 80 and for PA at 5YFU, the MET-h/wk of the last week were calculated for each patient and for each of the specific activity types. For baseline PA, information from all age decades was used to calculate the activity-specific lifetime MET-h/wk (considering the current age of the patient and the years spent in each decade) and information from the age decade preceding the patients´ current age was used to calculate the activity-specific MET-h/wk for the last age decade. The activity-specific MET-h/wk were summed up to create the variables baseline PA (lifetime, last decade) and 5YFU PA.

For the analyses on QOL and on fatigue, baseline PA was categorized into different PA domains (leisure time PA [walking, cycling, sports] and work-related PA [light work, hard work]) and intensities (light PA [light work], moderate PA [walking], and vigorous PA [cycling, sports, hard work]). Physical activity intensity was classified according to the Physical Activity Guidelines for Americans (U.S. Department of Health and Human Services, 2008): light-intensity PA= 1.1-2.9 METs, moderate PA= 3-5.9 METs, and vigorous PA= ≥6 METs.

For all analyses, quartiles for PA at baseline and 5YFU were calculated to differentiate between higher and lower levels of PA. Quartiles were calculated based on MET-h/wk. Patients in quartile 1 (Q1) were defined as physically inactive whereas patients in quartile 2 to quartile 4 (Q2-Q4) were defined as physically active.

Further, for the analyses on QOL and on fatigue these quartiles were used to classify participants into four groups: active maintainers (active at baseline and at 5YFU), increasers (inactive at baseline, active at 5YFU), decreasers (active at baseline, inactive at 5YFU), and inactive maintainers (inactive at baseline and at 5YFU).

In the analyses on QOL and on fatigue, PA of the preceding age decade was defined as pre-diagnosis PA and PA at 5YFU as post-diagnosis PA to emphasize the timing of assessment. In the analysis on determinants of physical inactivity, PA of the preceding age decade was defined as baseline PA.

2.2.4. Statistical analysis

The statistical software package SAS 9.4 (SAS Institute) was used to perform all data analyses. All statistically significant results mentioned in this dissertation refer to a p-value <0.05 in two-sided testing. For the analyses on QOL and on fatigue complete case analyses were performed since the number of missing variables was generally low. Due to some modifications during the data quality checks of the updated dataset there were less missing values for PA at 5YFU and therefore multiple imputation of missing values was not needed. Further, no adjustment for multiple testing was implemented, given the exploratory nature of the analysis. For the analysis on determinants of physical inactivity, multiple imputation of missing data for covariates and PA at 5YFU was performed with R, version 3.4.0, using the R package mice, version 2.30 (N = 25 imputed datasets).

2.2.4.1. Association between physical activity and quality of life

In descriptive analyses, age-adjusted mean levels of pre- and post-diagnosis PA measured in MET-h/wk were calculated according to patient characteristics and compared using linear regression models. To estimate the ordinal association between pre- and post-diagnosis PA, Kendall rank correlations were calculated.

Adjusted means with 95% confidence intervals (CI) were computed using multivariable linear regression models to explore the association of pre-diagnosis PA quartiles with QOL (using the lowest quartile as the reference category). Comprehensive covariate adjustment included baseline age, sex, marital status, residential area, education, comorbidities, alcohol intake, smoking, body mass index (BMI), cancer site, cancer stage, radiotherapy, chemotherapy, and stoma.

Multivariable linear regression analyses were repeated, calculating beta values (ß) with 95% CI and modeling pre-diagnosis PA as a continuous variable (per 100 MET-h/wk) for different domains (leisure time vs. work-related) and intensities of PA (low vs. moderate vs. vigorous) with QOL. In order to assess the independent associations of leisure time and work-related as well as light, moderate, and vigorous PA with QOL, these variables were jointly included in the analytical model.

Additionally, multivariable linear regression models were calculated to explore the association between post-diagnosis PA and QOL, using PA quartiles with the lowest quartile as the reference category. Covariate adjustment was conducted in three steps. Firstly including the same covariates (updated at 5YFU) as used in the analysis of pre-diagnosis PA and QOL, secondly adding pre-diagnosis PA to the model, and finally adding CRC recurrence. Since results did not substantially change using the different covariate adjustments, only results of the first covariate adjustment are reported.

Further, multiple linear regression models were repeated for the association between changes in PA and QOL, using inactive maintainers as the reference category. Covariate adjustment was performed as in the analysis of pre-diagnosis PA and QOL with covariates updated at 5YFU.

2.2.4.2. Association between physical activity and fatigue

All linear regression analyses as described in section 2.2.4.1 were repeated for the association of pre- and post-diagnosis PA with fatigue. Additionally, partial r^2-values were calculated to assess the independent proportion of the explained variance of fatigue by pre- and post-diagnosis PA after adjustment for potential confounders.

2.2.4.3. Potential determinants of physical inactivity

In descriptive analyses, the mean levels of PA at 5YFU measured in MET-h/wk were calculated according to patient characteristics and compared using the Kruskal-Wallis test. Based on previous literature (Courneya *et al.*, 2005; Fisher *et al.*, 2016; Lynch *et al.*, 2010; van Putten *et al.*, 2016), patient characteristics considered as potential determinants of physical inactivity at 5YFU included socio-demographic characteristics (baseline age, sex, marital status, residential area, citizenship, education), tumor-related characteristics (cancer site, cancer stage, primary therapy, recurrence, stoma), lifestyle factors (BMI, alcohol, smoking, baseline PA), and comorbidities. The following variables were measured both at baseline and at 5YFU: stoma, comorbidities, BMI, alcohol, and smoking.

Odds ratios and 95% CI were calculated using bivariate (unadjusted) and multivariable logistic regression to explore the association of baseline and 5YFU characteristics with physical inactivity (using the lowest quartile as the reference category). In order to unravel the interrelatedness of factors measured both at baseline and follow-up (such as stoma, comorbidities, BMI, alcohol, smoking, and PA) as well as the influence of disease recurrence on modifiable factors, different model strategies were employed as a starting point for variable selection:

- Model 1: Baseline variables only (age, sex, marital status, residential area, citizenship, education, cancer site, cancer stage, primary therapy, comorbidities, stoma, alcohol, smoking, BMI)
- Model 2: Model 1 plus baseline PA
- Model 3: Model 1 but baseline information regarding comorbidities, stoma, alcohol, smoking, and BMI was replaced by the corresponding information at 5YFU
- Model 4: Model 3 plus baseline PA
- Model 5: Model 4 plus recurrence

In all models, a backward elimination (removing factors with $p \geq 0.10$) was employed to restrict each of the respective modeling strategies to the most important factors of physical inactivity at 5YFU, while keeping age and sex as permanent covariates. This implies that, in each of the models, all covariates which were selected in at least one of the imputed datasets were included in the final model. Logistic regression analyses were then performed for all models using only these selected variables.

The Akaike information criterion was used to compare the relative quality of the five different modeling strategies by calculating its mean and standard deviation (SD) over all imputed datasets per model.

The selected covariates from model 2 were used for analyses within subgroups according to age and sex to gain more insight into PA patterns within each subgroup. Interaction terms were added to the model to test for heterogeneity in subgroup analyses.

3. RESULTS

3.1. Systematic review of the association between physical activity and quality of life in long-term colorectal cancer survivors

3.1.1. Literature search

The search identified 988 articles (Figure 1). After removing the duplicates, 740 publications remained. After checking titles and abstracts for eligibility, 80 relevant articles were identified. Thirty articles were excluded because they were not original articles, and 32 were excluded because they did not include long-term CRC survivors. Two articles (Johnson *et al.*, 2009; Schlesinger *et al.*, 2014) assessed QOL on only one scale and were therefore excluded. One article (Domati *et al.*, 2011) did not report any results regarding the association of PA and QOL. One article (Mosher *et al.*, 2009) did not report separate results for CRC survivors and four articles (Gunes-Bayir *et al.*, 2015; Hara and Kubo, 2015; Kripp *et al.*, 2015; Lonkvist *et al.*, 2013) were excluded for several other reasons.

In the end, ten articles based on seven studies were included in this systematic review. Two articles of Blanchard et al. (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010) were based on the same study population (American Cancer Society's Study of Cancer Survivors-II, SCS-II). Also the data for the two articles of van Roekel et al. (van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) were taken from an identical study population (Energy for life after ColoRectal cancer, EnCoRe). Further, all CRC patients diagnosed between 2000 and 2009 as registered in the PROFILES cancer registry were selected for the articles of Mols et al. (Mols *et al.*, 2015) and Husson et al. (Husson *et al.*, 2015). In case of multiple articles per study, each study only counted once but results from all articles are shown in the tables.

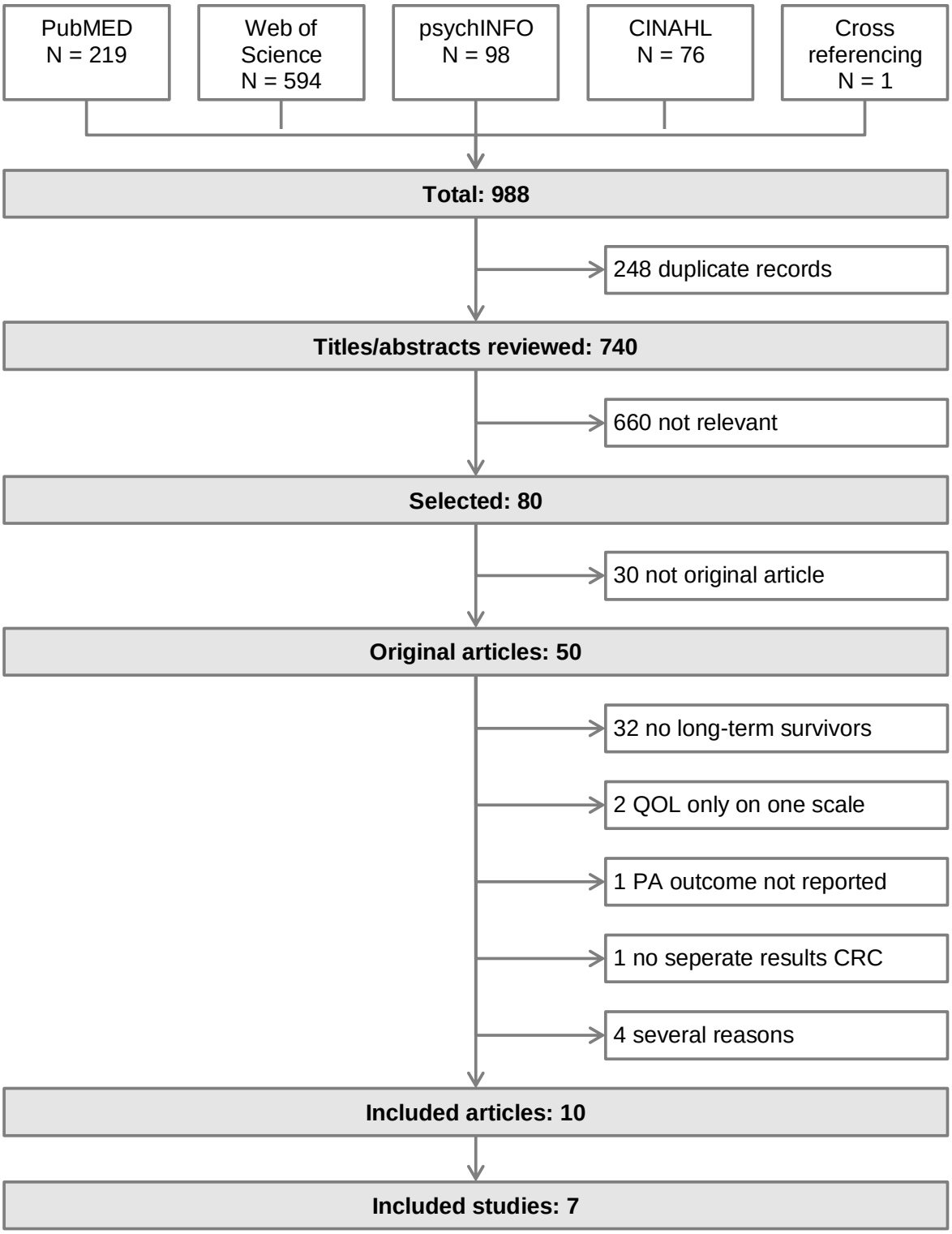


Figure 1 Flow diagram of the systematic literature search. QOL: quality of life, PA: physical activity, CRC: colorectal cancer

3.1.2. Study characteristics

3.1.2.1. Participants´ characteristics

Four studies were conducted in the US (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013), two (Husson *et al.*, 2015; Mols *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) in the Netherlands and one in Australia (Chambers *et al.*, 2012b) (Table 3). Sample sizes ranged from 86 (Blanchard *et al.*, 2004) to 1918 (Blanchard *et al.*, 2008). All of the included studies investigated female and male survivors, but most reported a slightly higher proportion of males. The mean age at time of QOL assessment ranged from 68.4 (Husson *et al.*, 2015) to 81.5 (Thraen-Borowski *et al.*, 2013) years. Two studies were restricted to long-term survivors only (Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013). All the other studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Chambers *et al.*, 2012b; Husson *et al.*, 2015; Mols *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) did not provide specific results for long-term CRC survivors, but comprised survivors with a mean of ≥5 years since diagnosis at the time of QOL assessment. Four studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Husson *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) included CRC survivors from two years post-diagnosis, one prospective study (Chambers *et al.*, 2012b) included participants from five months post-diagnosis, but the results for the association between PA and QOL was based on PA and QOL data collected five years post-diagnosis. Mols et al. (Mols *et al.*, 2015) included survivors from one year up to eleven years post-diagnosis.

The majority of the studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2004; Mols *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) provided information regarding treatment, such as proportions of patients undergoing surgery, chemotherapy and radiation. Three studies included patients with metastases (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Husson *et al.*, 2015; Mols *et al.*, 2015), three studies (Chambers *et al.*, 2012b; Rodriguez *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) excluded patients with metastases and one study (Thraen-Borowski *et al.*, 2013) did not report cancer stage. Four studies (Blanchard *et al.*, 2004; Chambers *et al.*, 2012b; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013) solely included survivors with a primary diagnosis of CRC, and the other studies did not give information about inclusion of survivors with other cancer diagnoses. Three studies (Blanchard *et al.*, 2010; Rodriguez *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) reported the inclusion of patients with cancer recurrence. Regarding cancer site, all studies included patients with colon as well as rectal cancers. Five studies (Chambers *et al.*, 2012b; Husson *et al.*, 2015; Mols *et al.*, 2015; Rodriguez *et*

al., 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) included solely patients with CRC, whilst two studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004) also included patients with other cancer types. However, the results regarding the association between PA and QOL as well as all figures shown in Table 3 are CRC-specific, only response rates are reported for all cancer types together (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004).

Table 3 Characteristics of the studies included in the review

First author (year) country	Study design	Sample size	Age at survey	Time since diagnosis[a]	Cancer treatment	Cancer stage	PA instrument	QOL instrument	Meeting PA recommendations
Blanchard (2004) USA	Cross-sectional, population-based	86	Mean (SD) 69.22 (12.5)	≥2 years 33.7% ≥5 years 30.2% ≥10 years 36.0%	Surgery Radiation Chemotherapy	I-IV	Adherence to PA recommen-dations	SF-36	69.8%
Blanchard (2008)[b] USA	Cross-sectional, population-based	1918	Mean (SD) 70.2 (11.0)	≥2 years 33.4% ≥5 years 35.3% ≥10 years 31.3%	Surgery Radiation Chemotherapy Hormone therapy Immuno therapy BMT	I-IV	GLTEQ	SF-36	35%
Blanchard (2010)[b] USA	Cross-sectional, population-based	668	Mean (SD) 70.2 (11.1)	≥2 years 26.8% ≥5 years 40.5% ≥10 years 32.0%	In treatment (not further specified)	I-IV	GLTEQ	SF-36	HW 20.0% OW 30.0% OB 24.4%
Chambers (2012) Australia	Cross-sectional & longitudinal, population-based	632	Mean 69.02	≥5 years Mean (SD) 5 (6.1)	Surgery Chemotherapy	I-III	AAS	FACT-C SWLS	–
Husson (2015)[c] The Netherlands	Cross-sectional & longitudinal, population-based	1739	Mean (SD) 68.4 (9.4)	≥2 years Mean (SD) 5.1 (2.8)	Radiation Chemotherapy	I-IV	EPIC	QLQ-C30	82%
Mols (2015)[c] The Netherlands	Cross-sectional, population-based	1648	Mean (SD) Chemotherapy: 66.7 (9.8) No chemotherapy: 70.6 (9.0)	1-11 years Mean (SD) Chemotherapy: 5.6 (2.8) No chemotherapy: 6.1 (2.8)	Surgery Radiation	I-IV	EPIC	QLQ-C30 QLQ-CIPN20	Chemotherapy: 93% No Chemotherapy: 89%
Rodriguez (2015) USA	Cross-sectional, population-based	593	Mean 73.8	Only ≥5 years Mean 6.2	Number of treatments	I-III	GLTEQ	PROMIS EQ-5D	–

Table 3 Characteristics of the studies included in the review *(continued)*

First author (year) country	Study design	Sample size	Age at survey	Time since diagnosis[a]	Cancer treatment	Cancer stage	PA instrument	QOL instrument	Meeting PA recommendations
Thraen-Borowski (2013) USA	Cross-sectional, population-based	832	Mean (SD) 81.5 (5.8)	Only ≥5 years Mean (SD) 8.2 (1.7)	-	-	CHAMPS	SF-36	52%
Van Roekel (2015)[d] The Netherlands	Cross-sectional, mono-centric	151	Mean (SD) 69.8 (8.7)	2-10 years Mean (SD) 5.7 (1.8)	Surgery Radiation Chemotherapy	I-III	SQUASH	QLQ-C30 WHODAS II CIS HADS	71%
Van Roekel (2016)[d] The Netherlands	Cross-sectional, mono-centric	145	Mean (SD) 70.0 (8.7)	2-10 years Mean (SD) 5.7 (1.9)	Surgery Radiation Chemotherapy	I-III	MMOXX1	QLQ-C30 WHODAS II CIS HADS	–

PA: physical activity; **QOL:** quality of life; **PA recommendations:** 150 minutes of moderate intensity exercise each week or 75 minutes of vigorous intensity activity each week or an equivalent combination of both; **SD:** standard deviation; **SF-36:** The Short Form Health Survey; **BMT:** Bone marrow transplantation; **GLTEQ:** Godin Leisure-Time Exercise Questionnaire; **HW:** healthy weight; **OW:** overweight; **OB:** obese; **AAS:** The Active Australian Survey; **FACT-C:** Functional Assessment of Cancer Therapy - Colorectal Cancer; **SWLS:** Satisfaction With Life Scale; **EPIC:** European Prospective Investigation into Cancer Physical Activity Questionnaire; **QLQ-C30:** Quality of Life Questionnaire-Core 30; **QLQ-CIPN20:** Quality of Life Questionnaire - Chemotherapy-Induced Peripheral Neuropathy; **PROMIS:** Patient-Reported Outcomes Measurement Information System; **EQ-5D**: EuroQol five dimensions questionnaire; **CHAMPS:** The Community Healthy Activities Model Program for Seniors; **SQUASH:** The Short Questionnaire to Assess Health-Enhancing Physical Activity; **WHODAS:** World Health Organization Disability Assessment Schedule; **CIS:** Checklist Individual Strength; **HADS:** Hospital Anxiety and Depression Scale; **MMOXX1:** Triaxial MOX activity monitor; [a]Time since diagnosis at time point of QOL assessment; [b]Articles based on same study population: American Cancer Society´s Study of Cancer Survivors-II (SCS-II); [c]Articles based on same study population: All patients diagnosed between 2000-2009 and registered in the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES registry); [d]Articles based on same study population: Energy for life after ColoRectal cancer (EnCoRe)

3.1.2.2. Study design

All included studies were observational in design. Recruitment methods varied across studies, six (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Chambers *et al.*, 2012b; Husson *et al.*, 2015; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013) used population-based recruitment, and one (van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) was completed in a single institution. Two of the articles (Chambers *et al.*, 2012b; Husson *et al.*, 2015) were prospective, longitudinal designs assessing PA and/or QOL at multiple points in time, while the remaining eight were cross-sectional (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016).

3.1.2.3. Response rate and follow-up rate

The response rates in the aforementioned cross-sectional studies ranged from 33% (Blanchard *et al.*, 2008) (not CRC-specific) to 83% (Mols *et al.*, 2015). Husson et al. (Husson *et al.*, 2015) reported a participation of 73% at baseline, 83% for the first and 82% for the second follow-up. In the study of Chambers et al. (Chambers *et al.*, 2012b) 56% of the survivors participated in the follow-up, however no information was given regarding baseline participation.

3.1.2.4. Quality assessment

The results of the quality assessment of the included studies are displayed in Table 4.

Table 4 Quality assessment of the studies included in the review

First author (year) country	Potential Limitations
Blanchard (2004) USA	- No validated PA questionnaire used - Possible response bias due to self-reported PA - Sample size <100 - Cross-sectional study design
Blanchard (2008)[a] USA	- Possible response bias due to self-reported PA - Only assessment of leisure-time PA - Cross-sectional study design
Blanchard (2010)[a] USA	- Possible response bias due to self-reported PA - Only assessment of leisure-time PA - Cross-sectional study design
Chambers (2012) Australia	- Possible response bias due to self-reported PA - Only assessment of leisure-time PA
Husson (2015)[b] The Netherlands	- Possible response bias due to self-reported PA
Mols (2015)[b] The Netherlands	- Possible response bias due to self-reported PA - Cross-sectional study design
Rodriguez (2015) USA	- Possible response bias due to self-reported PA - Cross-sectional study design
Thraen-Borowski (2013) USA	- Possible response bias due to self-reported PA - Only assessment of leisure-time PA - Cross-sectional study design
Van Roekel (2015)[c] The Netherlands	- Possible response bias due to self-reported PA - Cross-sectional study design
Van Roekel (2016)[c] The Netherlands	- Cross-sectional study design

PA: physical activity; [a]Articles based on same study population: American Cancer Society´s Study of Cancer Survivors-II (SCS-II); [b]Articles based on same study population: All patients diagnosed between 2000-2009 and registered in the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES registry); [c]Articles based on same study population: Energy for life after ColoRectal cancer (EnCoRe)

3.1.2.5. Assessment and categorization of physical activity

Apart from one article which measured PA prospectively at three points in time (Husson *et al.*, 2015), all other articles (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Chambers *et al.*, 2012b; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) assessed PA only once. One article (van Roekel *et al.*, 2016) measured PA by using the Triaxial MOX activity monitor (MMOXX1). The MMOXX1 is able to objectively measure sedentary, standing and PA time. Apart from Blanchard et al. (Blanchard *et al.*, 2004) who only reported the adherence or non-adherence to PA recommendations, all other studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Chambers *et al.*, 2012b; Husson *et al.*, 2015; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015) used validated PA instruments relying on self-report. The questionnaire most frequently applied was the GLTEQ. Several studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Husson *et al.*, 2015; Mols *et al.*, 2015; Thraen-Borowski *et al.*, 2013) used PA recommendations such as the one published by the ACS to differentiate between active and non-active survivors. The ACS recommends at least 150 min of moderate intensity exercise each week or 75 min of vigorous intensity activity each week or an equivalent combination of both (Kushi *et al.*, 2012). To further quantify the intensity of PAs, MET-h/wk were used in five articles (Husson *et al.*, 2015; Mols *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016). In four of these articles light PA was defined as <3 MET-h/wk, whereas moderate to vigorous PA was defined as an intensity of ≥3 MET-h/wk (Husson *et al.*, 2015; Mols *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015). One article (van Roekel *et al.*, 2016) defined PA as >1.5 MET-h/day and did not further differentiate between light PA and moderate to vigorous PA.

3.1.2.6. Assessment of quality of life

Quality of life was assessed only at one point in time in most of the studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016). Only the two longitudinal studies (Chambers *et al.*, 2012b; Husson *et al.*, 2015) assessed QOL at different intervals. Chambers et al. assessed QOL five months post-diagnosis and five years after diagnosis (Chambers *et al.*, 2012b). Husson et al. assessed QOL in yearly intervals over a three year period, starting with a baseline average time since diagnosis of 5.1 years (Husson *et al.*, 2015). The QOL questionnaires most commonly used were the QLQ-C30 (Husson *et al.*, 2015; Mols *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) and the SF-36 (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004).

Information was collected by mail in six studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Husson *et al.*, 2015; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015), by telephone in five studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Chambers *et al.*, 2012b; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013), and in person in one study (van Roekel *et al.*, 2016). One study (van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) assessed only some of the QLQ-C30 subscales and additionally used the *Hospital Anxiety and Depression Scale* (HADS), the *Checklist Individual Strength* (CIS), and the *World Health Organization Disability Assessment Schedule* (WHODAS) questionnaire to assess QOL in CRC survivors.

3.1.3. Analysis, statistical methods, and clinical relevance

All studies compared CRC survivors who were active with those who were less active or not active. Most of the studies compared survivors who met PA recommendations to those survivors who did not (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Husson *et al.*, 2015; Mols *et al.*, 2015; Thraen-Borowski *et al.*, 2013). Two studies compared different amounts of activity to a non-active reference group of CRC survivors (Chambers *et al.*, 2012b; Rodriguez *et al.*, 2015). Some studies compared survivors´ QOL according to higher and lower levels of light PA (Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015) and/or moderate to vigorous PA (Husson *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015). One study additionally compared lower with higher amounts of non-exercise (e.g. gardening) and planned exercise (PA that is planned, structured and repetitive e.g. jogging) (Thraen-Borowski *et al.*, 2013).

All studies examined possible confounding factors including age, sex, and comorbidities by some sort of multivariable regression modeling or analysis of (co)variance. Six studies adjusted for BMI and only three for smoking. Three studies performed stratified analyses by age, sex, comorbidities, treatment, and BMI for the association between PA and QOL.

One study (Husson *et al.*, 2015; Mols *et al.*, 2015) reported clinical relevance for the QLQ-C30. One study reported an overall clinical relevance for the SF-36 of 5-10 score points mean difference (Thraen-Borowski *et al.*, 2013). For some studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Chambers *et al.*, 2012b) the clinical relevance was not reported and could not be derived from the available information. Moreover, two studies used SDs to determine clinical relevance (Mols *et al.*, 2015; van Roekel *et al.*, 2016).

3.1.4. Study findings regarding the association between physical activity and quality of life

According to the included studies, 35-80% of the CRC survivors met the PA recommendations (Table 3). Table 5, Table 6, Table 7, and Appendix II show the study specific results regarding the association between PA and QOL according to type of analysis and type of QOL instrument. Since the included studies used various QOL questionnaires, which differ in the included scales, not all studies contributed to the results on every outcome and are thus not considered when summarizing the respective findings.

3.1.4.1. Physically active versus not active

Five of the six studies which compared active with non-active CRC survivors, found positive associations between PA and QOL (Table 5). Regarding specific subscales, homogenous results were found for global QOL, which was positively associated with PA in all of the five studies which investigated global QOL. Differences in global QOL between physically active versus non-active survivors were clinically relevant in two (Husson *et al.*, 2015; Thraen-Borowski *et al.*, 2013) of the five studies. Three out of four studies reported a positive association between PA and physical functioning, of these two (Husson *et al.*, 2015; Thraen-Borowski *et al.*, 2013) associations were of clinical relevance. Two studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2004) did not report any results on physical functioning. In contrast, results for role and social functioning were more heterogeneous and less often statistically significant.

Table 5 Association of physical activity and quality of life - active vs. not active

		Statistical significance (p<0.05) and clinical relevance										
		+/–: significant positive/negative association ns: not statistically significant .: not reported						[a,b,c]clinical relevance				
Study	**QLQ-C30**	**QL**		**PF**		**RF**		**EF**		**SF**		**CF**
Husson (2015)	Meeting vs. not meeting PA recommendations, Interindividual[d]	+[b]		+[b]		+[b]		+[b]		+[b]		+
	Meeting vs. not meeting PA recommendations, Intraindividual[e]	+		+		+		ns		ns		ns
Mols (2015)	Meeting vs. not meeting PA recommendations	+[c]		+[c]		+[c]		+[c]		+[c]		+[c]
Study	**SF-36**	**PF**	**RP**	**BP**	**SF**	**MH**	**RE**	**VT**	**GH**	**GCS**	**PCS**	**MCS**
Blanchard (2004)	Meeting vs. not meeting PA recommendations	.	.	.	.	.	.	.	.	+[c]	.	.
Blanchard (2008)	Meeting vs. not meeting PA recommendations	.	.	.	.	.	.	.	.	+[c]	.	.
Thraen-Borowski (2013)	Meeting vs. not meeting PA recommendations	+[a]	+[a]	+	+[a]	ns	ns	+[a]	+[a]	.	.	.
Study	**FACT-C/ SWLS**	**PWB**		**SWB**		**EWB**		**FWB**		**CCS**		**SWLS**
Chambers (2012)	Sedentary - Ref.											
	Insufficiently active (1-149 min/wk)	ns		ns		ns		ns		ns		ns
	Sufficiently active (≥150 min/wk)	ns		ns		ns		ns		ns		ns
Study	**PROMIS/ EQ-5D**	**Physical HRQOL**				**Mental HRQOL**				**Overall HRQOL**		
Rodriguez (2015)	PA min/wk No PA - Ref.											
	≤60, 61-149, 150-249, 250+	+[c] (≤ 60, 61-149, 150-249)				ns				+[c] (≤ 60, 61-149, 150-249)		

QOL: quality of life; **QLQ-C30** (Quality of Life Questionnaire-Core 30) *QL:* global QOL, *PF*: physical functioning, *RF*: role functioning, *EF*: emotional functioning, *SF*: social functioning, *CF*: cognitive functioning; **PA:** physical activity; **PA recommendations:** 150 minutes of moderate intensity exercise each week or 75 minutes of vigorous intensity activity each week or an equivalent combination of both; **SF-36** (The Short Form Health Survey) *PF*: physical functioning, *RP*: role limitations due to physical health problems, *BP*: bodily pain, *SF*: social functioning, *MH*: general mental health, *RE*: role limitations due to emotional problems, *VT*: vitality, *GH*: general health perceptions, *GCS*: global health composite score, *PCS*: physical composite score, *MCS*: mental composite score; **FACT-C** (Functional Assessment of Cancer Therapy - Colorectal Cancer) *PWB*: physical well-being, *SWB*: social well-being, *EWB*: emotional well-being, *FWB*: functional well-being, *CCS*: colorectal cancer scale; **SWLS** (Satisfaction with Life Scale); **Ref.:** reference; **min/wk:** minutes per week; **PROMIS** (Patient-Reported Outcomes Measurement Information System); **EQ-5D** (EuroQol five dimensions questionnaire); **HRQOL:** health-related QOL; [a]clinical relevance reported by authors; [b]clinical relevance calculated by RE; [c]clinical relevance: no values, no cut-off for calculation available; [d]interindividual: patients average amount of PA/ average level PA of total group; [e]intraindividual: patients PA level at one time point/ patients average PA level

3.1.4.2. Different intensities of physical activity and linear association of physical activity and quality of life

Table 6 shows the results from the studies examining the association between multiple intensities of PA and QOL. Higher QOL was associated with both, lower and higher PA intensities but the association between PA and QOL depended on the specific QOL dimension. For instance, survivors who had higher levels of light PA reported significantly and clinically relevant higher physical functioning than survivors who had lower light PA levels (Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015), but no association was found between global QOL, social functioning, and light PA (van Roekel *et al.*, 2015), respectively. Positive associations between moderate to vigorous PA and physical functioning were found in two (Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015) of three (Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015) studies. Survivors who reported higher moderate to vigorous PA reported significantly and clinically relevant higher physical functioning compared to survivors who had lower moderate to vigorous PA (Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015).

When assessing PA as a continuous variable, significant positive associations of moderate to vigorous PA with higher global QOL, physical, emotional, social, and cognitive functioning were found (Husson *et al.*, 2015). Van Roekel et al. reported significant positive associations between PA time (hour/day) and physical functioning and disability, however, no associations were found for global QOL, role and social functioning, fatigue, anxiety, and depression (van Roekel *et al.*, 2016).

Table 6 Association of physical activity and quality of life - different intensities of physical activity and linear association

		Statistical significance (p<0.05) and clinical relevance									
	Different intensities of PA	+/–: significant positive/negative association ns: not statistically significant .: not reported				[a,b,c]clinical relevance					
Study	**QLQ-C30**	**QL**		**PF**		**RF**		**EF**		**SF**	**CF**
Van Roekel (2015)	>LPA (Q4= ≥23.0 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)	ns		+[b]		+[b]		.		ns	.
	>LPA (Q3= 10-22 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)	.		.		.		.		.	.
	>MVPA (Q4= ≥15.5 h/wk) vs. <MVPA (Q1= ≤4.3 h/wk)	ns		+[b]		ns		.		ns	.
	>MVPA (Q3= 8.7-15 h/wk) vs. <MVPA (Q1= ≤4.3 h/wk)	ns		.		+[b]		.		+[b]	.
Study	**SF-36**	**PF**	**RP**	**BP**	**SF**	**MH**	**RE**	**VT**	**GH**	**GCS**	**PCS**	**MCS**
Thraen-Borowski (2013)	>MVPA (Q4= ≥11.25 h/wk) vs. <MVPA (Q1= 0.00 h/wk)	.	.	.	.	.	.	.	.	.	+[b]	ns
	>LPA (Q4= ≥13.0 h/wk) vs. <LPA (Q1= ≤1.50 h/wk)[d]	.	.	.	.	.	.	.	.	.	ns	ns
	>LPA (Q4= ≥9.0 h/wk) vs. <LPA (Q1= 0.0 h/wk)[e]	.	.	.	.	.	.	.	.	.	+[b]	+[b]
	>Planned exercise[f] (Q4= ≥9.50 h/wk) vs. <Planned exercise (Q1= 0.0 h/wk)	.	.	.	.	.	.	.	.	.	+[b]	ns
	>Non-exercise[g] (Q4= ≥16.50 h/wk) vs. <Non-exercise (Q1= ≤1.63 h/wk)	.	.	.	.	.	.	.	.	.	+	ns
Study	**WHODAS/ CIS/ HADS**	**DIS**				**FA**				**DIST**	
Van Roekel (2015)	>LPA (Q4= ≥23.0 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)	–[c]				ns				ns	
	>LPA (Q3= 10-22 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)	ns				–[c]				ns	
	>MVPA (Q4= ≥15.5 h/wk) vs. <MVPA (Q1= ≤4.3 h/wk)	ns				ns				ns	
	>MVPA (Q3= 8.7-15 h/wk) vs. <MVPA (Q1= ≤4.3 h/wk)	–[c]				–[c]				–[c]	
Study	**PROMIS/ EQ-5D**	**Physical HRQOL**				**Mental HRQOL**				**Overall HRQOL**	
Rodriguez (2015)	MVPA min/wk No MVPA - Ref. ≤60, 61-149, 150+	ns				ns				+[c] (61-149, 150+) ns (≤ 60)	

Table 6 Association of physical activity and quality of life - different intensities of physical activity and linear association *(continued)*

		Statistical significance (p<0.05) and clinical relevance					
	Linear association PA and QOL (continuous results)	+/–: significant positive/negative association ns: not statistically significant .: not reported			[a,b,c]clinical relevance		
Study	**QLQ-C30**	**QL**	**PF**	**RF**	**EF**	**SF**	**CF**
Husson (2015)	Continuous: Additional hour of MVPA/wk, Interindividual[h]	+	+	+	+	+	+
	Continuous: Additional hour of MVPA/wk, Intraindividual[i]	ns	+	ns	ns	ns	+
Van Roekel (2016)	Single-variable model, PA[j]	ns	+	ns	.	ns	.
	Partition model, PA[k]	ns	+	ns	.	ns	.
	Substituting 1 h/day of sedentary time with PA	ns	+[a]	ns	.	ns	.
	Substituting 1 h/day of standing time with PA	ns	ns	ns	.	ns	.
Study	**WHODAS/ CIS/ HADS**	**DIS**	**FA**		**ANX**	**DEP**	
Van Roekel (2016)	Single-variable model PA[j]	–[c]	ns		ns	ns	
	Partition model PA[k]	ns	ns		ns	ns	
	Substituting 1 h/day of sedentary time with PA	ns	ns		ns	ns	
	Substituting 1 h/day of standing time with PA	ns	ns		ns	ns	

PA: physical activity; **QOL:** quality of life; **QLQ-C30** (Quality of Life Questionnaire-Core 30) *QL*: global quality of life, *PF*: physical functioning, *RF*: role functioning, *EF*: emotional functioning, *SF*: social functioning, *CF*: cognitive functioning; **LPA:** light physical activity (<3 metabolic equivalent values [METs]); **Q:** quartile; **h/wk:** hours per week; **MVPA:** moderate to vigorous physical activity (≥3 METs); **SF-36** (The Short Form Health Survey) *PF*: physical functioning, *RP*: role limitations due to physical health problems, *BP*: bodily pain, *SF*: social functioning, *MH*: general mental health, *RE*: role limitations due to emotional problems, *VT*: vitality, *GH*: general health perceptions, *GCS*: global health composite score, *PCS*: physical composite score, *MCS*: mental composite score; **WHODAS** (World Health Organization Disability Assessment Schedule II) *DIS*: disability; **CIS** (Checklist Individual Strength) *FA*: fatigue; **HADS** (Hospital Anxiety and Depression Scale) *DIST:* distress, *ANX:* anxiety, *DEP:* depression*;* **PROMIS** (Patient-Reported Outcomes Measurement Information System); **EQ-5D** (EuroQol five dimensions questionnaire); **HRQOL:** health-related QOL; **Ref.:** reference; [a]clinical relevance reported by authors; [b]clinical relevance calculated by RE; [c]clinical relevance: no values, no cut-off for calculation available; [d]participants reported LPA and MVPA; [e]participants reported only LPA; [f]intentional exercise e.g. jogging, [g]non-intentional exercise e.g. gardening; [h]interindividual: patients average amount of PA/ average level PA of total group; [i]intraindividual: patients PA level at one time point/ patients average PA level; [j]PA was entered separately in a single confounder-adjusted model, without adjustment for any of the other activities (sedentary, standing); [k]all activity categories (sedentary, standing, PA) were entered simultaneously in a single confounder-adjusted model, to estimate independent associations of each activity category

3.1.4.3. Further subgroup analyses and changes in the association of physical activity and quality of life over time

Only the study by van Roekel et al. provided results stratified by age (van Roekel *et al.*, 2016) and sex (van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) (Table 7). The association between PA and QOL did not differ between younger and older survivors. However, the association between light PA/PA and QOL seemed to be stronger among women than among men. Women who had higher light PA levels reported significantly and clinically relevant higher physical, role, and social functioning and significantly less disability compared to women who had lower light PA levels. The association of PA with global QOL, fatigue, and distress was not statistically significant. When substituting one hour of sedentary time with PA, PA was clinically and significantly associated with higher physical functioning and lower disability in women. However, PA was not associated with global QOL, role and social functioning, fatigue, anxiety, and depression when substituting one hour of sedentary time with PA. In both investigations no significant associations were found in men.

Van Roekel et al. (van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) reported heterogeneous results for the association between light PA/PA and QOL stratified by number of comorbidities. Survivors with ≥2 comorbidities who reported higher levels of light PA reported significantly and clinically relevant higher physical and role functioning and significantly less disability than survivors with lower levels of light PA. No associations were observed between higher levels of light PA and global QOL, social functioning, fatigue, and distress. No associations were reported for light PA levels and any QOL scales for survivors with <2 comorbidities (van Roekel *et al.*, 2015). In contrast, when using sedentary time or standing time as a proxy measures of (lack of) PA, none of the QOL scales were associated with PA in neither survivors with <2 nor survivors ≥2 comorbidities (van Roekel *et al.*, 2016). Heterogeneous results were also reported regarding the association between PA and QOL with respect to BMI. According to van Roekel et al. (van Roekel *et al.*, 2016) non-obese survivors who were physically active reported higher global QOL, lower depression and anxiety than less active non-obese survivors. No association between PA and QOL was found among obese survivors. In contrast, in the study of Blanchard et al. (Blanchard *et al.*, 2010) no associations between PA and QOL were found according to BMI.

Survivors without chemotherapy treatment who were physically active scored significantly lower on the sensory, motor, and autonomic scale of the *Quality of Life Questionnaire - Chemotherapy-Induced Peripheral Neuropathy* (QLQ-CIPN20) of the EORTC, compared to

non-active survivors (Mols *et al.*, 2015). The association between PA and QOL among CRC survivors with chemotherapy treatment did not substantially differ, only no significant associations were found for PA and the autonomic scale. In both, survivors with and without chemotherapy treatment, associations between PA and the motor scale were of clinical relevance.

Only one study assessed PA and QOL at various points in time among the same patients (Husson *et al.*, 2015). In CRC survivors who were physically active over a three years period, role and social functioning improved whereas role and social functioning declined in non-active survivors. No associations were found between persistent PA and global QOL, physical, emotional, and cognitive functioning (Husson *et al.*, 2015).

Table 7 Association of physical activity and quality of life - subgroup analyses

		Statistical significance (p<0.05) and clinical relevance					
	Subgroup analyses	+/–: significant positive/negative association [a,b,c]clinical relevance ns: not statistically significant .: not reported					
Study	**QLQ-C30**	**QL**	**PF**	**RF**	**EF**	**SF**	**CF**
	Sex						
Van Roekel (2015)	>LPA (Q4= ≥23.0 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)						
	Women	ns	+[b]	+[b]	.	+[b]	.
	Men	ns	ns	ns	.	ns	.
	Comorbidities						
	>LPA (Q4= ≥23.0 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)						
	≥2 comorbidities	ns	+[b]	+[b]	.	ns	.
	<2 comorbidities	ns	ns	ns	.	ns	.
	Sex						
Van Roekel (2016)	Substituting 1 h/day of sedentary time with PA						
	Women	ns	+[a]	ns	.	ns	.
	Men	ns	ns	ns	.	ns	.
	Substituting 1 h/day of standing time with PA						
	Women	ns	ns	ns	.	ns	.
	Men	ns	ns	ns	.	ns	.
	Age						
	Substituting 1 h/day of sedentary time with PA						
	<70 years	ns	ns	ns	.	ns	.
	≥70 years	ns	ns	ns	.	ns	.
	Substituting 1 h/day of standing time with PA						
	<70 years	ns	ns	ns	.	ns	.
	≥70 years	ns	ns	ns	.	ns	.
	BMI						
	Substituting 1 h/day of sedentary time with PA						
	Non-obese	+[a]	ns	ns	.	ns	.
	Obese	ns	ns	ns	.	ns	.
	Substituting 1 h/day of standing time with PA						
	Non-obese	ns	ns	ns	.	ns	.
	Obese	ns	ns	ns	.	ns	.

Table 7 Association of physical activity and quality of life - subgroup analyses *(continued)*

		Statistical significance (p<0.05) and clinical relevance										
	Subgroup analyses	+/–: significant positive/negative association [a,b,c]clinical relevance ns: not statistically significant .: not reported										
Study	**QLQ-C30**	**QL**		**PF**		**RF**		**EF**		**SF**		**CF**
	Comorbidities											
Van Roekel (2016)	Substituting 1 h/day of sedentary time with PA											
	<2 comorbidities	ns		ns		ns		.		ns		.
	≥2 comorbidities	ns		ns		ns		.		ns		.
	Substituting 1 h/day of standing time with PA											
	<2 comorbidities	ns		ns		ns		.		ns		.
	≥2 comorbidities	ns		ns		ns		.		ns		.
	QLQ-CIPN20	**Sensory**				**Motor**				**Autonomic**		
	Treatment											
Mols (2015)	Meeting vs. not meeting PA recommendations											
	CT, PA vs. CT, no PA	+				+				ns		
	Meeting vs. not meeting PA recommendations											
	No CT, PA vs. no CT, no PA	+[a]				+				+		
	SF-36	**PF**	**RP**	**BP**	**SF**	**MH**	**RE**	**VT**	**GH**	**GCS**	**PCS**	**MCS**
	BMI											
Blanchard (2010)	Meeting vs. not meeting PA recommendations											
	Healthy weight	.	.	.	.	.	.	.	.	.	ns	ns
	Overweight	.	.	.	.	.	.	.	.	.	ns	ns
	WHODAS/ CIS/ HADS	**DIS**				**FA**				**DIST**		
	Sex											
Van Roekel (2015)	>LPA (Q4= ≥23.0 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)											
	Women	–[c]				ns				ns		
	Men	ns				ns				ns		
	Comorbidities											
	>LPA (Q4= ≥23.0 h/wk) vs. <LPA (Q1= ≤2.0 h/wk)											
	≥2 comorbidities	–[c]				ns				ns		
	<2 comorbidities	ns				ns				ns		

Table 7 Association of physical activity and quality of life - subgroup analyses *(continued)*

		Statistical significance (p<0.05) and clinical relevance			
	Subgroup analyses	+/–: significant positive/negative association ns: not statistically significant .: not reported		[a,b,c]clinical relevance	
Study	**WHODAS/ CIS/ HADS**	**DIS**	**FA**	**ANX**	**DEP**
Van Roekel (2016)	***Sex***				
	Substituting 1 h/day of sedentary time with PA				
	Women	–[a]	ns	ns	ns
	Men	ns	ns	ns	ns
	Substituting 1 h/day of standing time with PA				
	Women	ns	ns	ns	ns
	Men	ns	ns	ns	ns
	Age				
	Substituting 1 h/day of sedentary time with PA				
	<70 years	ns	ns	ns	ns
	≥70 years	ns	ns	ns	ns
	Substituting 1 h/day of standing time with PA				
	>70 years	ns	ns	ns	ns
	≥70 years	ns	ns	ns	ns
	BMI				
	Substituting 1 h/day of sedentary time with PA				
	Non-obese	ns	ns	–	–
	Obese	ns	ns	ns	ns
	Substituting 1 h/day of standing time with PA				
	Non-obese	ns	ns	–[a]	–
	Obese	ns	ns	ns	ns

Table 7 Association of physical activity and quality of life - subgroup analyses *(continued)*

		Statistical significance (p<0.05) and clinical relevance			
	Subgroup analyses	+/–: significant positive/negative association ns: not statistically significant .: not reported		[a,b,c]clinical relevance	
Study	**WHODAS/ CIS/ HADS**	**DIS**	**FA**	**ANX**	**DEP**
	Comorbidities				
Van Roekel (2016)	Substituting 1 h/day of sedentary time with PA				
	<2 comorbidities	ns	ns	ns	ns
	≥2 comorbidities	ns	ns	ns	ns
	Substituting 1 h/day of standing time with PA				
	<2 comorbidities	ns	ns	ns	ns
	≥2 comorbidities	ns	ns	ns	ns

QOL: quality of life; **QLQ-C30** (Quality of Life Questionnaire-Core 30) *QL*: global quality of life, *PF*: physical functioning, *RF*: role functioning, *EF*: emotional functioning, *SF*: social functioning, *CF*: cognitive functioning; **LPA:** light physical activity (<3 metabolic equivalent values); **Q:** quartile; **h/wk:** hours per week; **h/day:** hours per day; **PA:** physical activity; **BMI:** body mass index; **QLQ-CIPN20** (Quality of Life Questionnaire - Chemotherapy-Induced Peripheral Neuropathy); **PA recommendations**: 150 minutes of moderate intensity exercise each week or 75 minutes of vigorous intensity activity each week or an equivalent combination of both; **CT:** chemotherapy; **SF-36** (The Short Form Health Survey) *PF*: physical functioning, *RP*: role limitations due to physical health problems, *BP*: bodily pain, *SF*: social functioning, *MH*: general mental health, *RE*: role limitations due to emotional problems, *VT*: vitality, *GH*: general health perceptions, *GCS*: global health composite score, *PCS*: physical composite score, *MCS*: mental composite score; **WHODAS** (World Health Organization Disability Assessment Schedule II) *DIS*: disability; **CIS** (Checklist Individual Strength) *FA*: fatigue; **HADS** (Hospital Anxiety and Depression Scale) *DIST*: distress, *ANX*: anxiety, *DEP*: depression; [a]clinical importance reported by authors; [b]calculated by RE; [c]no values, no cut-off for calculation available

3.2. Results from the DACHS study

3.2.1. Association between physical activity and quality of life

3.2.1.1. Descriptive analyses

Overall, 1781 long-term CRC survivors were included in the analysis. Participants were on average 66.1 years old at baseline and 60% were male and 40% female (Table 8). The tumor was located in the colon in around 60% and confined to the intestine (UICC stage I or II) in almost 60% of all cases. Primary treatment included radiotherapy and chemotherapy in 20% and 42% of cases, respectively. Five years after diagnosis, 22% of all survivors still had a stoma and around 9% of the survivors had experienced a CRC recurrence. Average pre-diagnosis PA levels were two to three times as high as post-diagnosis PA levels. Baseline characteristics such as living in a village, being less educated, and having <2 comorbidities were associated with higher mean MET-h/wk pre- and post-diagnosis. The comparison of pre- and post-diagnosis PA quartiles revealed a weak correlation (Kendall rank correlation coefficient = 0.15; $p < 0.0001$).

Table 8 Patient characteristics according to pre- and post-diagnosis physical activity

	Total sample	Pre-diagnosis PA[a,d] (MET-h/wk)		Post-diagnosis PA[b,d] (MET-h/wk)	
	N (Col. %)	Mean (SD)	p-value[f]	Mean (SD)	p-value[f]
Overall	1781	143.5 (107.1)		54.9 (60.4)	
Age			-		-
30-59 years	431 (24.2)	185.1 (122.7)		57.5 (60.3)	
60-69 years	655 (36.8)	157.4 (112.4)		58.8 (59.0)	
70-79 years	560 (31.4)	109.7 (76.2)		53.6 (63.7)	
80+ years	135 (7.6)	82.8 (55.0)		33.4 (47.1)	
Mean (SD)	66.1 (9.9)				
Sex			0.5432		0.1260
Female	706 (39.6)	145.4 (95.0)		52.2 (58.6)	
Male	1075 (60.4)	142.2 (114.3)		56.7 (61.4)	
Marital status[c]			0.0008		0.0480
Unmarried	89 (5.0)	152.0 (113.8)		56.6 (54.3)	
Married	1338 (75.1)	146.8 (110.6)		56.2 (60.3)	
Divorced	106 (6.0)	147.9 (111.5)		54.5 (66.5)	
Widowed	245 (13.8)	120.5 (77.4)		47.4 (59.9)	
Residential area			0.0022		0.0005
Village (<10,000)	635 (35.7)	152.9 (125.2)		62.1 (67.5)	
Small town	611 (34.3)	142.5 (102.1)		51.6 (55.5)	
City (>100,000)	535 (30.0)	133.6 (86.8)		50.0 (55.7)	
Education[c]			<0.0001		0.0613
≤9 years	1153 (64.7)	151.1 (115.9)		56.8 (64.2)	
10-11 years	312 (17.5)	131.9 (88.8)		52.9 (55.8)	
≥12 years	313 (17.6)	127.0 (84.9)		50.0 (49.0)	
BMI (kg/m^2)[c]			0.9075		0.2659
<25	651 (36.6)	146.5 (105.1)		55.4 (60.3)	
25-30	781 (43.9)	139.2 (101.8)		56.7 (60.0)	
>30	347 (19.5)	147.9 (121.5)		49.9 (61.2)	
Smoking[c]			0.0391		0.9625
Never	763 (43.0)	141.2 (101.2)		54.2 (59.9)	
Former (>1 year)	760 (42.8)	140.0 (107.6)		56.5 (60.0)	
Current	253 (14.3)	162.4 (121.4)		52.5 (63.2)	
Alcohol (grams/day)[d]			0.6470		0.0023
None	456 (25.6)	141.1 (105.1)		47.0 (57.7)	
0.9-6.1	360 (20.2)	148.5 (115.5)		52.9 (58.6)	
>6.1-14.4	292 (16.4)	148.1 (106.2)		57.3 (56.7)	
>14.4-30.7	330 (18.5)	141.6 (103.3)		64.6 (63.2)	
>30.7	319 (17.9)	139.2 (102.6)		55.3 (65.2)	
Comorbidities[c,g]			<0.0001		0.0004
<2	945 (53.1)	160.8 (113.0)		59.7 (62.7)	
≥2	835 (46.9)	124.2 (96.5)		49.4 (57.1)	
Cancer site[c]			0.0779		0.9296
Proximal colon	524 (29.4)	136.2 (109.4)		54.6 (61.0)	
Distal colon	510 (28.6)	145.4 (108.9)		55.7 (59.8)	
Rectum	742 (41.7)	147.4 (104.1)		54.4 (60.2)	
Cancer stage[c]			0.2813		0.2810
I	511 (28.7)	145.6 (103.4)		59.1 (60.3)	
II	616 (34.6)	134.0 (107.4)		51.7 (61.0)	
III	591 (33.2)	151.6 (109.7)		54.5 (59.2)	
IV	56 (3.1)	147.9 (109.2)		55.4 (66.9)	

Table 8 Patient characteristics according to pre- and post-diagnosis physical activity *(continued)*

	Total sample	Pre-diagnosis PA[a,d] (MET-h/wk)		Post-diagnosis PA[b,d] (MET-h/wk)	
	N (Col. %)	Mean (SD)	p-value[f]	Mean (SD)	p-value[f]
Overall	1781	143.5 (107.1)		54.9 (60.4)	
Radiotherapy[c]			0.0960		0.8332
Yes	353 (19.8)	152.1 (108.1)		55.5 (62.8)	
No	1427 (80.1)	141.5 (106.8)		54.7 (59.8)	
Chemotherapy[c]			<0.0001		0.5153
Yes	751 (42.2)	156.0 (113.3)		53.8 (59.2)	
No	1029 (57.8)	134.5 (101.4)		55.7 (61.3)	
Stoma[e] until 5YFU			0.5526		0.1891
Yes	405 (22.7)	141.3 (99.0)		51.8 (60.4)	
No	1327 (74.5)	144.9 (109.8)		56.3 (60.5)	
Recurrence[c] until 5YFU			0.1294		0.0659
Yes	162 (9.1)	155.5 (115.2)		45.6 (57.2)	
No	1617 (90.8)	142.5 (106.2)		55.9 (60.6)	

[a]last age decade before diagnosis; [b]at five-year follow-up; [c]1-10 missings; [d]11-27; [e]47 missings; [f]linear model age-adjusted; [g]including heart attack, heart failure, stroke, diabetes, depression, other cancers, hypotension, circulatory disturbances heart, circulatory disturbances brain, circulatory disturbances legs, gout, arthritis, rheumatism, arthrosis, morbus crohn, colitis ulcerosa; **PA:** physical activity; **MET-h/wk:** metabolic equivalent hours per week; **Col.:** column; **SD:** standard deviation; **BMI:** body mass index; **5YFU:** five-year follow-up; apart from post-diagnosis PA, stoma, and recurrence all presented variables only include baseline information

3.2.1.2. Association of pre- and post-diagnosis physical activity with quality of life

Survivors reporting higher pre-diagnosis PA did not have significant or clinically relevant higher scores on any of the QOL functioning scales or global QOL, compared to survivors reporting lower pre-diagnosis PA, apart from physical functioning which was significantly associated with Q2 and Q3 versus Q1 (Figure 2). In contrast, higher post-diagnosis PA quartiles were positively and significantly associated with all QOL functioning scales and global QOL (Figure 3). The observed differences in physical, role, and social functioning and global QOL were of clinical relevance.

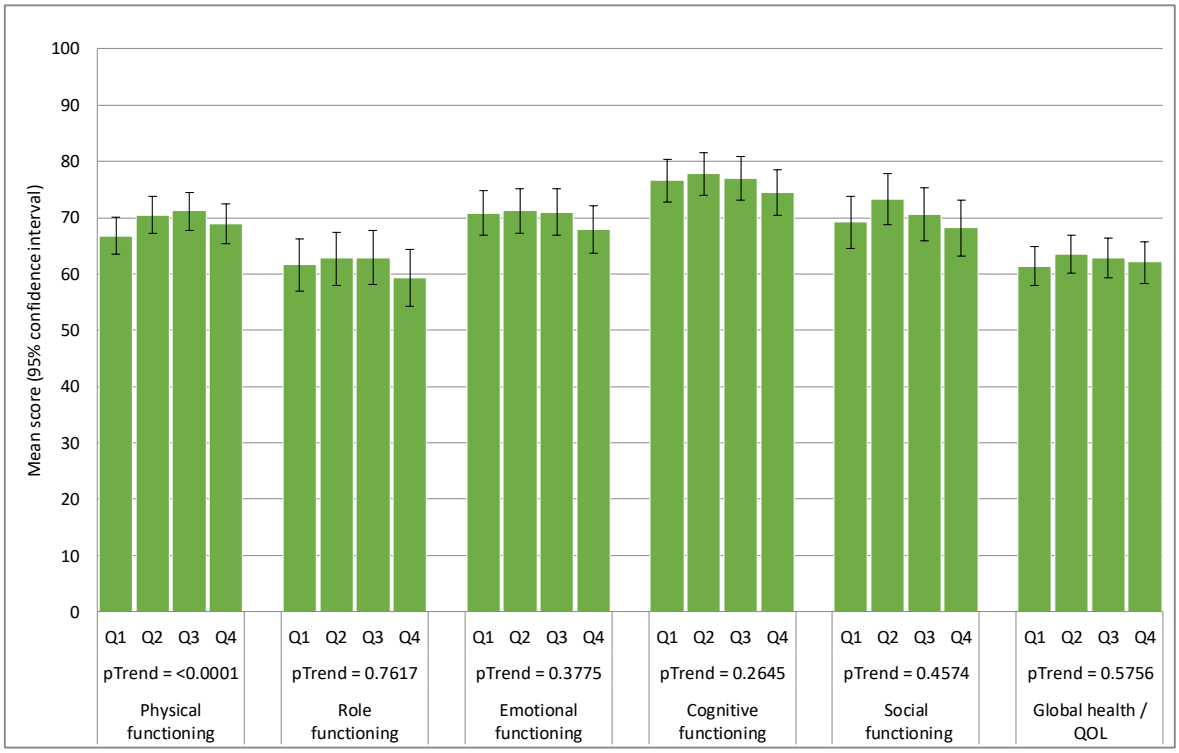


Figure 2 Associations of pre-diagnosis physical activity with global health/QOL (global QOL) and QOL functioning scales. Q: physical activity quartile; QOL: quality of life; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma

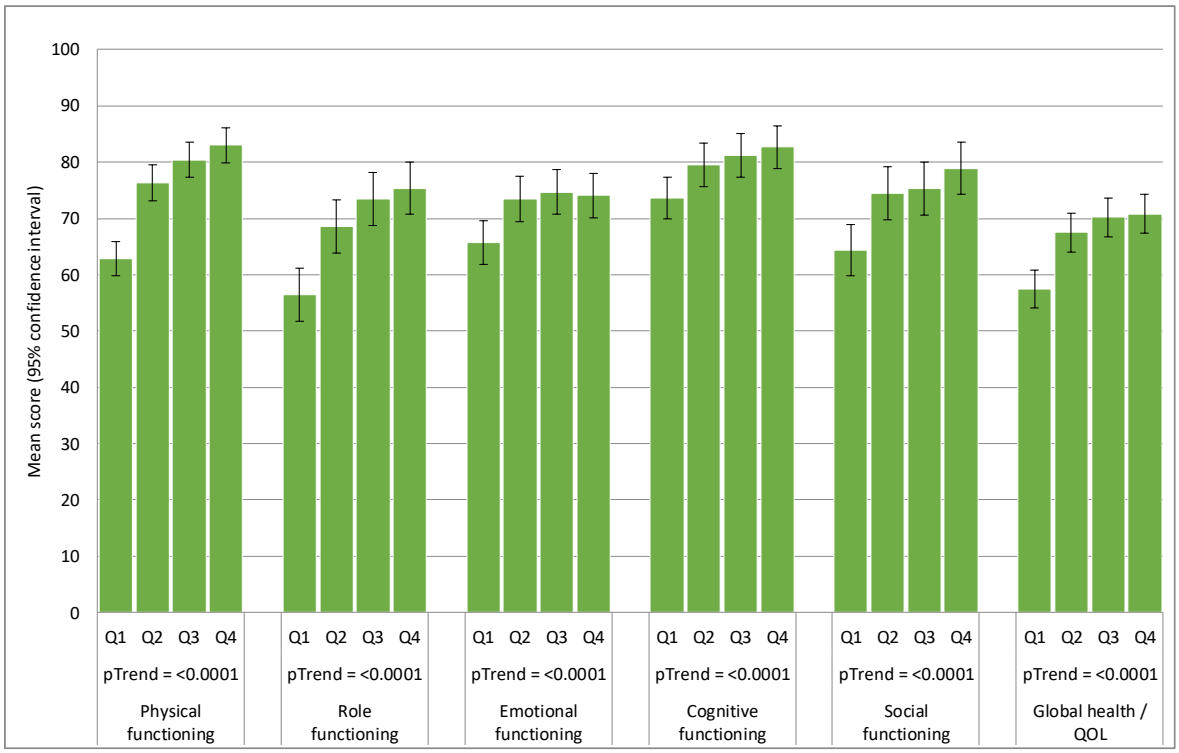


Figure 3 Associations of post-diagnosis physical activity with global health/QOL (global QOL) and QOL functioning scales. Q: physical activity quartile; QOL: quality of life; 5YFU: five-year follow-up; BMI: body mass index; linear regression analyses adjusted for age at 5YFU, sex, marital status, residential area, education, number of comorbidities including information from baseline until 5YFU, alcohol intake at 5YFU, smoking including information from baseline until 5YFU, BMI at 5YFU, cancer site, cancer stage, treatment, stoma

Of the symptom scales only nausea and vomiting was significantly associated with pre-diagnosis PA (Q2 vs. Q1) (Figure 4). Contrarily, the cross-sectional analysis revealed statistically significant and inverse associations between post-diagnosis PA and almost all symptom scales with clinically relevant differences for fatigue, pain, and dyspnoea (Figure 5). In addition, a significant trend was observed for post-diagnosis PA and all scales of the QLQ-C30, except for insomnia and diarrhoea. In sensitivity analyses using lifetime PA instead of PA of the last decade, to investigate the association between pre-diagnosis PA and QOL, the aforementioned pattern of the results did not change (data not shown).

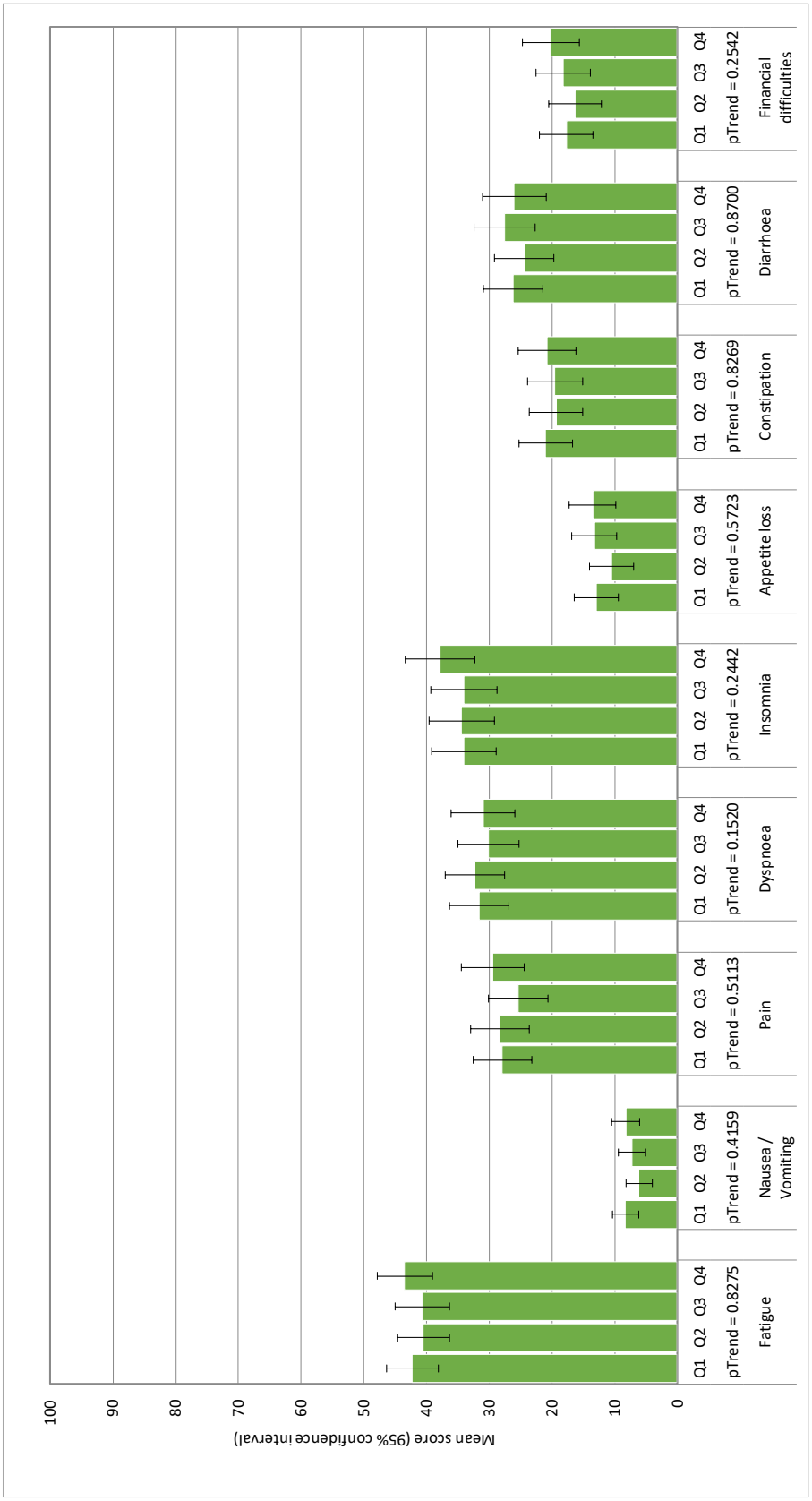


Figure 4 Associations between pre-diagnosis physical activity and quality of life symptom scales. Q: physical activity quartile; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma

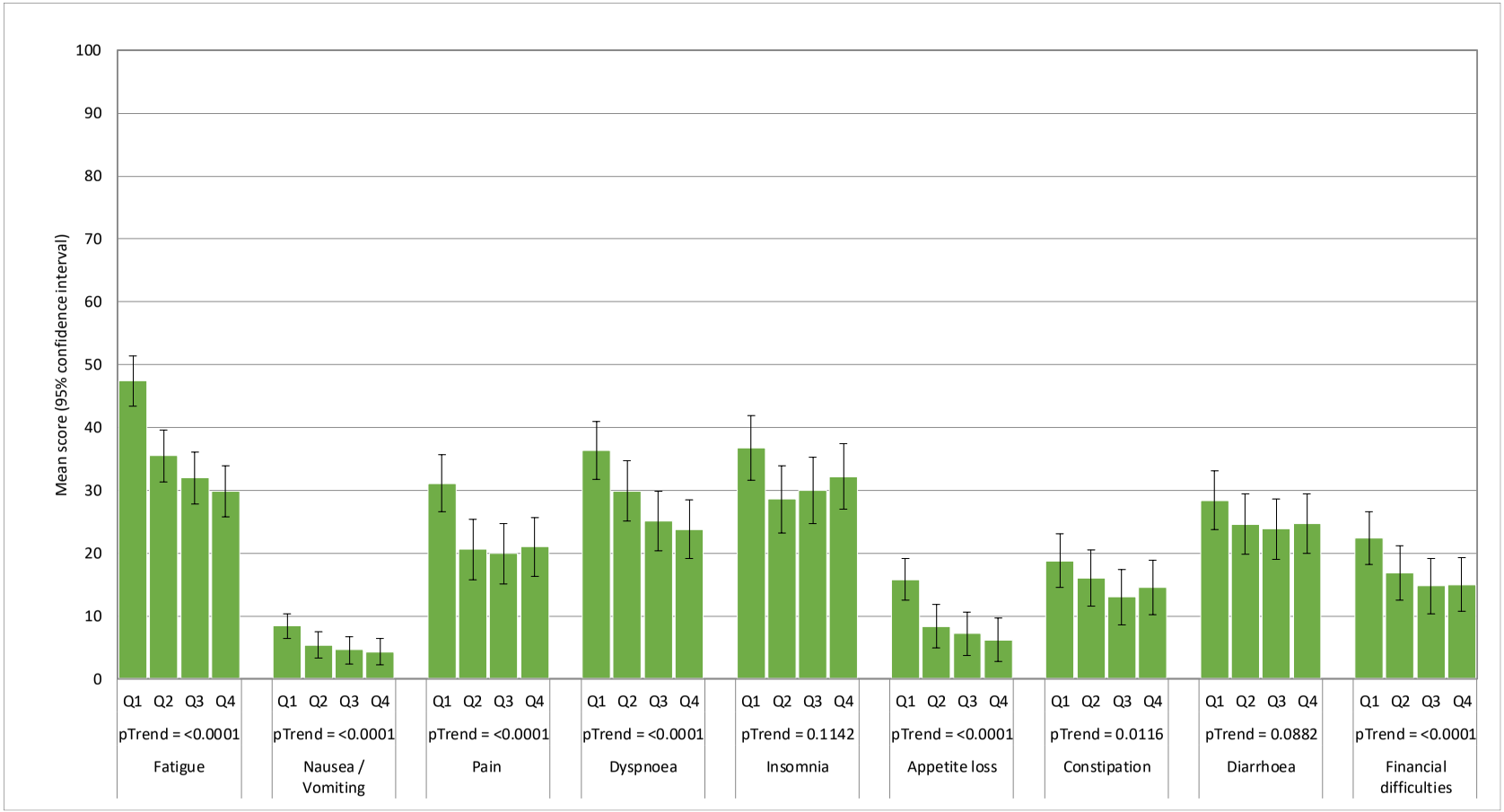


Figure 5 Associations between post-diagnosis physical activity and quality of life symptom scales. Q: physical activity quartile; 5YFU: five-year follow-up; BMI: body mass index; linear regression analyses adjusted for age at 5YFU, sex, marital status, residential area, education, number of comorbidities including information from baseline until 5YFU, alcohol intake at 5YFU, smoking including information from baseline until 5YFU; BMI at 5YFU, cancer site, cancer stage, treatment, stoma

3.2.1.3. Associations between changes in physical activity from pre- to post-diagnosis and quality of life

Active maintainers and increasers showed significantly higher scores on all QOL functioning scales and global QOL compared to inactive maintainers (Figure 6). Moreover, active maintainers and increasers scored significantly lower on almost all QOL symptom scales compared to inactive maintainers (Figure 7). Clinically relevant differences were observed for physical, role, and social functioning, global QOL, fatigue, and pain. No differences in QOL were found when comparing decreasers to inactive maintainers.

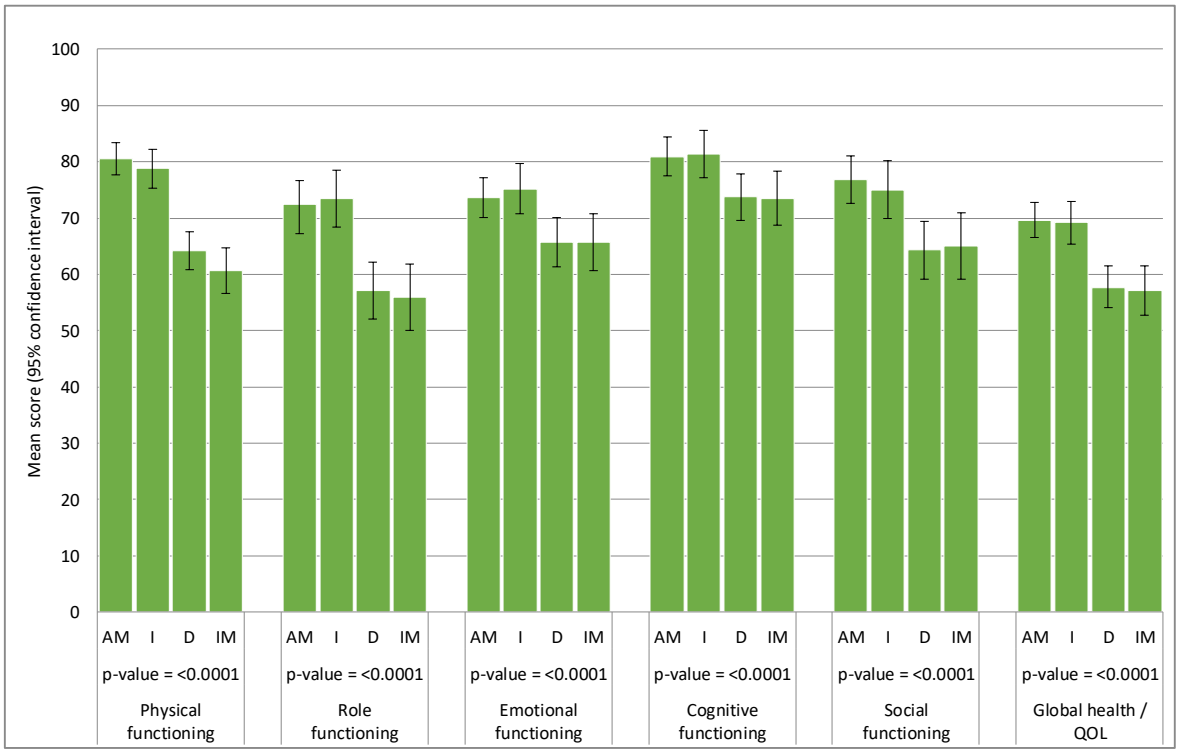


Figure 6 Associations of changes in physical activity from pre- to post-diagnosis with global health/QOL (global QOL) and QOL functioning scales. AM: active maintainers, I: increasers, D: decreasers, IM: inactive maintainers; QOL: quality of life; 5YFU: five-year follow-up; BMI: body mass index; linear regression analyses adjusted for age at 5YFU, sex, marital status, residential area, education, number of comorbidities including information from baseline until 5YFU, alcohol intake at 5YFU, smoking including information from baseline until 5YFU, BMI at 5YFU, cancer site, cancer stage, treatment, stoma

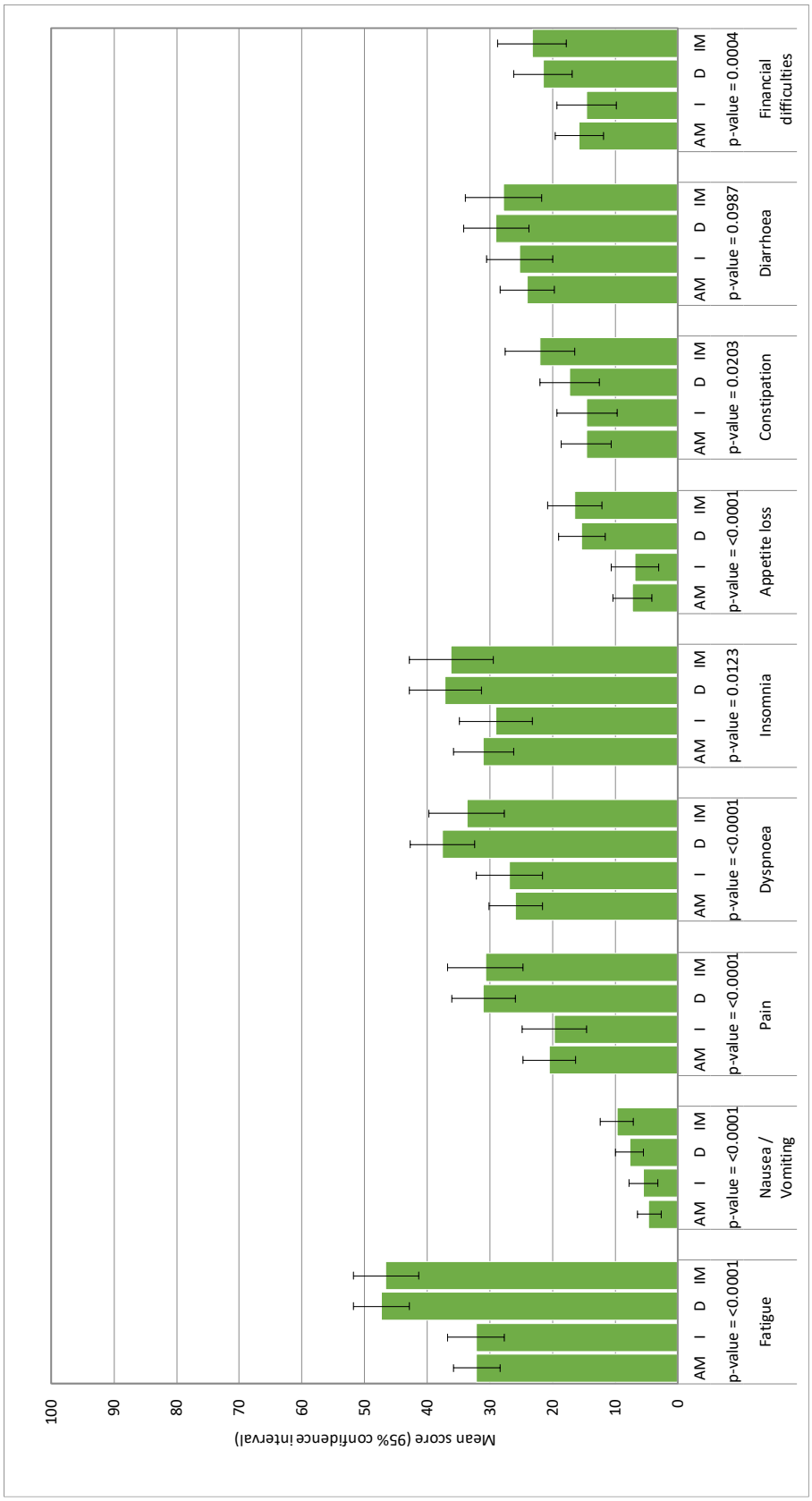


Figure 7 Associations of changes in physical activity from pre- to post-diagnosis and quality of life symptom scales. AM: active maintainers, I: increasers, D: decreasers, IM: inactive maintainers; 5YFU: five-year follow-up; BMI: body mass index; linear regression analyses adjusted for age at 5YFU, sex, marital status, residential area, education, number of comorbidities including information from baseline until 5YFU, alcohol intake at 5YFU, smoking including information from baseline until 5YFU, BMI at 5YFU, cancer site, cancer stage, treatment, stoma

3.2.1.4. Different domains/ intensities of pre-diagnosis physical activity and quality of life

Pre-diagnosis leisure time PA (per 100 MET-h/wk) was positively and significantly associated with global QOL and physical and cognitive functioning and negatively associated with dyspnoea. In contrast, increased pre-diagnosis work-related PA (per 100 MET-h/wk) was significantly associated with decreased physical, role, emotional, and cognitive functioning and increased fatigue, pain, insomnia, appetite loss, and financial difficulties (Figure 8). Although pre-diagnosis moderate PA showed to have the largest effects, no significant associations were found for pre-diagnosis light or moderate PA with QOL. However, increased pre-diagnosis vigorous PA (per 100 MET-h/wk) was significantly associated with decreased emotional and cognitive functioning and increased fatigue, insomnia, and financial difficulties (Figure 9). None of the reported associations between pre-diagnosis PA (domains/intensities) and QOL were of clinical relevance.

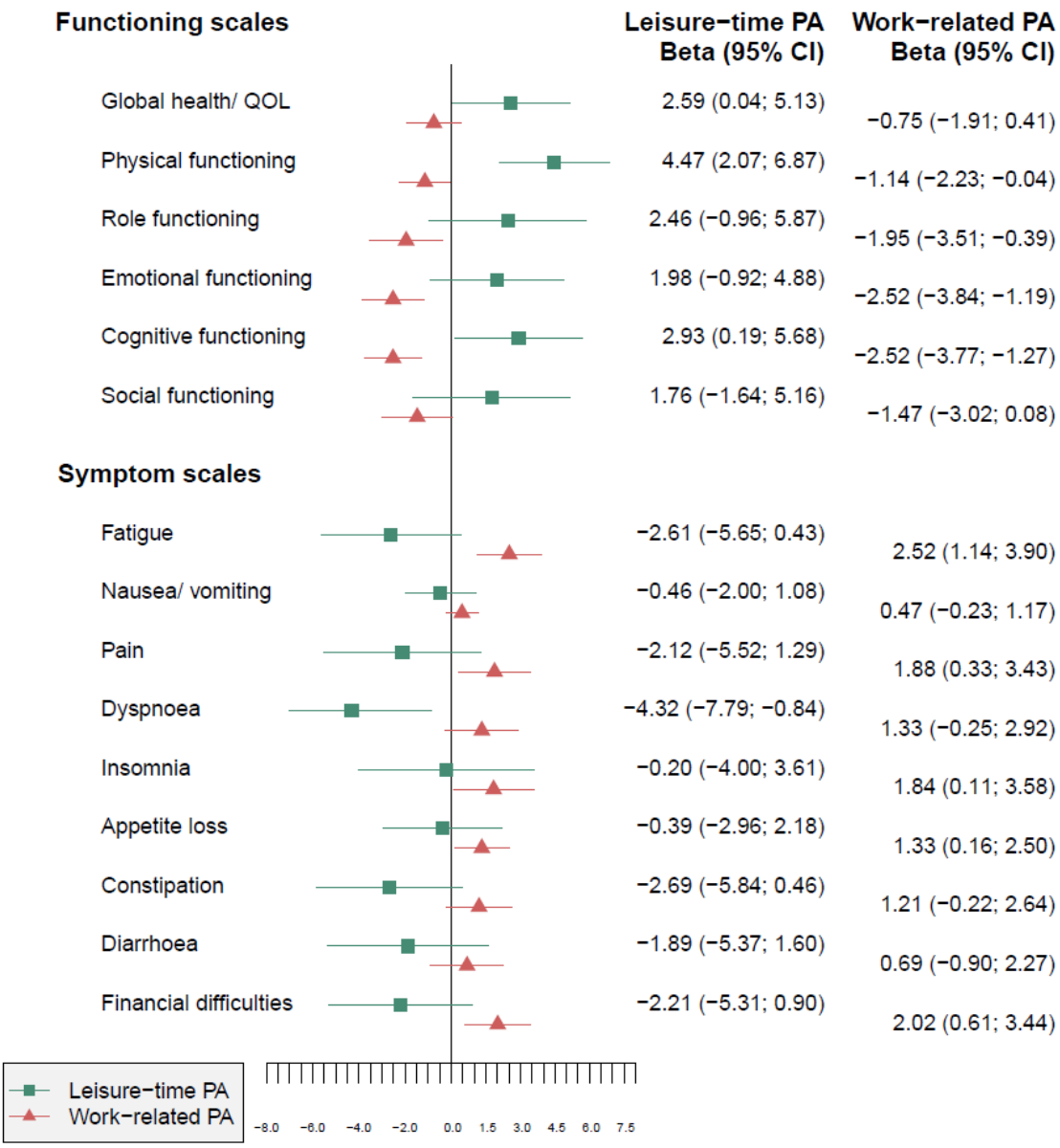


Figure 8 Associations between different domains of pre-diagnosis physical activity and quality of life. PA: physical activity; CI: confidence interval; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma, leisure time PA or work-related; leisure time including walking, cycling, sports; work-related PA including light work, hard work

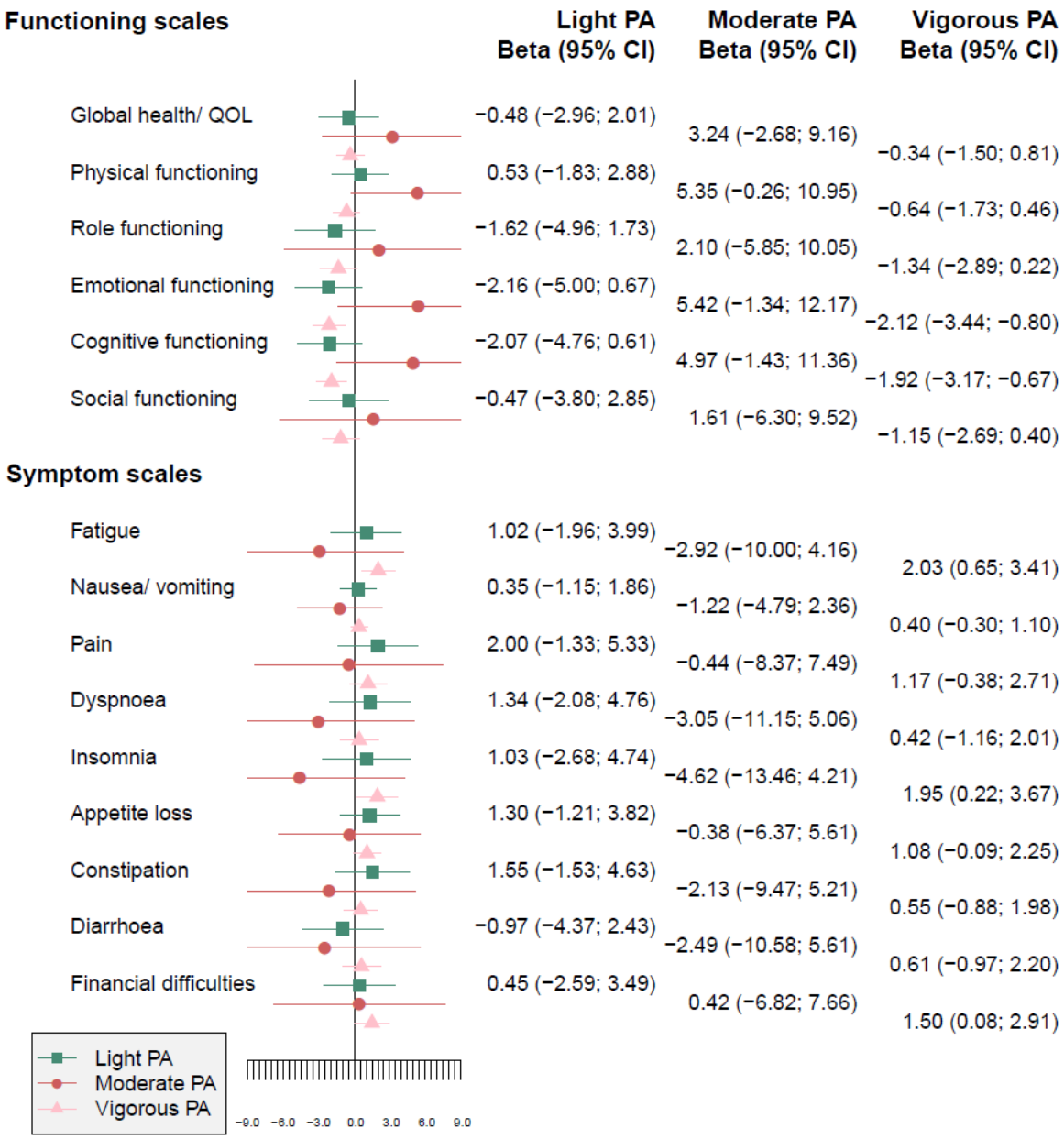


Figure 9 Associations between different intensities of pre-diagnosis physical activity and quality of life. PA: physical activity; CI: confidence interval; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma, light or moderate or vigorous PA; light PA including light work; moderate PA including walking; vigorous including hard work, cycling, sports

3.2.2. Association between physical activity and fatigue

3.2.2.1. Descriptive analyses

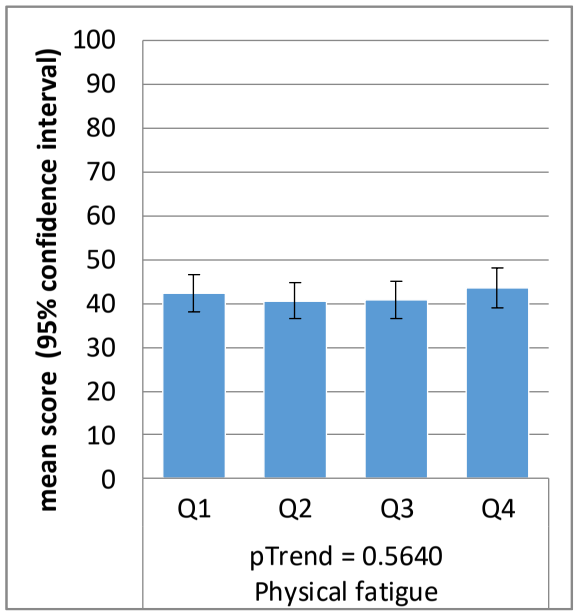
The characteristics of the 1781 CRC patients according to pre- and post-diagnosis PA have been already described in section 3.2.1.1.

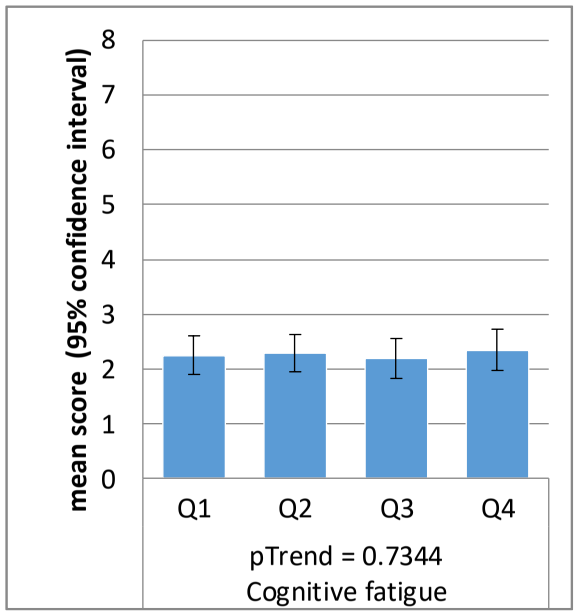
3.2.2.2. Association of pre- and post-diagnosis physical activity with fatigue

As shown in Figure 10, survivors who were physically active pre-diagnosis did not report significantly lower physical, cognitive, or affective fatigue five years post-diagnosis compared to survivors who were physically inactive pre-diagnosis. Pre-diagnosis PA also explained very little of the variance of long-term fatigue with 0.2% on the physical, 0.06% on the cognitive fatigue, and 0.1% on the affective fatigue scale.

In contrast, higher post-diagnosis PA was significantly associated with lower physical, cognitive, and affective fatigue with the strongest association for physical fatigue. Only the association between Q2 vs. Q1 was not significantly associated with lower cognitive fatigue (Figure 11). Post-diagnosis PA explained around 30% of the variability of physical fatigue but only approximately 1% of the variability of cognitive and affective fatigue. Additionally, a significant trend was observed for post-diagnosis PA and all fatigue scales.

In sensitivity analyses using lifetime PA instead of PA of the last decade, to investigate the association between pre-diagnosis PA and fatigue, the aforementioned pattern of the results did not change (data not shown).





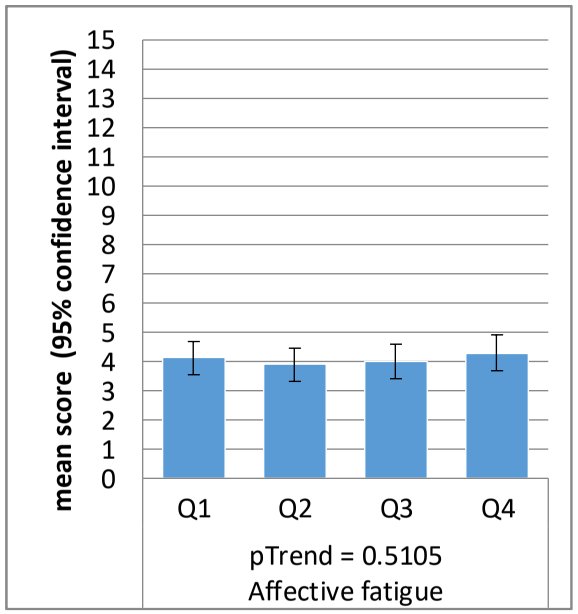


Figure 10 Associations between pre-diagnosis physical activity and fatigue. Q: physical activity quartile; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma

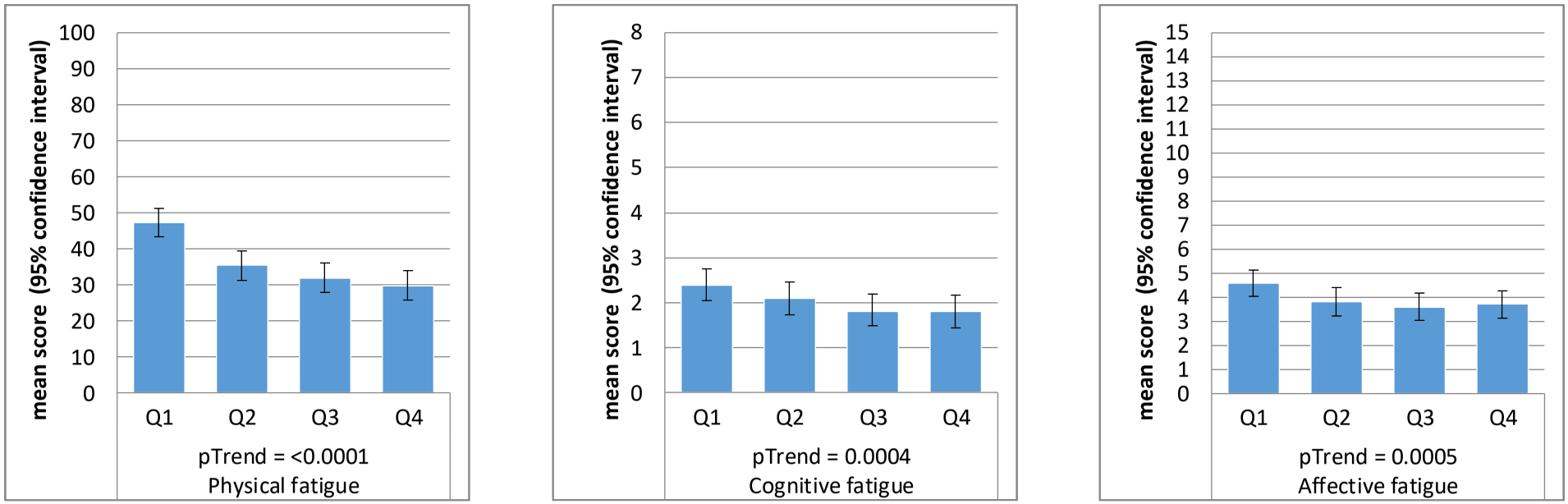


Figure 11 Associations between post-diagnosis physical activity and fatigue. Q: physical activity quartile; 5YFU: five-year follow-up; BMI: body mass index; linear regression analyses adjusted for age at 5YFU, sex, marital status, residential area, education, number of comorbidities including information from baseline until 5YFU, alcohol intake at 5YFU, smoking including information from baseline until 5YFU, BMI at 5YFU, cancer site, cancer stage, treatment, stoma

3.2.2.3. Associations between changes in physical activity from pre- to post-diagnosis and fatigue

Active maintainers and increasers scored significantly lower on all fatigue scales compared to inactive maintainers with the strongest associations for physical fatigue (Figure 12). No differences were found when comparing decreasers to inactive maintainers.

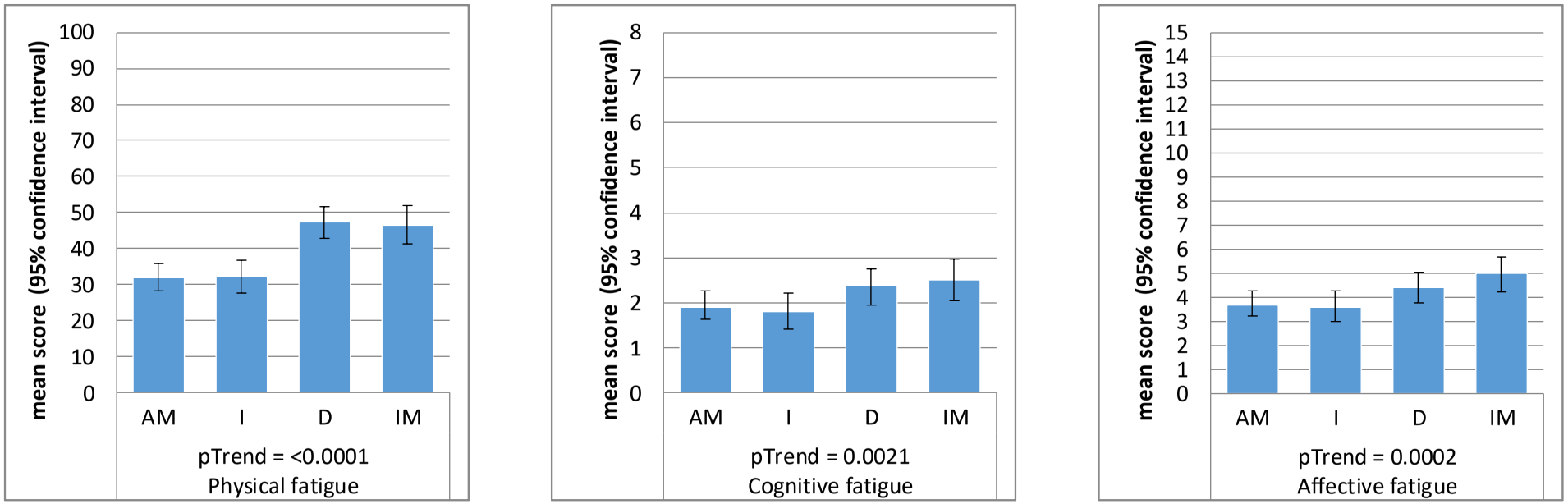


Figure 12 Associations between changes in physical activity from pre- to post-diagnosis and fatigue. AM: active maintainers, I: increasers, D: decreasers, IM: inactive maintainers; 5YFU: five-year follow-up; BMI: body mass index; linear regression analyses adjusted for age at 5YFU, sex, marital status, residential area, education, number of comorbidities including information from baseline until 5YFU, alcohol intake at 5YFU, smoking including information from baseline until 5YFU, BMI at 5YFU, cancer site, cancer stage, treatment, stoma

3.2.2.4. Different domains/ intensities of pre-diagnosis physical activity and fatigue

No association was found between increased pre-diagnosis leisure time PA (per 100 MET-h/wk) and any of the fatigue scales. Increased pre-diagnosis work-related PA (per 100 MET-h/wk) was significantly associated with increased levels of physical, cognitive, and affective fatigue (Figure 13). No associations were found for pre-diagnosis light or moderate PA with fatigue, apart from increased pre-diagnosis moderate PA (per 100 MET-h/wk) being significantly associated with lower affective fatigue. In contrast, increased pre-diagnosis vigorous PA (per 100 MET-h/wk) was significantly associated with increased physical, cognitive, and affective fatigue (Figure 14).

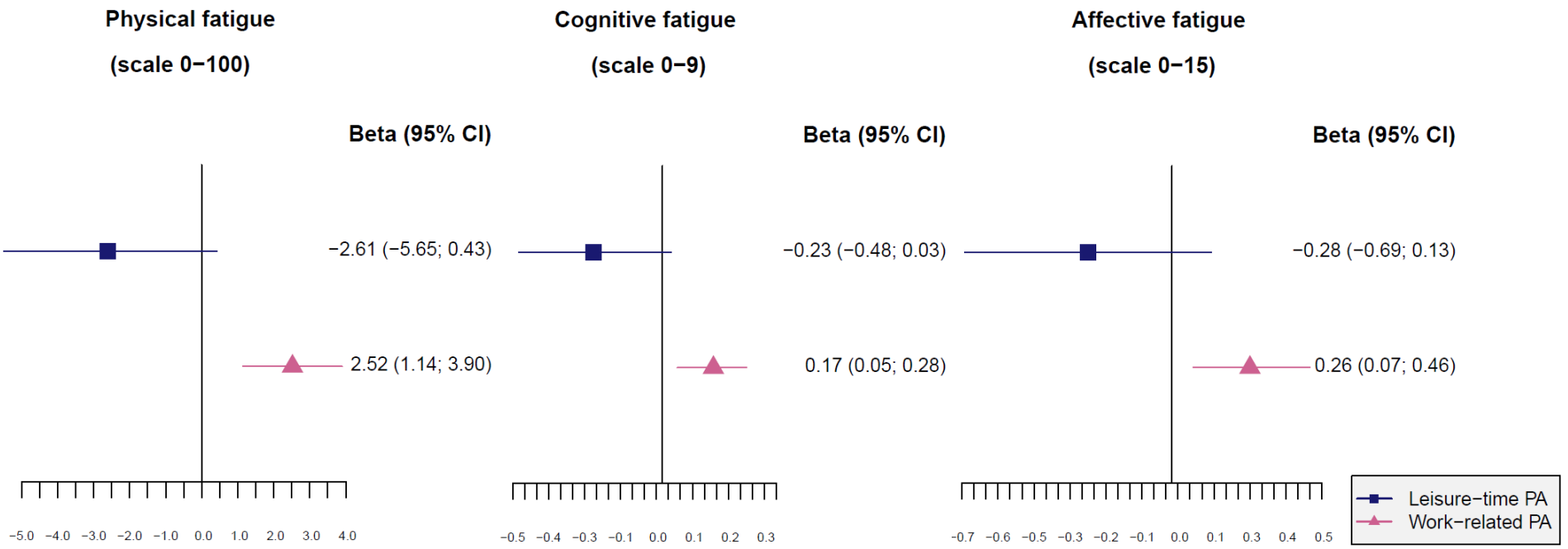


Figure 13 Associations between different domains of pre-diagnosis physical activity and fatigue. CI: confidence interval; PA: physical activity; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma, leisure time PA or work-related; leisure time including walking, cycling, sports; work-related PA including light work, hard work

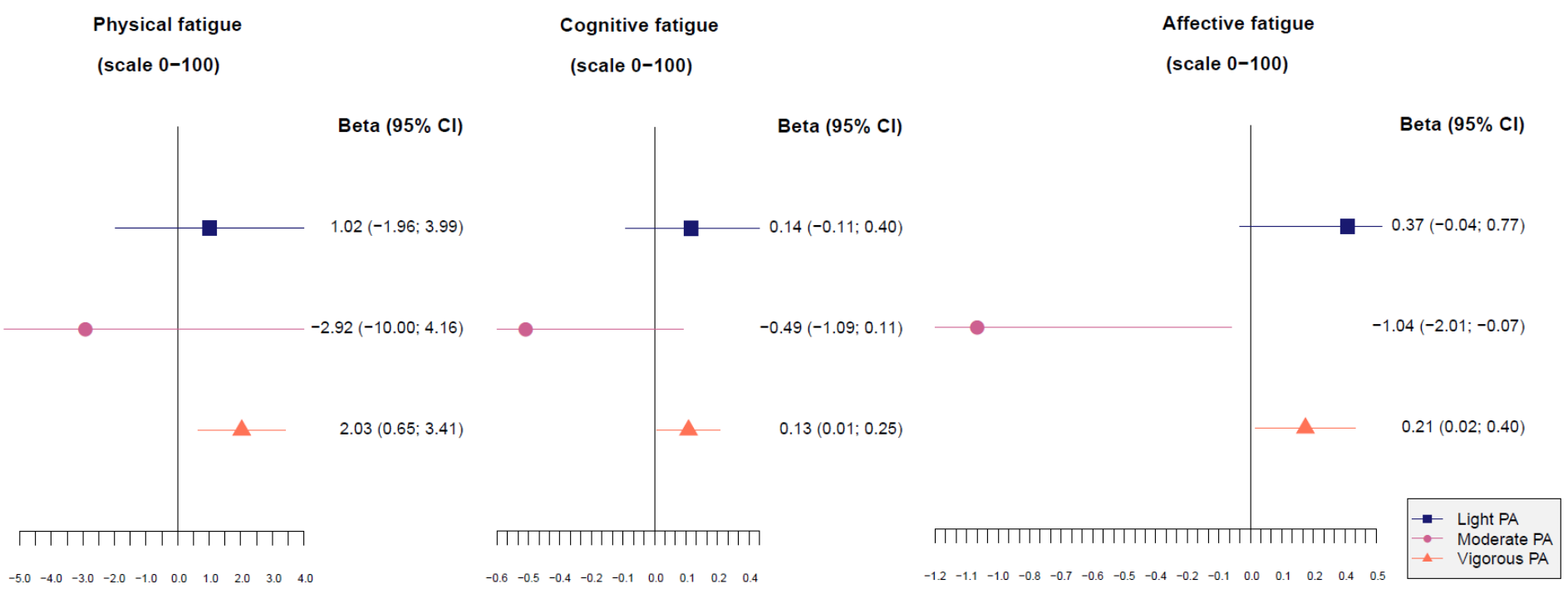


Figure 14 Associations between different intensities of pre-diagnosis physical activity and fatigue. CI: confidence interval; PA: physical activity; BMI: body mass index; linear regression analyses adjusted for age at baseline, sex, marital status, residential area, education, number of comorbidities at baseline, alcohol intake at baseline, smoking at baseline, BMI at baseline, cancer site, cancer stage, treatment, stoma, light or moderate or vigorous PA; light PA including light work; moderate PA including walking; vigorous including hard work, cycling, sports

3.2.3. Potential determinants of physical inactivity

3.2.3.1. Descriptive analyses

Descriptive analyses of PA at 5YFU overall and according to patient characteristics, before and after imputation, are summarized in Table 9. The mean age of the 1343 patients at baseline was 66.2 years. More than half of the patients were male (60.5%), and almost all were German. At baseline, average PA levels were more than twice as high as PA levels reported at 5YFU. The tumor was located in the colon in around 60% of patients and confined to the intestine (UICC stage I or II) in two thirds of all cases. Primary treatment included radiation and chemotherapy in 20% and 42% of cases, respectively, and surgery resulted in a stoma in 28% of all patients. Five years later, the proportion of patients still having a stoma was 21%. During the 5YFU period, the tumor recurred in 9% of all surviving patients. The proportion of patients reporting to drink alcohol or to smoke cigarettes declined. In contrast, the proportion of obese patients increased from 20% to 25%.

Baseline characteristics such as older age, living in communities with 10,000 or more inhabitants, having ≥2 comorbidities, and being obese, as well as information from the 5YFU, such as still having a stoma, were associated with lower mean PA levels at 5YFU in the descriptive analyses. In particular, PA at baseline was shown to be strongly correlated with PA at 5YFU. Means (SD) calculated on imputed data did not substantially differ from means (SD) calculated on unimputed data.

Table 9 Description of study population and crude association of patient characteristics with physical activity at five-year follow-up before and after multiple imputation of missing data

	Before Multiple Imputation					After Multiple Imputation			
	Patients		PA[d] at 5YFU (MET-h/wk)			Patients		PA at 5YFU (MET-h/wk)	
Total	N	(Col%)	Mean	(SD)	p-value[e]	N	(Col%)	Mean	(SD)
	1343		60.3	(60.6)		1343		59.9	(60.4)
			Baseline characteristics						
Age									
Mean (SD) = 66.2 (9.7) years									
30-59 years	316	(23.5)	61.2	(63.0)	0.0227	316	(23.5)	61.0	(62.8)
60-69 years	511	(38.1)	61.2	(57.5)		511	(38.1)	61.1	(57.6)
70-79 years	417	(31.1)	61.6	(64.6)		417	(31.1)	61.5	(64.3)
80+ years	99	(7.4)	43.9	(46.6)		99	(7.4)	44.2	(45.8)
Sex									
female	530	(39.5)	56.6	(59.4)	0.0599	530	(39.5)	56.0	(58.9)
male	813	(60.5)	62.7	(61.3)		813	(60.5)	62.5	(61.2)
Marital status[a]									
single	70	(5.2)	59.8	(57.0)	0.0911	70	(5.2)	59.5	(57.0)
married	1007	(75.0)	62.0	(61.0)		1009	(75.1)	61.7	(60.9)
divorced	76	(5.7)	61.2	(70.7)		76	(5.7)	61.1	(69.9)
widowed	187	(13.9)	51.2	(54.8)		188	(14.0)	50.3	(53.7)
Residential area									
village (<10,000)	471	(35.1)	69.8	(67.6)	0.0022	471	(35.1)	69.2	(67.1)
small town	461	(34.3)	55.8	(55.1)		461	(34.3)	55.8	(55.2)
city (>100,000)	411	(30.6)	54.3	(56.7)		411	(30.6)	54.1	(56.6)
Citizenship[a]									
German	1301	(96.9)	60.4	(60.5)	0.5280	1305	(97.2)	60.1	(60.3)
other	38	(2.8)	56.9	(66.4)		38	(2.8)	56.2	(64.6)
Education[a]									
≤9 years	898	(66.9)	62.8	(63.4)	0.4540	899	(66.9)	62.2	(62.9)
10-11 years	222	(16.5)	59.6	(59.4)		222	(16.5)	59.1	(58.8)
>12 years	221	(16.5)	51.9	(49.8)		222	(16.5)	51.7	(49.8)
Cancer site[a]									
proximal colon	403	(30.0)	59.8	(62.5)	0.6383	406	(30.2)	59.6	(61.9)
distal colon	387	(28.8)	61.0	(59.2)		387	(28.8)	60.6	(59.1)
rectum	550	(41.0)	60.1	(60.5)		550	(41.0)	59.7	(60.2)
Cancer stage[a]									
I	392	(29.2)	63.3	(60.8)	0.1055	394	(29.3)	62.7	(60.3)
II	468	(34.9)	57.2	(62.4)		471	(35.1)	57.0	(61.8)
III	439	(32.7)	60.7	(58.3)		440	(32.8)	60.8	(58.7)
IV	38	(2.8)	59.8	(65.4)		38	(2.8)	58.2	(63.9)

Table 9 Description of study population and crude association of patient characteristics with physical activity at five-year follow-up before and after multiple imputation of missing data *(continued)*

	Before Multiple Imputation					After Multiple Imputation			
	Patients		PA[d] at 5YFU (MET-h/wk)			Patients		PA at 5YFU (MET-h/wk)	
Total	N	(Col%)	Mean	(SD)	p-value[e]	N	(Col%)	Mean	(SD)
	1343		60.3	(60.6)		1343		59.9	(60.4)
			Baseline characteristics						
Radiation[a]									
yes	267	(19.9)	58.0	(60.1)	0.3113	268	(20.0)	57.8	(60.0)
no	1074	(80.0)	60.9	(60.8)		1075	(80.0)	60.5	(60.5)
Chemotherapy[a]									
yes	559	(41.6)	58.9	(58.5)	0.5917	560	(41.7)	58.9	(58.5)
no	783	(58.3)	61.3	(62.1)		783	(58.3)	60.7	(61.7)
Stoma									
yes	376	(28.0)	58.8	(61.6)	0.1843	377	(28.1)	58.5	(61.2)
no	963	(71.7)	60.9	(60.3)		966	(71.9)	60.5	(60.1)
Comorbidities[a,f]									
<2	697	(51.9)	63.1	(62.7)	0.0158	697	(51.9)	62.8	(62.5)
≥2	645	(48.0)	57.1	(57.9)		646	(48.1)	56.8	(57.9)
Physical activity (MET-h/wk)[b]									
Mean (SD) = 144.4 (111.7)									
Q1 (<70)	330	(24.6)	46.9	(52.5)	<.0001	336	(25.0)	48.1	(53.0)
Q2 (70-117)	331	(24.7)	58.4	(59.8)		335	(24.9)	58.2	(59.5)
Q3 (117-184)	331	(24.7)	59.0	(53.8)		333	(24.8)	59.2	(54.2)
Q4 (>184)	331	(24.7)	74.3	(71.0)		339	(25.2)	74.2	(70.5)
Alcohol (grams/day)[b]									
none	339	(25.2)	52.8	(55.6)	0.0188	346	(25.8)	52.3	(55.0)
0.1-5.5	209	(15.6)	57.5	(62.2)		211	(15.7)	58.3	(62.0)
>5.5-13.5	260	(19.4)	64.1	(59.1)		265	(19.7)	64.4	(59.7)
>13.5-29.5	250	(18.6)	64.4	(63.7)		254	(18.9)	64.1	(63.2)
>29.5	266	(19.8)	63.4	(63.3)		267	(19.9)	62.8	(63.0)
Smoking[a]									
never	584	(43.5)	60.8	(62.2)	0.0724	585	(43.6)	60.3	(61.7)
former	568	(42.3)	61.5	(58.3)		568	(42.3)	61.2	(58.5)
current	189	(14.1)	55.1	(62.6)		190	(14.2)	55.1	(61.7)
BMI (kg/m^2)[a]									
<25	484	(36.0)	59.8	(60.0)	0.0154	485	(36.1)	59.6	(60.0)
25-30	590	(43.9)	63.5	(61.8)		591	(44.0)	63.5	(61.7)
>30	267	(19.9)	53.4	(58.7)		267	(19.9)	52.8	(57.8)

Table 9 Description of study population and crude association of patient characteristics with physical activity at five-year follow-up before and after multiple imputation of missing data *(continued)*

	Before Multiple Imputation					After Multiple Imputation			
	Patients		PA[d] at 5YFU (MET-h/wk)			Patients		PA at 5YFU (MET-h/wk)	
Total	N	(Col%)	Mean	(SD)	p-value[e]	N	(Col%)	Mean	(SD)
	1343		60.3	(60.6)		1343		59.9	(60.4)
			5YFU characteristics						
Stoma[c]									
yes	286	(21.3)	55.7	(59.1)	0.0416	295	(22.0)	55.7	(58.9)
no	1010	(75.2)	61.9	(61.2)		1048	(78.0)	61.1	(60.8)
Comorbidities[a,f]									
<2	668	(49.7)	63.8	(63.2)	0.0052	669	(49.8)	63.7	(63.1)
≥2	674	(50.2)	56.6	(57.4)		674	(50.2)	56.3	(57.4)
Recurrence[a]									
yes	120	(8.9)	51.9	(57.7)	0.0605	120	(8.9)	52.1	(57.9)
no	1222	(91.0)	61.1	(60.8)		1223	(91.1)	60.7	(60.6)
Alcohol (grams/day)[b]									
none	513	(38.2)	59.3	(62.3)	0.0471	522	(38.9)	58.6	(61.6)
0.1-5.5	145	(10.8)	52.2	(52.3)		148	(11.0)	52.0	(52.2)
>5.5-13.5	311	(23.2)	58.0	(55.8)		315	(23.5)	57.9	(55.9)
>13.5-29.5	231	(17.2)	69.0	(64.6)		232	(17.3)	69.0	(64.8)
>29.5	123	(9.2)	63.7	(65.8)		126	(9.4)	63.2	(65.2)
Smoking[b]									
never	575	(42.8)	60.7	(61.8)	0.3387	581	(43.3)	59.9	(61.3)
former	646	(48.1)	59.9	(57.3)		651	(48.5)	59.7	(57.4)
current	109	(8.1)	60.3	(73.8)		111	(8.3)	61.2	(72.3)
BMI (kg/m^2)[a]									
<25	424	(31.6)	61.6	(60.1)	0.0272	425	(31.7)	61.8	(60.3)
25-30	576	(42.9)	62.1	(61.7)		581	(43.3)	61.8	(61.5)
>30	334	(24.9)	54.9	(59.0)		337	(25.1)	54.5	(58.4)

[a]1-10 missings; [b]11-20 missings; [c]47 missings; [d]130 missings; [e]Kruskal-Wallis-Test; [f]including heart attack, heart failure, stroke, diabetes, depression, other cancers, hypotension, circulatory disturbances heart, circulatory disturbances brain, circulatory disturbances legs, gout, arthritis, rheumatism, arthrosis; **PA:** physical activity; **5YFU:** five-year follow-up; **MET-h/wk:** metabolic equivalent hours per week; **Col.:** column; **SD:** standard deviation; **Q:** quartile; **BMI:** body mass index

3.2.3.2. Physical inactivity: bivariate and multivariate analyses

The results of the bivariate and multivariable analyses of the association between patient characteristics and physical inactivity are displayed in Table 10 (baseline characteristics, models 1 and 2) and Table 11 (baseline and 5YFU characteristics, models 3-5).

Both bivariate and multivariable analyses showed a fairly homogenous pattern with respect to potential determinants of physical inactivity. Older age, being divorced, living in a more populated residential area, stage II cancer, a higher number of comorbidities, having a stoma, current smoking, and a higher BMI were associated with physical inactivity, irrespective of the modeling strategy applied and with minor variations regarding the strength and significance of each specific association in models 1 to 5. Baseline PA itself represented a strong predictor of PA at 5YFU (p trend <0.0001). Inclusion of baseline PA in multivariable analyses slightly attenuated the association of age at baseline, cancer stage, and comorbidities with physical inactivity at 5YFU, but it did not substantially affect the model-building process, which implies that variables selected by the selection algorithm did not substantially change between different models (models 2, 4, and 5). With respect to time-varying factors, such as alcohol consumption, smoking, BMI, and comorbidities, the replacement of baseline information by pertinent information from the 5YFU substantially affected neither the model estimates nor the model-building process (models 1-4). Likewise, the inclusion of disease recurrence as a potential covariate did not alter the effect estimates of the other potential determinants (model 5). Only alcohol consumption at 5YFU seemed to be more strongly associated with physical inactivity compared to alcohol consumption at baseline.

Considering only baseline variables as potential determinants of physical inactivity (Table 10), the model with the best model fit was model 2. According to this model, having a stoma (OR = 1.51, 95% CI = 1.12-2.04), living in a small town or city (OR = 1.46, 95% CI = 1.05-2.02; OR = 1.42, 95% CI = 1.01-2.02), and being a current smoker (OR = 1.54, 95% CI = 1.04-2.29) was significantly associated with an increased likelihood of being physically inactive five years after diagnosis. Further, survivors physically active at baseline were significantly less likely to be physically inactive at 5YFU. In addition, survivors being older, divorced, obese, having ≥2 comorbidities, or with stage II disease were more likely to be physically inactive. However, the latter results were not of statistical significance, and no clear monotonic trend between stage and physical inactivity was observed.

Table 10 Potential baseline determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis

			Model 1 *No adjustment for baseline PA nor recurrence*	**Model 2** *Adjustment for baseline PA, no adjustment for recurrence*
	PIA	**Bivariate analysis**	**Backward selection**	**Backward selection**
	%	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Age				
30-59 years	22.4	ref	ref	ref
60-69 years	21.8	0.97 (0.69; 1.38)	0.96 (0.66; 1.38)	0.90 (0.62; 1.31)
70-79 years	30.0	1.44 (1.01; 2.06)	1.48 (1.00; 2.22)	1.20 (0.79; 1.82)
80+ years	33.8	1.71 (1.00; 2.90)	1.89 (1.05; 3.42)	1.44 (0.80; 2.58)
Sex				
female	26.4	ref	ref	ref
male	24.4	0.89 (0.68; 1.15)	1.07 (0.77; 1.47)	1.00 (0.73; 1.37)
Marital status				
married	23.6	ref	ref	ref
single	29.2	1.31 (0.75; 2.27)	1.31 (0.74; 2.33)	1.28 (0.70; 2.34)
divorced	35.3	1.67 (0.99; 2.80)	1.60 (0.93; 2.78)	1.72 (0.96; 3.07)
widowed	27.8	1.26 (0.87; 1.83)	1.00 (0.65; 1.52)	1.00 (0.66; 1.53)
Residential area				
village (<10,000)	21.1	ref	ref	ref
small town	27.0	1.37 (1.00; 1.87)	1.42 (1.03; 1.95)	1.46 (1.05; 2.02)
city (>100,000)	27.7	1.44 (1.04; 2.00)	1.37 (0.97; 1.94)	1.42 (1.01; 2.02)
Citizenship				
German	25.1	ref	-	-
other	27.3	1.12 (0.53; 2.40)		
Education				
≤9 years	26.6	1.16 (0.81; 1.64)	-	1.04 (0.71; 1.53)
10-11 years	20.7	0.86 (0.54; 1.36)		0.76 (0.47; 1.23)
>12 years	23.8	ref		ref
Cancer site				
rectum	26.2	ref	-	-
proximal colon	27.5	1.04 (0.76; 1.41)		
distal colon	21.4	0.79 (0.57; 1.09)		
Cancer stage				
I	21.0	ref	ref	ref
II	29.5	1.51 (1.09; 2.10)	1.42 (1.01; 2.00)	1.38 (0.98; 1.94)
III	23.9	1.15 (0.81; 1.63)	1.12 (0.78; 1.60)	1.13 (0.79; 1.63)
IV	32.4	1.76 (0.83; 3.74)	1.88 (0.86; 4.12)	1.79 (0.81; 3.95)
Radiation				
yes	28.6	1.23 (0.90; 1.69)	-	-
no	24.3	ref		
Chemotherapy				
yes	25.9	1.06 (0.81; 1.38)	-	-
no	24.6	ref		
Comorbidities				
<2	21.7	ref	ref	ref
≥2	29.1	1.45 (1.11; 1.88)	1.32 (0.99; 1.76)	1.24 (0.92; 1.66)

Table 10 Potential baseline determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis *(continued)*

			Model 1 *No adjustment for baseline PA nor recurrence*	**Model 2** *Adjustment for baseline PA, no adjustment for recurrence*
	PIA	**Bivariate analysis**	**Backward selection**	**Backward selection**
	%	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Stoma				
yes	30.1	1.40 (1.06; 1.85)	1.57 (1.17; 2.11)	1.51 (1.12; 2.04)
no	23.2	ref	ref	ref
Physical activity (MET-h/wk)				
Q1 (<75.2)	34.8	ref	-	ref
Q2 (≥75.2-121.2)	27.2	0.74 (0.53; 1.05)		0.74 (0.51; 1.06)
Q3 (≥121.2-185.0)	23.2	0.59 (0.42; 0.84)		0.64 (0.44; 0.92)
Q4 (≥185.0)	16.8	0.40 (0.27; 0.58)		0.45 (0.30; 0.68)
Alcohol (grams/day)				
none	28.7	ref	ref	ref
0.1-5.5	31.4	1.05 (0.71; 1.57)	1.14 (0.75; 1.73)	1.17 (0.77; 1.77)
>5.5-13.5	22.4	0.69 (0.47; 1.03)	0.75 (0.49; 1.13)	0.77 (0.50; 1.17)
>13.5-29.5	21.0	0.64 (0.43; 0.96)	0.68 (0.44; 1.05)	0.71 (0.46; 1.10)
>29.5	23.3	0.75 (0.51; 1.11)	0.77 (0.50; 1.17)	0.78 (0.51; 1.21)
Smoking				
never	25.8	ref	ref	ref
former (>1 year)	21.6	0.82 (0.61; 1.09)	0.80 (0.59; 1.10)	0.80 (0.58; 1.09)
current	33.7	1.39 (0.96; 2.00)	1.48 (1.00; 2.20)	1.54 (1.04; 2.29)
BMI (kg/m^2)				
<25	23.9	ref	ref	ref
25-30	23.8	0.99 (0.73; 1.33)	1.03 (0.75; 1.41)	1.02 (0.74; 1.40)
>30	30.8	1.42 (0.99; 2.03)	1.46 (0.99; 2.16)	1.43 (0.96; 2.13)
Mean (SD) AIC over imputed data sets			1497.90 (10.95)	1487.06 (10.85)

PA: physical activity; **PIA %:** percentages of inactive participants, calculated on unimputed data; **OR:** odds ratio; **CI:** confidence interval; **ref:** reference group; **MET-h/wk:** metabolic equivalent hours per week; **Q:** quartile; **BMI:** body mass index; **SD:** standard deviation; **AIC:** Akaike information criterion; PA quartiles based on MET-h/wk for PA at baseline and five-year follow-up: Q1=physically inactive, Q2-Q4= physically active; OR >1 are in favor of physical inactivity yes

Table 11 Potential baseline and five-year follow-up determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis

			Model 3 *No adjustment for baseline PA nor recurrence*	**Model 4** *Adjustment for baseline PA, no adjustment for recurrence*	**Model 5** *Adjustment for baseline PA and recurrence*
	PIA %	**Bivariate analysis** OR (CI 95%)	**Backward Selection** OR (CI 95%)	**Backward Selection** OR (CI 95%)	**Backward Selection** OR (CI 95%)
			Determinants at baseline		
Age					
30-59 years	22.4	ref	ref	ref	ref
60-69 years	21.8	0.97 (0.69; 1.38)	0.94 (0.65; 1.35)	0.91 (0.63; 1.31)	0.92 (0.64; 1.33)
70-79 years	30.0	1.44 (1.01; 2.06)	1.43 (0.96; 2.12)	1.20 (0.80; 1.80)	1.21 (0.81; 1.82)
80+ years	33.8	1.71 (1.00; 2.90)	1.75 (0.96; 3.19)	1.37 (0.74; 2.55)	1.40 (0.76; 2.61)
Sex					
female	26.4	ref	ref	ref	ref
male	24.4	0.89 (0.68; 1.15)	1.01 (0.74; 1.39)	1.02 (0.74; 1.40)	1.00 (0.73; 1.39)
Marital status					
married	23.6	ref	ref	ref	ref
single	29.2	1.31 (0.75; 2.27)	1.37 (0.77; 2.44)	1.33 (0.75; 2.37)	1.32 (0.74; 2.36)
divorced	35.3	1.67 (0.99; 2.80)	1.70 (0.98; 2.95)	1.68 (0.96; 2.93)	1.69 (0.97; 2.95)
widowed	27.8	1.26 (0.87; 1.83)	1.07 (0.70; 1.64)	1.09 (0.71; 1.66)	1.08 (0.71; 1.66)
Residential area					
village (<10,000)	21.1	ref	ref	ref	ref
small town	27.0	1.37 (1.00; 1.87)	1.40 (1.01; 1.93)	1.43 (1.04; 1.99)	1.43 (1.03; 1.98)
city (>100,000)	27.7	1.44 (1.04; 2.00)	1.38 (0.98; 1.95)	1.38 (0.98; 1.96)	1.38 (0.97; 1.96)
Citizenship					
German	25.1	ref	-	-	-
other	27.3	1.12 (0.53; 2.40)			
Education					
≤9 years	26.6	1.16 (0.81; 1.64)	-	-	-
10-11 years	20.7	0.86 (0.54; 1.36)			
>12 years	23.8	ref			
Cancer site					
rectum	26.2	ref	ref	-	-
proximal colon	27.5	1.04 (0.76; 1.41)	1.00 (0.69; 1.46)		
distal colon	21.4	0.79 (0.57; 1.09)	0.79 (0.55; 1.15)		
Cancer stage					
I	21.0	ref	ref	ref	ref
II	29.5	1.51 (1.09; 2.10)	1.38 (0.98; 1.96)	1.35 (0.96; 1.91)	1.35 (0.96; 1.91)
III	23.9	1.15 (0.81; 1.63)	1.04 (0.72; 1.49)	1.06 (0.73; 1.53)	1.05 (0.73; 1.51)
IV	32.4	1.76 (0.83; 3.74)	1.70 (0.77; 3.74)	1.65 (0.74; 3.67)	1.53 (0.68; 3.45)
Radiation					
yes	28.6	1.23 (0.90; 1.69)	-	-	-
no	24.3	ref			
Chemotherapy					
yes	25.9	1.06 (0.81; 1.38)	-	-	-
no	24.6	ref			

Table 11 Potential baseline and five-year follow-up determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis *(continued)*

			Model 3 *No adjustment for baseline PA nor recurrence*	**Model 4** *Adjustment for baseline PA, no adjustment for recurrence*	**Model 5** *Adjustment for baseline PA and recurrence*
	PIA %	**Bivariate analysis** OR (CI 95%)	**Backward Selection** OR (CI 95%)	**Backward Selection** OR (CI 95%)	**Backward Selection** OR (CI 95%)
Determinants at baseline					
Physical activity (MET-h/wk)					
Q1 (<75.2)	34.8	ref	-	ref	ref
Q2 (≥75.2-121.2)	27.2	0.74 (0.53; 1.05)		0.74 (0.52; 1.07)	0.74 (0.52; 1.06)
Q3 (≥121.2-185.0)	23.2	0.59 (0.42; 0.84)		0.64 (0.45; 0.93)	0.64 (0.44; 0.93)
Q4 (≥185.0)	16.8	0.40 (0.27; 0.58)		0.45 (0.30; 0.67)	0.45 (0.30; 0.67)
Determinants at 5YFU					
Alcohol (grams/day)					
none	27.5	ref	ref	ref	ref
0.1-5.5	34.3	1.35 (0.89; 2.05)	1.58 (1.02; 2.45)	1.59 (1.02; 2.48)	1.59 (1.02; 2.48)
>5.5-13.5	24.0	0.82 (0.58; 1.17)	0.91 (0.63; 1.32)	0.92 (0.64; 1.34)	0.93 (0.64; 1.35)
>13.5-29.5	18.4	0.58 (0.39; 0.87)	0.63 (0.41; 0.97)	0.61 (0.39; 0.93)	0.61 (0.40; 0.95)
>29.5	18.7	0.62 (0.37; 1.04)	0.66 (0.38; 1.13)	0.62 (0.36; 1.07)	0.63 (0.36; 1.09)
Smoking					
never	25.4	ref	ref	ref	ref
former (>1 year)	23.3	0.88 (0.67; 1.16)	0.90 (0.67; 1.22)	0.89 (0.66; 1.21)	0.90 (0.67; 1.22)
current	34.0	1.37 (0.88; 2.15)	1.51 (0.93; 2.45)	1.46 (0.90; 2.38)	1.47 (0.90; 2.40)
BMI (kg/m^2)					
<25	22.7	ref	ref	ref	ref
25-30	24.2	1.10 (0.81; 1.49)	1.19 (0.85; 1.66)	1.18 (0.84; 1.65)	1.18 (0.84; 1.65)
>30	30.4	1.48 (1.05; 2.08)	1.58 (1.10; 2.28)	1.57 (1.09; 2.28)	1.58 (1.09; 2.28)
Comorbidities					
<2	21.1	ref	ref	ref	ref
≥2	29.4	1.52 (1.17; 1.98)	1.35 (1.01; 1.81)	1.26 (0.94; 1.68)	1.26 (0.94; 1.69)
Recurrence					
yes	31.5	1.39 (0.91; 2.11)	-	-	1.27 (0.80; 2.00)
no	24.5	ref			ref
Stoma					
yes	31.3	1.43 (1.07; 1.92)	1.52 (1.06; 2.18)	1.57 (1.14; 2.15)	1.54 (1.12; 2.12)
no	23.1	ref	ref	ref	ref
Mean (SD) AIC over imputed data sets			1494.85 (10.47)	1482.48 (10.91)	1483.32 (11.00)

PA: physical activity; **PIA %:** percentages of inactive participants, calculated on unimputed data; **OR:** odds ratio; **CI:** confidence interval; **ref:** reference group; **MET-h/wk:** metabolic equivalent hours per week; **Q:** quartile; **5YFU:** five-year follow-up; **BMI:** body mass index; **SD:** standard deviation; **AIC:** Akaike information criterion; PA quartiles based on MET-h/wk for PA at baseline and 5YFU: Q1=physically inactive, Q2-Q4= physically active; OR >1 are in favor of physical inactivity yes

3.2.3.3. Subgroup analyses according to age and sex

Overall, the aforementioned pattern did not substantially change when logistic regression analyses with the variables selected for model 2 (Table 10) were performed in subgroups according to age and sex. When testing for interaction, only the results of two subgroups were statistically significantly different (Table 12).

The association between having a stoma and higher odds of being physically inactive was restricted to younger survivors (30-69 years). The aforementioned association between stage II CRC and higher odds of physical inactivity was only found in older survivors (≥70 years). Furthermore, the association between residential area and physical inactivity was confined to older survivors and stronger in women than in men. Men with ≥2 comorbidities were more likely to be physically inactive, compared to men with <2 comorbidities, but no associations were found in women. In contrast, the association between BMI and physical inactivity was stronger in women than in men.

Table 12 Potential baseline determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis - subgroup analyses

Model 2 *Adjustment for baseline PA, no adjustment for recurrence* **Backward selection**

			by age			by sex				
Total			**30-69 years**		**70-80+ years**			**Women**		**Men**		
N = 1343	**PIA%**	**OR (95% CI)**	**PIA%**	**OR (95% CI)**	$P_{Heterogeneity}$	**PIA%**	**OR (95% CI)**	**PIA%**	**OR (95% CI)**	$P_{Heterogeneity}$
Age										
30-59 years	-	-	-	-	-	18.0	ref	25.3	ref	
60-69 years						26.4	1.36 (0.73; 2.56)	19.0	0.70 (0.43; 1.15)	0.24
70-79 years						30.4	1.28 (0.60; 2.72)	29.8	1.16 (0.69; 1.97)	
80+ years						38.5	1.85 (0.70; 4.85)	28.6	1.06 (0.43; 2.58)	
Sex										
female	28.1	ref	38.5	ref	0.60	-	-	-	-	-
male	23.8	0.80 (0.52; 1.23)	28.6	1.47 (0.82; 2.65)						
Marital status										
married	23.9	ref	30.8	ref		23.0	ref	23.9	ref	
single	33.3	1.57 (0.80; 3.08)	0.0	1.09 (0.30; 3.91)	0.20	45.0	2.07 (0.74; 5.78)	22.2	1.02 (0.47; 2.21)	0.28
divorced	36.6	1.89 (0.99; 3.62)	50.0	1.16 (0.38; 3.59)		27.5	1.18 (0.52; 2.68)	46.4	2.12 (0.93; 4.87)	
widowed	26.5	0.55 (0.24; 1.26)	38.7	1.38 (0.81; 2.35)		31.03	1.18 (0.69; 2.02)	19.6	0.76 (0.34; 1.70)	
Residential area										
village (<10,000)	21.0	ref	26.3	ref		20.9	ref	21.2	ref	
small town	26.7	1.37 (0.91; 2.07)	36.4	1.77 (1.00; 3.10)	0.18	28.7	1.75 (1.01; 3.02)	25.9	1.32 (0.86; 2.01)	0.65
city (>100,000)	29.0	1.04 (0.65; 1.68)	36.4	2.15 (1.23; 3.37)		29.2	1.53 (0.86; 2.72)	26.6	1.27 (0.81; 1.99)	
Education										
≤9 years	27.4	1.01 (0.63; 1.61)	32.5	1.05 (0.52; 2.10)		28.6	1.16 (0.58; 2.29)	25.3	1.04 (0.64; 1.68)	
10-11 years	17.1	0.64 (0.35; 1.18)	37.5	0.91 (0.38; 2.17)	0.65	19.6	0.64 (0.29; 1.42)	21.8	0.78 (0.41; 1.48)	0.83
>12 years	23.5	ref	33.3	ref		25.8	ref	23.0	ref	
Cancer site										
rectum	26.7	ref	27.3	ref		29.3	ref	24.8	ref	
proximal colon	28.5	1.17 (0.68; 2.00)	41.4	0.98 (0.48; 1.98)	0.45	29.1	0.86 (0.44; 1.69)	26.2	1.05 (0.61; 1.81)	0.46
distal colon	20.8	0.85 (0.49; 1.45)	30.4	0.91 (0.46; 1.80)		20.7	0.68 (0.34; 1.36)	22.1	1.01 (0.59; 1.72)	

Table 12 Potential baseline determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis - subgroup analyses *(continued)*

Model 2 *Adjustment for baseline PA, no adjustment for recurrence* **Backward selection**

		by age				by sex				
Total		**30-69 years**		**70-80+ years**			**Women**		**Men**	
N = 1343	**PIA%**	**OR (95% CI)**	**PIA%**	**OR (95% CI)**	**$P_{Heterogeneity}$**	**PIA%**	**OR (95% CI)**	**PIA%**	**OR (95% CI)**	**$P_{Heterogeneity}$**
Cancer stage										
I	21.6	ref	24.0	ref		23.7	ref	19.3	ref	
II	30.9	1.15 (0.72; 1.83)	34.8	1.74 (1.01; 3.01)	0.51	29.2	1.22 (0.70; 2.15)	29.6	1.56 (0.98; 2.50)	0.74
III	22.2	1.06 (0.67; 1.67)	45.8	1.21 (0.66; 2.21)		25.5	1.12 (0.63; 2.01)	22.9	1.22 (0.75; 1.97)	
IV	34.8	1.39 (0.46; 4.18)	0.0	2.32 (0.69; 7.81)		33.3	2.19 (0.47; 10.2)	32.0	1.94 (0.73; 5.13)	
Physical activity (MET-h/wk)										
Q1 (<75.2)	35.2	ref	34.4	ref		41.8	ref	32.0	ref	
Q2 (≥75.2-121.2)	28.6	0.71 (0.41; 1.23)	28.0	0.73 (0.44; 1.22)	0.38	28.4	0.59 (0.32; 1.08)	26.4	0.81 (0.50; 1.31)	0.48
Q3 (≥121.2-185.0)	20.6	0.78 (0.47; 1.28)	46.2	0.47 (0.25; 0.88)		26.2	0.65 (0.34; 1.23)	20.7	0.62 (0.38; 1.02)	
Q4 (≥185.0)	17.4	0.44 (0.26; 0.73)	25.0	0.53 (0.25; 1.15)		13.5	0.31 (0.14; 0.70)	18.9	0.54 (0.32; 0.91)	
Alcohol (grams/day)										
none	30.5	ref	41.7	ref		31.0	ref	24.5	ref	
0.1-5.5	31.3	1.18 (0.68; 2.06)	37.5	1.14 (0.59; 2.22)		21.5	0.65 (0.36; 1.18)	43.7	2.28 (1.18; 4.41)	
>5.5-13.5	23.7	0.94 (0.55; 1.62)	28.6	0.60 (0.29; 1.23)	0.46	27.5	1.12 (0.61; 2.03)	19.2	0.78 (0.40; 1.50)	0.04
>13.5-29.5	20.1	1.03 (0.59; 1.81)	20.0	0.42 (0.20; 0.87)		20.0	0.69 (0.32; 1.48)	21.3	0.94 (0.51; 1.76)	
>29.5	22.6	0.98 (0.56; 1.74)	30.0	0.61 (0.30; 1.25)		28.6	0.89 (0.34; 2.37)	22.6	0.99 (0.56; 1.77)	
Smoking										
never	25.3	ref	44.1	ref		28.3	ref	23.0	ref	
former (>1 year)	22.2	0.82 (0.54; 1.24)	25.6	0.76 (0.46; 1.26)	0.70	19.7	0.75 (0.43; 1.32)	22.2	0.85 (0.56; 1.28)	0.64
current	37.9	1.38 (0.85; 2.25)	0.0	1.85 (0.84; 4.07)		29.3	1.25 (0.65; 2.40)	37.1	1.62 (0.94; 2.79)	

Table 12 Potential baseline determinants of physical inactivity among colorectal cancer survivors five years post-diagnosis - subgroup analyses *(continued)*

Model 2 *Adjustment for baseline PA, no adjustment for recurrence* **Backward selection**

			by age			by sex				
Total	**30-69 years**		**70-80+ years**			**Women**		**Men**		
N = 1343	**PIA%**	**OR (95% CI)**	**PIA%**	**OR (95% CI)**	**$P_{Heterogeneity}$**	**PIA%**	**OR (95% CI)**	**PIA%**	**OR (95% CI)**	**$P_{Heterogeneity}$**
BMI (kg/m^2)										
<25	22.9	ref	32.5	ref		20.7	ref	27.0	ref	
25-30	24.6	1.03 (0.68; 1.58)	28.6	1.04 (0.63; 1.72)	0.82	31.0	1.82 (1.10; 3.00)	20.4	0.69 (0.45; 1.08)	0.03
>30	31.6	1.46 (0.87; 2.46)	66.7	1.59 (0.84; 3.01)		31.4	1.62 (0.85; 3.08)	30.4	1.31 (0.76; 2.23)	
Comorbidities										
<2	22.2	ref	25.9	ref	0.60	22.9	ref	20.8	ref	0.43
≥2	28.2	1.16 (0.78; 1.73)	38.3	1.26 (0.79; 1.99)		30.3	1.08 (0.66; 1.75)	28.3	1.47 (1.00; 2.17)	
Stoma										
yes	30.7	1.81 (1.12; 2.92)	25.0	1.13 (0.57; 2.25)	0.15	32.7	1.53 (0.78; 2.99)	20.1	1.49 (0.91; 2.45)	0.66
no	23.5	ref	36.2	ref		24.8	ref	21.9	ref	

PA: physical activity; **PIA %:** percentages of inactive participants, calculated on unimputed data; **OR:** odds ratio; **CI:** confidence interval; **ref:** reference group; **MET-h/wk:** metabolic equivalent hours per week; **Q:** quartile; **BMI:** body mass index; PA quartiles based on MET-h/wk for PA at baseline and five-year follow-up: Q1=physically inactive, Q2-Q4= physically active; OR >1 are in favor of physical inactivity yes

4. DISCUSSION

4.1. Systematic review of the association between physical activity and quality of life in long-term colorectal cancer survivors

The results from the systematic review demonstrate that long-term CRC survivors who were more physically active generally reported higher QOL than non-active survivors. Moreover, different PA intensities such as light PA and moderate to vigorous PA seemed to be positively associated with QOL in long-term CRC survivors. The association between PA and QOL appeared to be stronger among women than among men. However, no general conclusion can be drawn, since only few studies performed specific subgroup analyses. Although the findings of the review support a positive association between PA and QOL in long-term CRC survivors, the evidence is limited as most studies were based on a cross-sectional and observational design and no intervention studies were included.

To my knowledge, three review articles (Cramer *et al.*, 2014; Lynch *et al.*, 2016; Otto *et al.*, 2015) have been published on the associations between PA and QOL in CRC survivors. However, the articles (Cramer *et al.*, 2014; Lynch *et al.*, 2016; Otto *et al.*, 2015) published so far were based on studies which mainly included short-term CRC survivors and no systematic review has specifically focused on long-term CRC survivors. The results which were found in this systematic review are quite homogenous. Eight of the ten included articles found positive associations between PA and QOL, whereas the results of the previous reviews are more inconsistent. In line with my findings, Lynch et al. who included short-term and long-term survivors, also reported associations between PA and QOL in observational studies, although the evidence was much weaker from intervention studies (Lynch *et al.*, 2016). The review article and meta-analysis of Otto et al., which focused on short-term CRC survivors, found a positive association between PA and QOL which was reported to be stable over time (Otto *et al.*, 2015). In contrast, the review article and meta-analysis of Cramer et al., which included only short-term survivors, did not find an association between PA and QOL (Cramer *et al.*, 2014). The inconsistent findings between my review and the previous review articles might be explained in parts by the different study population characteristics. The most obvious difference is the varying time since diagnosis. Due to the heterogeneous findings, it remains unclear whether the overall effect of PA on QOL differs for short-term and long-term CRC survivors.

Even though the majority of the studies included in my review had large sample sizes, were population-based, examined possible confounding factors like age, sex, and comorbidities and used validated QOL and PA questionnaires, most of the included studies have some

shortcomings which might limit their contributions to existing evidence. Nine of ten included articles assessed the association between PA and QOL using a cross-sectional design. For these studies no causality can be assumed, only an association between PA and QOL at one point in time. Moreover, only few studies reported results stratified by important covariates such as age, sex, or treatment. Although the focus of this review was on long-term CRC survivors, only two studies (Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013) were identified that solely included long-term CRC survivors. All other studies included short- and long-term survivors with a mean of five or more years since diagnosis. Thus, results of my review are in parts not only based on long-term CRC survivors.

A further limitation of the included studies is that the majority used self-reported PA measures. Only one study (van Roekel *et al.*, 2016) used an activity monitor to assess PA. In this context, information bias such as reporting bias might occur in studies relying on self-reported PA or only assessing leisure time PA, but not work-related PA. Furthermore, there were differences in the measurement tools used to assess QOL, which may also introduce information bias. Some studies (Chambers *et al.*, 2012b; Husson *et al.*, 2015; Mols *et al.*, 2015; van Roekel *et al.*, 2015; van Roekel *et al.*, 2016) used cancer-specific QOL questionnaires and other studies (Blanchard *et al.*, 2008; Blanchard *et al.*, 2010; Blanchard *et al.*, 2004; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013) used general QOL instruments. Therefore the differences in the QOL assessment might limit the comparability of the results. In addition, many QOL instruments specifically designed for cancer patients under active treatment, such as the QLQ-C30 and the *Functional Assessment of Cancer Therapy-Colorectal Cancer* (FACT-C), with their supplementary condition-specific or symptom-specific modules, are not entirely appropriate or sufficient for assessing the experience of disease free cancer survivors.

Furthermore, the sensitivity of QOL instruments and scales to detect subtle differences in QOL may have had an impact on the results. For example, two of the included articles (Blanchard *et al.*, 2010; Chambers *et al.*, 2012b) did not find any association between PA and QOL. An explanation for the non-significant results in the article of Chambers et al. (Chambers *et al.*, 2012b) might be the use of particular questionnaires (FACT-C, *Satisfaction with Life Scale* [SWLS]), which might not be sufficiently sensitive. The other article (Blanchard *et al.*, 2010) not finding significant associations is based on the same study population as another included article (Blanchard *et al.*, 2008) which found associations between PA and QOL. However, the article of Blanchard et al. which did not report significant results (Blanchard *et al.*, 2010), did not present the results for the general associations of PA with QOL again, but only reported the association between PA and QOL stratified by BMI. Therefore BMI might have been a confounding factor.

4.2. Analyses within the DACHS study

The discussion of the analysis on PA and QOL and the analysis on PA and fatigue are in parts similar due to methodological and content-related overlaps of the analyses.

4.2.1. Association between physical activity and quality of life

The results of this analysis do not support a positive association between pre-diagnosis PA and long-term QOL in CRC survivors. Pre-diagnosis work-related PA and vigorous PA might even decrease some QOL domains such as cognitive and emotional functioning. Consequently, pre-diagnosis PA does not seem to provide a buffer which may mitigate or prevent cancer-related detriments in QOL among long-term CRC survivors. In contrast, post-diagnosis PA was strongly associated with improved QOL five years after diagnosis. Also, survivors being physically active both pre- and post-diagnosis and survivors who increased their PA from pre- to post-diagnosis had a significantly higher long-term QOL compared to survivors being inactive pre- and post-diagnosis. The results support and emphasize the need of maintaining PA after CRC diagnosis. However, the cross-sectional results should be interpreted with caution due to possible reverse causality.

To my knowledge, so far no other study has investigated the association of pre-diagnosis PA with QOL five years after CRC diagnosis. Earlier studies found a significant, positive association between PA and QOL in CRC survivors after treatment (Buffart *et al.*, 2012; Grimmett *et al.*, 2011; Lynch *et al.*, 2008; Vallance *et al.*, 2015) and also multimodal prehabilitation programs improved the physical and psychological health of cancer patients (Silver and Baima, 2013). Therefore, I hypothesized that also pre-diagnosis PA might be beneficial for the QOL of CRC survivors five years after diagnosis. However, the results do not support a positive association between pre-diagnosis PA and long-term QOL. The findings even suggest that pre-diagnosis work-related PA and also vigorous PA might be associated with poorer long-term QOL on domains such as emotional and cognitive functioning, fatigue, insomnia, and financial difficulties. Thus, CRC survivors who had a job requiring hard physical work may still suffer from these impairments on functional- and symptom-related QOL even years after CRC diagnosis. Although analyses were adjusted for education, another possible explanation for these findings could be residual confounding such as low socioeconomic status (working class jobs with less autonomy and lower pay).

The cross-sectional findings regarding the association between post-diagnosis PA and QOL at 5YFU among long-term CRC survivors confirm previous findings which reported PA to be positively associated with QOL in CRC survivors. In line with my results, Husson et al. and Mols et al. reported positive associations of PA with global QOL and all functioning

scales of the QLQ-C30 (Husson *et al.*, 2015; Mols *et al.*, 2015). Comparable to my findings, Husson et al. also found differences of ≥10 points for global QOL and almost all functioning scales (Husson *et al.*, 2015).

In line with previous findings (Husson *et al.*, 2015; Mols *et al.*, 2015; Rodriguez *et al.*, 2015; Thraen-Borowski *et al.*, 2013), physical functioning was one of the scales most strongly associated with QOL in this analysis. Due to the substantial overlap between the constructs physical functioning and PA, this apparent association may partly represent an artifact.

The results regarding changes in PA support the cross-sectional findings on post-diagnosis PA and QOL and the assumption that ongoing PA may be important for the QOL of CRC survivors. Only active maintainers and increasers had a significantly higher long-term QOL compared to inactive maintainers, but no differences in QOL were found for survivors decreasing their PA levels. Compared to inactive maintainers, decreasers scored even worse on some symptom scales such as dyspnoea, insomnia, and diarrhoea. These findings may be explained by decreasers having a more severe health condition following CRC diagnosis and treatment which prevents them from maintaining PA levels compared to inactive maintainers who reported to be physically inactive pre- and post-diagnosis.

Quality of life has been shown to be positively associated with survival (Montazeri, 2009). Although a recent analysis using DACHS data found significant associations between pre-diagnosis PA and overall and CRC-specific survival (Walter *et al.*, 2017), I did not find an association between pre-diagnosis PA and QOL. The variation in the results might be explained by differences in PA classification since Walter et al. only included leisure time PA in their main analyses and not work-related PA as I did. In subgroup analyses comparing different domains of PA, I also found significant and positive associations between pre-diagnosis leisure time PA and global QOL, physical, and cognitive functioning. However, the findings might not be completely comparable since inclusion of participants (in this analysis only survivors who survived five years were included), sample sizes, and covariate adjustment differed.

Contrarily to my prior hypothesis, the results indicate that pre-diagnosis PA does not provide any protection for detriments in QOL five years after diagnosis, but clearly emphasize the importance of post-diagnosis PA for the QOL of long-term CRC survivors five years after diagnosis. Thus, these findings suggest that pre-diagnosis PA cannot replace ongoing PA after diagnosis under the assumption that the association between ongoing PA and better QOL is not entirely a result of reverse causality.

In addition to the positive results of this analysis regarding post-diagnosis PA and QOL among long-term survivors, findings from other studies assessing PA shortly after treatment

also found positive associations between PA and QOL (Bourke *et al.*, 2011; Lewis *et al.*, 2014; Lynch *et al.*, 2008; Vallance *et al.*, 2014). Moreover, one randomized trial reported positive effects of PA during cancer treatment such as an increased fitness capacity and reduced fatigue (Medscape, 2018). However, although pertinent studies have not found significant associations between prehabilitation programs including PA and QOL, they reported improvements in other important health outcomes such as fitness capacity (Gillis *et al.*, 2014; Li *et al.*, 2013; Singh *et al.*, 2017).

Since studies have suggested that PA at all points in time after diagnosis seem to be beneficial for CRC survivors, effective PA motivation techniques at an early stage after diagnosis and consistently repeated throughout the years of survival may help to improve the well-being of CRC patients. Although in this analysis pre-diagnosis work-related PA and vigorous PA in the years prior to CRC diagnosis were negatively associated with long-term QOL among CRC survivors, individually-tailored PA interventions throughout the years of survivorship might also be beneficial for this population. Health care providers should inform patients for example about the beneficial associations between light PA and QOL (Thraen-Borowski *et al.*, 2013; van Roekel *et al.*, 2015).

Although guidelines such as the S3-guideline “colorectal cancer” point out the necessity for physicians to recommend PA to CRC patients (Schmiegel *et al.*, 2017), oncologists often do not prescribe PA to cancer patients (Sabatino *et al.*, 2007; Spellman *et al.*, 2013). Reasons which hinder health care providers from recommending PA to cancer patients include lack of time, lack of reimbursement, and lack of exercise programs for cancer patients as well as safety concerns (Haussmann *et al.*, 2018; Karvinen *et al.*, 2010; Park *et al.*, 2015; Spellman *et al.*, 2013). However, it has been shown that oncologists´ encouragement to engage in PA is crucial for cancer patients to participate in PA interventions (Eggly *et al.*, 2008; Jones *et al.*, 2004). Therefore, it is important that health care providers motivate and encourage cancer survivors to be physically active also in the years of survivorship. Also, more supervised exercise programs which focus on the specific needs of CRC survivors throughout the years of survivorship would be beneficial.

4.2.2. Association between physical activity and fatigue

For the analysis on PA and fatigue, a comparable pattern of results, similar to the analysis on PA and QOL, was found. Higher levels of pre-diagnosis PA did not seem to mitigate fatigue of CRC survivors five years after diagnosis. Pre-diagnosis work-related PA and vigorous PA were even associated with higher physical, cognitive, and affective fatigue. In contrast, post-diagnosis PA was strongly associated with lower physical, cognitive, and affective fatigue. Moreover, survivors being physically active pre- and post-diagnosis and survivors becoming physically active post-diagnosis scored significantly lower on all fatigue scales compared to survivors who remained inactive from pre- to post-diagnosis. The results of this analysis point out the importance of ongoing PA throughout CRC survivorship, particularly for fatigue, which is the symptom most frequently reported among cancer patients. However, the cross-sectional results should be interpreted with caution due to possible reverse causality.

To my knowledge, so far, no other study has investigated associations between pre-diagnosis PA and fatigue five years post-diagnosis. Prehabilitation programs including PA before cancer treatment and studies assessing PA after treatment found PA to be beneficial for CRC survivors´ physical and psychological health. Therefore, it was hypothesized that pre-diagnosis PA might also be advantageous for fatigue in long-term CRC survivors. However, in line with my previous findings on pre-diagnosis PA and QOL, no beneficial effects of pre-diagnosis PA on long-term fatigue were found, and higher levels of pre-diagnosis work-related PA and vigorous PA were even positively associated with all fatigue scales. Therefore, it is assumed that survivors who had a physically demanding job before cancer diagnosis might not only have detriments in QOL, but also suffer from fatigue years after their CRC diagnosis. However, residual confounding, for example by lower socioeconomic status (working class jobs with less autonomy and lower pay) could be another possible explanation for these findings.

The results regarding changes in PA support the cross-sectional findings on post-diagnosis PA and fatigue, and the assumption that ongoing PA may be important for fatigue of long-term CRC survivors. Only active maintainers and increasers had a significantly lower long-term fatigue compared to inactive maintainers, but no differences in fatigue were found for survivors decreasing their PA levels. These findings may be explained by decreasers having a more severe health condition following CRC diagnosis and treatment which prevents them from maintaining PA levels compared to inactive maintainers who reported to be physically inactive pre- and post-diagnosis.

In line with my findings, several observational studies reported post-diagnosis PA to be associated with lower fatigue in CRC survivors (Breedveld-Peters *et al.*, 2018; Grimmett *et al.*, 2011; Mols *et al.*, 2015; Peddle *et al.*, 2008; van Roekel *et al.*, 2015). However, a recent systematic review which performed a meta-analysis of randomized controlled trails, failed to show a significant association between PA and fatigue among CRC survivors, although in all studies PA was accompanied by reduced levels of fatigue. Further, inconclusive results regarding the association between PA and fatigue for observational prospective studies were reported. The review concludes that some of the trials might not have been appropriately powered to detect differences in fatigue (Brandenbarg *et al.*, 2018).

Although a multidimensional concept of fatigue is well accepted, most studies unidimensionally assessed the association between PA and physical fatigue. Therefore, studies might have missed some aspects of fatigue such as cognitive or affective fatigue and thus only few findings regarding the association of PA with multiple fatigue scales exist. Moreover, it has been discussed that the different fatigue dimensions might not be expressions of one symptom but rather expressions of independent symptoms (de Raaf, 2013) since some fatigue dimensions have been observed to behave differently (de Raaf *et al.*, 2013). Also, specific subtypes of cancer-related fatigue among long-term CRC survivors were identified (Thong *et al.*, 2018). Based on these findings it can be concluded that survivors might benefit from interventions targeted to the personal fatigue experience. For example, cancer survivors suffering from physical fatigue might benefit more from being physically active than survivors suffering from cognitive or affective fatigue for which interventions such as mental training or psychosocial interventions might be more beneficial. Although my results show that post-diagnosis PA was strongly associated with all fatigue scales, the association was lowest for PA and cognitive fatigue. Thus, it could be hypothesized that survivors who reported higher levels of cognitive fatigue would have benefitted from additional mental training or psychosocial interventions.

So far most studies focused on fatigue shortly after CRC diagnosis. However, as mentioned in section 1.2.4, it has been reported that fatigue can persist years after diagnosis. Therefore, it is important to find out if PA is beneficial to mitigate long-term fatigue of CRC survivors. The findings of this analysis add to current knowledge that pre-diagnosis PA cannot replace ongoing PA after diagnosis among long-term CRC survivors, under the assumption that the association between ongoing PA and better fatigue is not entirely a result of reverse causality.

Fatigue is often reported as the symptom most burdensome among cancer survivors (Ryan *et al.*, 2007) and it has been shown to affect QOL more than other symptoms such as pain or depression (Cheng and Lee, 2011; Hofman *et al.*, 2007). Since fatigue can persist over

years of survivorship (Thong *et al.*, 2013), it is of great relevance to find out more about interventions that have the potential to decrease fatigue in CRC survivors, also in the long run. Contrary to my prior hypothesis, pre-diagnosis PA was not associated with lower fatigue and does not seem to provide a buffer for fatigue in the years after CRC diagnosis. Instead, ongoing PA after CRC diagnosis might be important to mitigate fatigue among long-term CRC survivors. Therefore, based on these results, health care providers should encourage CRC survivors to be physically active in survivorship, regardless of pre-diagnosis PA levels. Although pre-diagnosis work-related PA and vigorous PA in the years prior to CRC diagnosis were positively associated with long-term fatigue among CRC survivors, individually-tailored PA interventions throughout the years of survivorship might also be beneficial for this population. Health care providers should inform patients for example about the beneficial associations not only between light PA and QOL but also about the beneficial associations of light PA and fatigue among cancer survivors (Serda *et al.*, 2018; van Roekel *et al.*, 2015). Despite the reasons which may hinder health care providers from recommending PA to cancer survivors, as mentioned in section 4.2.1, it is important that health care providers motivate cancer survivors to be physically active also in the years of survivorship. Moreover, the provision of more supervised exercise programs which focus on the specific needs of the population of CRC survivors throughout the years of survivorship would be beneficial.

4.2.3. Potential determinants of physical inactivity

Since the findings of the first two analyses suggest that ongoing PA seems to be relevant for the well-being of long-term CRC survivors, an analysis was conducted to investigate potential barriers of PA among long-term CRC survivors. A number of factors such as having a stoma, living in a small town or city, older age, being divorced, a current smoker, and obese were associated with higher odds of physical inactivity at 5YFU with minor variations regarding the strength and significance of each specific association. Survivors who were physically active at baseline were less likely to be physically inactive at 5YFU. Participants drinking small amounts of alcohol at 5YFU were more likely to be physically inactive, and survivors reporting a high alcohol consumption at 5YFU were less likely to be physically inactive. No associations were found for sex, citizenship, education, cancer site, or primary treatment. Some associations between patient characteristics and physical inactivity might be restricted to subgroups according to age and sex.

A few studies such as Fisher et al. (Fisher *et al.*, 2016), McGowan et al. (McGowan *et al.* 2013), and van Putten et al. (van Putten *et al.* 2016) have already investigated potential determinants of physical inactivity among CRC survivors, but to my knowledge, this is the first study which investigated potential determinants of physical inactivity specifically in long-term CRC survivors. Comparable to the results of my analysis, van Putten et al. (van Putten *et al.* 2016) and Fisher et al. (Fisher *et al.* 2016) identified older age as a barrier for PA in CRC survivors. Moreover, van Putten et al. (van Putten *et al.* 2016) also reported that obesity was associated with lower PA among CRC survivors. In accordance with my results, other studies also did not find any cancer site-specific (McGowan *et al.*, 2013; van Putten *et al.*, 2016), cancer treatment-specific (Fisher *et al.*, 2016; McGowan *et al.*, 2013), or education-specific (van Putten *et al.*, 2016) associations with physical inactivity. In contrast to the findings of this analysis, previous studies reported men to be more physically active than women (McGowan *et al.*, 2013; van Putten *et al.*, 2016). These differences in results might be explained by the different PA questionnaires used, which might have asked especially for PAs that are more popular among men. In the present analysis, having a stoma was a strong predictor of physical inactivity in long-term CRC survivors, although previous studies did not find stoma use to be associated with physical inactivity (McGowan *et al.*, 2013; van Putten *et al.*, 2016). Since it was observed that the association between having a stoma and physical inactivity was restricted to the younger age group (30-69 years), the different results in this study compared to other studies might be explained by the inclusion of a higher number of younger participants having a stoma in the DACHS study. Younger survivors may be more afraid of the stoma leaking and thus might feel more ashamed going out or being physically active compared to older survivors who may be

better adjusted to handling the side effects of other diseases. Moreover, younger survivors with a stoma might not be able to perform sports that they had done before, and thus, they are less physically active. In previous studies, heterogeneous results were found regarding the associations of comorbidity with physical inactivity (Fisher *et al.*, 2016; van Putten *et al.*, 2016). In this analysis, almost all models indicated an association between having ≥2 comorbidities and physical inactivity. However, these results are hard to compare since different comorbidities were assessed in previous studies and the categorization of the number of comorbidities was not the same.

The results regarding alcohol were counter-intuitive at first sight. Survivors drinking small amounts of alcohol at 5YFU were more likely to be physically inactive, and survivors reporting high alcohol consumption at 5YFU were less likely to be physically inactive. A possible explanation for these findings could be the present health condition of those survivors. Participants who have fully recovered may be more physically active and able to participate in social life again and thus might drink more alcohol. Survivors who still suffer from comorbidities and long-term treatment side effects might not be physically active and not drinking much alcohol.

In general, the different results in this study compared to previous studies might be caused by country-specific PA habits and the heterogeneity between studies regarding the inclusion criteria or PA assessment. Furthermore, one of the most obvious differences of this study compared to other studies is the exclusion of short-term CRC survivors.

No clear distinction between healthy people and CRC survivors can be made regarding potential determinants of physical inactivity. In both healthy populations (Chastin *et al.*, 2015; Koeneman *et al.*, 2011) and CRC survivors, studies reported heterogeneous results. However, having a higher BMI seemed to be associated with physical inactivity in both healthy populations as well as CRC survivors.

Since PA was found to be positively associated with several health outcomes such as better prognosis and QOL among CRC patients, understanding the potential determinants of physical inactivity in the growing population of long-term CRC survivors has strong clinical relevance. The findings of this analysis suggest that predominantly patients having a stoma, living in a more populated area, being older, divorced, a current smoker, or obese were more likely to be physically inactive. Those survivors might suffer from problems such as pain or a poor psychological or physical health condition which may hinder them from being vigorously or moderately physically active. Health care providers could give specific PA advice to those patients and inform them for example about the positive associations found for light PA and QOL as well as fatigue (Serda *et al.*, 2018; Thraen-Borowski *et al.*, 2013;

van Roekel *et al.*, 2015). Since results further showed that PA at baseline was significantly associated with PA at 5YFU, survivors being physically inactive at baseline might stay physically inactive in the years after CRC diagnosis. Therefore, an effective strategy to encourage PA in these high-need groups at an early point in time may help to reduce or even prevent physical inactivity in CRC survivors.

4.3. Strengths and limitations

4.3.1. Systematic review of the association between physical activity and quality of life in long-term colorectal cancer survivors

The systematic review has some specific strengths and limitations. Major strengths of this systematic review include the comprehensive search strategy in multiple databases, the adherence to criteria for conducting and reporting of systematic reviews, and the consideration of the methodological quality of the included studies. A further strength of this systematic review is that it is the first to summarize and evaluate the association of PA and QOL, specifically in long-term CRC survivors. This systematic review also has some shortcomings. Due to the heterogeneity of the study methods and results, pooling of the results was not possible and therefore no meta-analysis could be performed. Valuable information regarding the association between PA and QOL might have been missed by excluding studies that assessed QOL only on one dimension, by excluding observational and intervention studies which assessed the association between PA and QOL not only in long-term CRC survivors (mean of time since diagnosis <five years), by using databases which only detect published literature, or by excluding studies conducted in languages other than English or German.

4.3.2. Analyses within the DACHS study

Some overall strengths and limitations for the analyses carried out within the DACHS study demand careful consideration. Major strengths include a large population-based study sample, detailed and complete follow-up information, a prospective study design, comprehensive adjustment for confounders, tests for linear trends, and detailed investigations of differences in subgroups such as for pre-diagnosis PA, domain and intensity-specific evaluations. Furthermore, results of the analyses were solely based on long-term CRC survivors with a primary CRC diagnosis and the assessment of QOL, fatigue, and PA at 5YFU was performed using validated and standardized questionnaires. In general, the number of missing values was relatively low due to the collection of information by trained interviewers. For the analysis on determinants of physical inactivity, potential bias caused by missing values was minimized by performing multiple imputation. The results of the analyses performed within the DACHS study add to the limited knowledge about the benefits of PA and the potential determinants of physical inactivity among the growing population of long-term CRC survivors.

Certain limitations should also be considered. Due to the observational and partly cross-sectional study design, the findings can give only indirect support for recommendations of

encouraging and maintaining PA among long-term CRC survivors and preventing CRC long-term survivors from being physically inactive after diagnosis. Physical activity information was only available before diagnosis and five years after, therefore, it is not known how patients changed their PA habits over the course of their disease. Furthermore, since the reported PA of the last age decade (40, 50, 60 years…etc.) was used as pre-diagnosis PA, some bias might have been introduced. For example, someone diagnosed with CRC at age 61 might not have been very active at age 60 due to undiagnosed cancer/poor health, whereas someone diagnosed with CRC at age 69 will have a measure of their PA nearly a decade earlier. Moreover, recall or desirability bias may have occurred through self-reported PA measurement at baseline and 5YFU. In addition, high baseline PA levels were observed which challenge the validity of the baseline PA instrument and its comparability with the IPAQ used at 5YFU. Although the FAQ is a validated and standardized fatigue questionnaire, the physical scale was not assessed and therefore for the analysis on fatigue, the fatigue scale from the QLQ-C30 was used, even though the fatigue scales might not have been fully comparable. Despite being one of the largest studies worldwide on long-term CRC survivors, some patient subgroups especially of the analysis on determinants of physical inactivity were very small and subgroup analysis results should be interpreted with caution. Moreover, owing to the partly cross-sectional design of the analyses, the results should be interpreted with caution due to possible reverse causality. Finally, although I adjusted for several potential confounders in all analyses, residual confounding cannot be ruled out.

4.4. Conclusion

Physical activity has been shown to be effective in the primary prevention of CRC. Despite the growing interest for the role of PA in tertiary prevention, research on PA and QOL specifically among long-term CRC survivors is scarce. This dissertation aimed to investigate whether PA is associated with better QOL and to identify potential determinants that prevent long-term CRC survivors from being physically active. Results from the literature review showed that only few studies investigated the association between PA and QOL especially in long-term survivors. Summarizing the findings of the included studies, higher as well as lower intensities of post-diagnosis PA were positively associated with CRC survivors´ QOL, however, most studies were based on a cross-sectional and observational study design.

In the DACHS study, PA was assessed shortly after CRC diagnosis, asking for pre-diagnosis PA and PA five years post-diagnosis, concurrent with QOL and fatigue. Therefore, a prospective assessment of pre-diagnosis PA with long-term factors such as QOL or fatigue was feasible. Results regarding the associations between PA and QOL as well as PA and fatigue suggest that pre-diagnosis PA might not provide any protection of cancer-related detriments neither in QOL nor in fatigue among long-term CRC survivors. Pre-diagnosis work-related PA and vigorous PA were even associated with decreased QOL in some domains and increased physical, cognitive, and affective fatigue. However, the results of the analyses support and emphasize the need of ongoing PA after CRC diagnosis to improve QOL and reduce fatigue in this population.

In a further analysis within the DACHS study, cancer-specific factors such as having a stoma, socio-demographic factors such as living in a small town or city, older age, or being divorced as well as lifestyle factors such as being a current smoker, or being obese were associated with physical inactivity among long-term CRC survivors. Moreover, baseline PA was identified as a strong predictor of physical inactivity five years later. Further subgroup analyses showed that the association between BMI and physical inactivity was stronger in women than in men.

The results of this dissertation are promising since it can be concluded that it is never too late to start exercising to improve the QOL of long-term CRC survivors and that PA is positively associated with QOL, even if completed at low intensity. This information might be motivating for CRC survivors who experience the cancer disease as a teachable moment, and therefore are more receptive for a lifestyle change. In addition, CRC survivors such as older survivors or survivors with poor health who may not be able to participate in higher intensity PA, have the potential to improve their QOL with low intensity PA. Subgroups of survivors who suffer from detriments in QOL five years after diagnosis as well

as groups at higher risk for post-diagnosis physical inactivity were identified. In clinical practice, addressing high-need groups among CRC survivors might help to contribute to the development of specific, individually-tailored PA interventions to overcome physical inactivity and improve the long-term well-being of CRC survivors. Although guidelines such as the S3-guideline “colorectal cancer” point out the necessity for physicians to recommend PA to CRC patients, health care providers often do not prescribe PA to cancer patients. However, the encouragement by health care providers to engage in PA is crucial for cancer patients to participate in PA interventions. Therefore, it is important that health care providers motivate and encourage cancer survivors to be physically active also in the years of survivorship.

The findings of this dissertation add to the limited evidence on the crucial role of PA among long-term CRC survivors. However, more prospective studies and randomized controlled trials are needed to further evaluate and confirm the causality of the findings, in order to provide more solid evidence for individual PA recommendations and strategies to overcome barriers to PA. Moreover, prospective studies should focus on the association between PA and QOL or fatigue at multiple points in time pre- and post-diagnosis to determine if and how the effect of the association changes. In addition, future studies should complement self-reported PA information by using objective activity monitoring to minimize reporting bias. Future studies may also consider incorporating QOL questionnaires that cover psychological as well as physical aspects specifically relevant for long-term cancer survivors to gain a greater understanding of the specific needs relevant for this population.

5. SUMMARY

Colorectal cancer is the third most common cancer and the second most common cause of cancer-related death worldwide. Early detection and improvements in treatment as well as the aging and growth of the population have substantially contributed to the increasing number of long-term (five or more years after diagnosis) colorectal cancer survivors. However, many colorectal cancer survivors experience detriments in quality of life in the years well beyond their diagnosis and quality of life is affected by fatigue more than by other symptoms. Thus, improving the quality of life and reducing fatigue of the increasing population of long-term colorectal cancer survivors has strong clinical and population health relevance. Evidence has accumulated that physical activity is prognostically relevant for colorectal cancer survivors and studies further reported positive associations between physical activity and quality of life among this population. However, so far studies have mainly focused on short-term colorectal cancer survivors.

A systematic review was conducted to summarize the current state of research with respect to the association between physical activity and quality of life in long-term colorectal cancer survivors. Only two of the seven included studies were restricted to long-term survivors, the other studies comprised survivors with a mean of five or more years since diagnosis. The results of this review demonstrate that long-term colorectal cancer survivors who were more physically active after diagnosis generally reported higher quality of life than non-active survivors. Moreover, different activity intensities such as light and moderate to vigorous physical activity were positively associated with quality of life in long-term colorectal cancer survivors. Further, the association between physical activity and quality of life appeared to be stronger among women than among men. Although the findings of this systematic review support a positive association between physical activity and quality of life in long-term colorectal cancer survivors, the evidence is limited as most studies were based on a cross-sectional and observational design.

The findings of the systematic review were confirmed and extended in the analyses among long-term colorectal cancer survivors of the DACHS study. The DACHS study is a population-based study with ongoing follow-up. In addition to the results of the review, the analysis of the DACHS data revealed no positive association between pre-diagnosis physical activity and long-term quality of life in colorectal cancer survivors. Pre-diagnosis work-related physical activity and vigorous physical activity might even decrease some quality of life domains such as cognitive and emotional functioning. Consequently, pre-diagnosis physical activity does not seem to provide a buffer that may mitigate or prevent cancer-related detriments in quality of life among long-term colorectal cancer survivors. In

contrast, post-diagnosis physical activity was strongly associated with quality of life five years after diagnosis in line with the findings of the review. Also, survivors being physically active both pre- and post-diagnosis and survivors who increased their physical activity from pre- to post-diagnosis had a significantly higher long-term quality of life compared to survivors being inactive pre- and post-diagnosis. Due to the important role of fatigue in the context of quality of life, the association between pre- and post-diagnosis physical activity and long-term physical, cognitive, and affective fatigue was evaluated. Although, a positive association between pre-diagnosis work-related physical activity as well as vigorous physical activity and long-term physical, cognitive, and affective fatigue was found, post-diagnosis physical activity was strongly associated with reduced levels of fatigue on all scales. Also, survivors who remained physically active from pre- to post-diagnosis and survivors becoming physically active post-diagnosis, scored significantly lower on all fatigue scales compared to non-active survivors pre- and post-diagnosis. The results of both analyses support and emphasize the need of maintaining physical activity after colorectal cancer diagnosis. However, the cross-sectional results should be interpreted with caution due to possible reverse causality.

Since physical activity has been shown to be associated with better prognosis and quality of life in colorectal cancer patients, an analysis was conducted which focused on the barriers of physical activity among long-term colorectal cancer survivors. A number of factors such as having a stoma, living in a small town or city, older age, being divorced, a current smoker, or obese were associated with higher odds of physical inactivity five years post-diagnosis. Further, baseline physical activity was a strong predictor for physical activity five years later.

In conclusion, the findings of this dissertation add to the limited evidence on the crucial role of physical activity among long-term colorectal cancer survivors and its positive association with quality of life. Further, the results may be used to target high-need groups for post-diagnosis physical inactivity. However, more prospective studies and randomized controlled trials are needed to further evaluate and confirm the causality of the findings, in order to provide more solid evidence for individual physical activity recommendations and strategies to overcome barriers to physical activity. Moreover, prospective studies should focus on the association between physical activity and quality of life or fatigue at multiple points in time pre- and post-diagnosis to determine if and how the effect of the association changes. In addition, future studies should complement self-reported PA information by using objective activity monitoring to minimize reporting bias. Future studies may also consider incorporating quality of life questionnaires that cover psychological as well as physical aspects specifically relevant for long-term cancer survivors to gain a greater understanding of the specific needs relevant for this population.

ZUSAMMENFASSUNG

Darmkrebs als dritthäufigste Krebsart ist für jeden zweiten Krebstod weltweit verantwortlich. Früherkennung, verbesserte Therapiemöglichkeiten sowie das Älterwerden und Wachstum der Bevölkerung haben maßgeblich dazu beigetragen, dass sich die Anzahl der langzeitüberlebenden Darmkrebspatienten (fünf Jahre nach Diagnose oder länger) kontinuierlich erhöhte. Viele Darmkrebspatienten erleben jedoch noch lange nach ihrer Diagnose Einbußen in der Lebensqualität (dabei ist Fatigue ein Symptom, das sich besonders negativ auf die Lebensqualität von Krebspatienten auswirkt). Demzufolge ist die Verbesserung der Lebensqualität als auch die Verringerung von Fatigue von langzeitüberlebenden Darmkrebspatienten von großer klinischer Relevanz. Evident ist, dass körperliche Aktivität bzgl. Darmkrebs prognostisch relevant ist und zudem positiv mit Lebensqualität assoziiert ist. Bisherige Studien beziehen sich allerdings fast ausschließlich auf den Zusammenhang zwischen körperlicher Aktivität und Lebensqualität bei Darmkrebspatienten binnen der ersten fünf Jahre nach Diagnose.

Um den aktuellen Wissensstand in Bezug auf den Zusammenhang zwischen körperlicher Aktivität und Lebensqualität bei langzeitüberlebenden Darmkrebspatienten aufzuzeigen wurde ein systematischer Review durchgeführt. Darin zeigte sich, dass sowohl höhere als auch niedrigere Intensitäten körperlicher Aktivität positiv mit der Lebensqualität von langzeitüberlebenden Darmkrebspatienten assoziiert waren. Zudem schien dieser Zusammenhang bei Frauen stärker zu sein als bei Männern. Allerdings ist die Aussagekraft des systematischen Reviews begrenzt, da er hauptsächlich auf querschnittlichen Beobachtungsstudien beruht und nur zwei der sieben einbezogenen Studien sich ausschließlich auf Langzeitüberlebende fokussierten.

In anschließenden Auswertungen wurden anhand der Daten aus der bevölkerungsbezogenen DACHS-Studie, mit Follow-up fünf Jahre nach Diagnose, die Ergebnisse des Reviews bestätigt und erweitert. Es zeigte sich keine positive Assoziation zwischen körperlicher Aktivität vor Diagnose und der Lebensqualität von Überlebenden fünf Jahre nach Diagnose. Arbeitsbedingte und schwere körperliche Aktivität vor Diagnose gingen sogar mit Beeinträchtigungen in einigen Lebensqualitätsbereichen einher. Insgesamt scheint also körperliche Aktivität vor Diagnose die Folgen von krebsbedingten Beeinträchtigungen in der Lebensqualität von langzeitüberlebenden Darmkrebspatienten weder zu verhindern noch abzumildern. Im Gegensatz dazu war körperliche Aktivität fünf Jahre nach Diagnose stark mit verbesserter Lebensqualität assoziiert. Darüber hinaus hatten Überlebende, die sowohl vor als auch nach Diagnose körperlich aktiv waren sowie Überlebende, die ihre körperliche Aktivität nach der Diagnose steigerten, eine signifikant höhere Lebensqualität als inaktive Überlebende vor und nach Diagnose.

Aufgrund der großen Bedeutung von Fatigue in Hinblick auf die Lebensqualität von Krebspatienten wurde gezielt die Assoziation zwischen körperlicher Aktivität sowohl vor als auch nach Diagnose und Fatigue untersucht. Dabei zeigte sich analog der vorherigen Auswertung eine starke Assoziation zwischen körperlicher Aktivität nach Diagnose und signifikant verringerter körperlicher, kognitiver und affektiver Fatigue. Auch Überlebende, die vor und nach Diagnose körperlich aktiv waren und Überlebende, die nach Diagnose körperlich aktiv wurden, wiesen auf allen Fatigueskalen einen signifikant niedrigeren Wert auf als inaktive Überlebende vor und nach Diagnose. Die Ergebnisse beider Analysen unterstreichen die Notwendigkeit körperlicher Aktivität nach einer Darmkrebsdiagnose. Die querschnittlichen Assoziationen zwischen körperlicher Aktivität und Lebensqualität als auch Fatigue sollten jedoch wegen möglicher reverser Kausalität mit Vorsicht interpretiert werden.

Da gezeigt werden konnte, dass körperliche Aktivität neben einer verbesserten Prognose mit verbesserter Lebensqualität von Darmkrebspatienten assoziiert ist, wurde eine weitere Analyse durchgeführt, die sich mit den Barrieren körperlicher Aktivität bei langzeitüberlebenden Darmkrebspatienten befasste. Eine Reihe von Faktoren, wie das Leben mit einem Stoma, das Wohnen in einer bevölkerungsreicheren Gegend, ein höheres Lebensalter, Scheidung, Rauchen oder Fettleibigkeit waren fünf Jahre nach Diagnose mit einer höheren Wahrscheinlichkeit körperlicher Inaktivität assoziiert. Darüber hinaus war die körperliche Aktivität vor Diagnose ein starker Prädiktor bezüglich der körperlichen Aktivität fünf Jahre nach Diagnose.

Die Ergebnisse dieser Dissertation ergänzen den aktuellen Forschungstand bzgl. der zentralen Rolle von körperlicher Aktivität für die Lebensqualität von langzeitüberlebenden Darmkrebspatienten. Darüber hinaus könnten die Ergebnisse genutzt werden, um Risikogruppen für körperliche Inaktivität gezielt zu unterstützen. Weitere prospektive und randomisierte kontrollierte Studien sind jedoch erforderlich, um mehr über die kausalen Zusammenhänge der gefundenen Ergebnisse aussagen zu können und um somit eine solide Grundlage für Empfehlungen zur körperlichen Aktivität und für Strategien zur Überwindung von körperlicher Inaktivität bereitzustellen. Darüber hinaus sollten prospektive Studien die Assoziation zwischen körperlicher Aktivität und Lebensqualität oder Fatigue zu mehreren Zeitpunkten vor und nach Diagnose untersuchen, um zu bestimmen, ob und in welcher Weise sich der Effekt der Assoziation verändert. Zukünftige Studien sollten objektive Messungen von körperlicher Aktivität und auch Lebensqualitätsfragebögen in Betracht ziehen, die sowohl psychische als auch körperliche Aspekte abdecken, welche speziell für langzeitüberlebende Krebspatienten relevant sind.

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7. LIST OF OWN PUBLICATIONS

Articles related to this dissertation

1. Eyl, R. E., Xie, K., Koch-Gallenkamp, L., Brenner, H. and Arndt, V. (2018). **Quality of life and physical activity in long-term (≥5 years post-diagnosis) colorectal cancer survivors - systematic review.** Health and Quality of Life Outcomes *16(1)*, 112.

2. Eyl, R. E., Koch-Gallenkamp, L., Jansen, L., Walter, V., Carr, P. R., Hoffmeister, M., Chang-Claude, J., Brenner, H. and Arndt, V. (2018). **Potential determinants of physical inactivity among long-term colorectal cancer survivors.** Journal of Cancer Survivorship *12(5)*, 679-690.

3. Eyl, R. E., Koch-Gallenkamp, L., Jansen, L., Walter, V., Carr, P. R., Hoffmeister, M., Chang-Claude, J., Brenner, H. and Arndt, V. **Physical activity and long-term quality of life among colorectal cancer survivors - a population-based prospective study.** (article submitted to the International Journal of Cancer)

4. Eyl, R. E., Thong, M., Carr, P. R., Jansen, L., Koch-Gallenkamp, L., Hoffmeister, M., Chang-Claude, J., Brenner, H. and Arndt, V. **Physical activity and long-term fatigue among colorectal cancer survivors - a population-based prospective study.** (article in preparation)

The first two articles included in this dissertation were accepted for publication, the third article has been submitted to the International Journal of Cancer, and the fourth article is still in preparation but will also be submitted to a renowned international journal. The authors´ contribution on article 1-4 include the drafting of the study proposal, the performance of the statistical analyses and the interpretation of the results, as well as the writing of the manuscript. Co-authors provided guidance and support regarding possible contents of data analyses and interpretation of the results, especially the last co-author Priv.-Doz. Dr. Volker Arndt.

Article 1 is based on sections 2.1., 3.1., 4.1., and 4.3.1 of this dissertation.

Article 2 is based on sections 2.2., 3.2.3., 4.2.3., and 4.3.2 of this dissertation.

Article 3 is based on sections 2.2., 3.2.1., 4.2.1., and 4.3.2 of this dissertation.

Article 4 is based on sections 2.2., 3.2.2., 4.2.2., and 4.3.2 of this dissertation.

Other articles

Xie, K., Eyl, R. E., Brenner, H. and Mons, U. **The relationship of glycemic control, hypoglycemia and hypertension with cognitive function in type 2 diabetes patients: a systematic review and meta-analysis.** (article submitted)

Poster presentations

Eyl, R. E., Xie, K., Koch-Gallenkamp, L., Brenner, H. and Arndt, V. **Quality of life and physical activity in long-term (≥5 years post-diagnosis) colorectal cancer survivors - systematic review.** 4th International Congress “Sport und Krebs”, Munich, 2017.

Eyl, R. E., Koch-Gallenkamp, L., Jansen, L., Walter, V., Carr, P. R., Hoffmeister, M., Chang-Claude, J., Brenner, H. and Arndt, V. **Potential determinants of physical inactivity among long-term colorectal cancer survivors**. Helmholtz International Graduate School for Cancer Research PhD Student Poster Presentation, Heidelberg, 2017.

Poster talk

Eyl, R. E., Xie, K., Koch-Gallenkamp, L., Brenner, H. and Arndt, V. **Quality of life and physical activity in long-term (≥5 years post-diagnosis) colorectal cancer survivors - systematic review.** 19th World Congress of Psycho-Oncology and Psychosocial Academy, Berlin, 2017.

8. APPENDICES

Appendix I Search terms systematic review

The following combinations of search terms were used:

(colorectal cancer OR colorectal neoplasms OR colorectal carcinoma OR colon cancer OR colon carcinoma OR rectal cancer OR rectal carcinoma OR rectal neoplasms OR colonic neoplasms OR intestinal cancer OR intestinal neoplasms OR lower gastrointestinal tract OR bowel cancer)

AND

(quality of life OR well-being OR mental health OR QOL OR HRQOL OR life quality OR qualities of life OR life satisfaction OR personal satisfaction)

AND

(motor activity OR physical activity OR exercise OR sedentary lifestyle)

In the database PubMed, the following Mesh terms were used additionally:

(colorectal neoplasms OR intestinal neoplasms OR colon OR rectum OR rectal neoplasms OR colonic neoplasms OR lower gastrointestinal tract)

AND

(quality of life OR mental health OR personal satisfaction)

AND

(motor activity OR exercise OR sedentary lifestyle)

Appendix II Association of physical activity and quality of life - symptom scales

		Statistical significance (p<0.05) and clinical relevance								
		+/–: significant positive/negative association [a,b,c]clinical relevance ns: not statistically significant								
Study	**QLQ-C30**	**Pain**	**Fatigue**	**Nausea, Vomiting**	**Appetite loss**	**Constipation**	**Diarrhoea**	**Dyspnoea**	**Insomnia**	**Financial difficulties**
Mols (2015)	Meeting vs. not meeting PA recommendations Low neuropathy[d]	–[a]	–	ns	–	ns	–[a]	–[a]	ns	ns
	Meeting vs. not meeting PA recommendations High neuropathy[e]	–[a]	–[a]	ns	–	ns	–[a]	–[a]	ns	ns
	Meeting vs. not meeting PA recommendations	–	–	ns	–	ns	–	–	ns	ns

QOL: quality of life; **QLQ-C30**: Quality of Life Questionnaire-Core 30; **PA:** physical activity; **PA recommendations:** 150 minutes of moderate intensity exercise each week or 75 minutes of vigorous intensity activity each week or an equivalent combination of both; **QLQ-CIPN20:** Quality of Life Questionnaire - Chemotherapy-Induced Peripheral Neuropathy; [a]clinical importance reported by authors; [b]calculated by RE; [c]no values, no cut-off for calculation available; [d]70% of patients with lowest scores of QLQ-CIPN20; [e]30% of patients with highest scores of QLQ-CIPN20

Appendix III Relevant section from the DACHS study baseline questionnaire: physical activity

Interviewer: Die nun folgenden Fragen beziehen sich auf Ihre körperliche Aktivität in unterschiedlichen Lebensabschnitten. Hierbei geht es sowohl um berufliche Aktivitäten, als auch um körperliche Aktivitäten im Haushalt, im Garten, zur Fortbewegung und in der Freizeit.

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77. Wie viele Stunden pro Woche haben Sie **in verschiedenen Lebensaltern im Durchschnitt** die folgenden Aktivitäten ausgeübt? (*Interviewer: Bitte auf ganze Zahlen runden.*)

Stunden pro Woche mit...	20 Jahren	30 Jahren	40 Jahren	50 Jahren
Körperlich anstrengende Arbeit (z.B. in der Landwirtschaft, als Bauarbeiter, in der Alten- und Krankenpflege, in Kriegsgefangenschaft)	___	___	___	___
Leichtere, vorwiegend gehende oder stehende Arbeit (z.B. Hausarbeit, Gartenarbeit, als Verkäufer, Friseur, etc.)	___	___	___	___
Fußwege außerhalb des Hauses und außerhalb der Arbeitszeiten (z.B. Wege von und zur Arbeit, zum Einkaufen, Spaziergänge und Wanderungen)	___	___	___	___
Fahrradfahrten (als Fortbewegungsmittel im Alltag, einschl Wegen von und zur Arbeit und in der Freizeit)	___	___	___	___
Körperlich anstrengende sportliche Aktivitäten (z.B. Fußball, Schwimmen, Skifahren, Bergsteigen, Tennis, Joggen, Radrennen)	___	___	___	___

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Stunden pro Woche mit...	60 Jahren	70 Jahren	80 Jahren
Körperlich anstrengende Arbeit (z.B. in der Landwirtschaft, als Bauarbeiter, in der Alten- und Krankenpflege, in Kriegsgefangenschaft)	___	___	___
Leichtere, vorwiegend gehende oder stehende Arbeit (z.B. Hausarbeit, Gartenarbeit, als Verkäufer, Friseur, etc.)	___	___	___
Fußwege außerhalb des Hauses und außerhalb der Arbeitszeiten (z.B. Wege von und zur Arbeit, zum Einkaufen, Spaziergänge und Wanderungen)	___	___	___
Fahrradfahrten (als Fortbewegungsmittel im Alltag, einschl Wegen von und zur Arbeit und in der Freizeit)	___	___	___
Körperlich anstrengende sportliche Aktivitäten (z.B. Fußball, Schwimmen, Skifahren, Bergsteigen, Tennis, Joggen, Radrennen)	___	___	___

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Appendix IV Relevant section from the DACHS study five-year follow-up questionnaire: quality of life (QLQ-C30)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie das Kästchen ankreuzen, das am besten auf Sie zutrifft. Es gibt keine „richtigen" oder „falschen" Antworten.

	Über-haupt nicht	Wenig	Mäßig	Sehr
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	☐	☐	☐	☐
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	☐	☐	☐	☐
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	☐	☐	☐	☐
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	☐	☐	☐	☐
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	☐	☐	☐	☐

Während der letzten Woche:	Über-haupt nicht	Wenig	Mäßig	Sehr
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	☐	☐	☐	☐
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	☐	☐	☐	☐
8. Waren Sie kurzatmig?	☐	☐	☐	☐
9. Hatten Sie Schmerzen?	☐	☐	☐	☐
10. Mussten Sie sich ausruhen?	☐	☐	☐	☐
11. Hatten Sie Schlafstörungen?	☐	☐	☐	☐
12. Fühlten Sie sich schwach?	☐	☐	☐	☐
13. Hatten Sie Appetitmangel?	☐	☐	☐	☐
14. War Ihnen übel?	☐	☐	☐	☐

Während der letzten Woche:	Über-haupt nicht	Wenig	Mäßig	Sehr
15. Haben Sie erbrochen?	☐	☐	☐	☐
16. Hatten Sie Verstopfung?	☐	☐	☐	☐
17. Hatten Sie Durchfall?	☐	☐	☐	☐
18. Waren Sie müde?	☐	☐	☐	☐
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	☐	☐	☐	☐
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitungslesen oder das Fernsehen?	☐	☐	☐	☐
21. Fühlten Sie sich angespannt?	☐	☐	☐	☐
22. Haben Sie sich Sorgen gemacht?	☐	☐	☐	☐
23. Waren Sie reizbar?	☐	☐	☐	☐
24. Fühlten Sie sich niedergeschlagen?	☐	☐	☐	☐
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	☐	☐	☐	☐
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	☐	☐	☐	☐
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	☐	☐	☐	☐
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	☐	☐	☐	☐

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft.

+	Sehr schlecht						Ausge-zeichnet	
29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	+
30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	

Appendix V Relevant section from the DACHS study five-year follow-up questionnaire: fatigue (FAQ)

Wir bitten Sie, die folgenden Fragen zu beantworten, indem Sie die für Sie passende Antwort ankreuzen. Die Antwort muss sich auf die Zeit der vergangenen Woche (inklusive heute) beziehen.

	Überhaupt nicht	Wenig	Mäßig	Sehr
1. Hatten Sie Schwierigkeiten sich zu konzentrieren?	☐	☐	☐	☐
2. Fühlten Sie sich vergesslicher als normalerweise?	☐	☐	☐	☐
3. War es für Sie schwierig, aufmerksam zu bleiben, zum Beispiel beim Zuhören oder Lesen?	☐	☐	☐	☐
4. Hatten Sie den Wunsch, die Gedanken „abzuschalten"?	☐	☐	☐	☐
5. Verspürten Sie Angst?	☐	☐	☐	☐
6. Fühlten Sie sich angespannt?	☐	☐	☐	☐
7. Fühlten Sie sich ungeduldig?	☐	☐	☐	☐
8. Fühlten Sie sich traurig, deprimiert?	☐	☐	☐	☐

Appendix VI Relevant section from the DACHS study five-year follow-up questionnaire: physical activity (IPAQ Short Form)

Bei den folgenden Fragen geht es um Ihre körperliche Aktivität während der vergangenen 7 Tage. Wichtig: Wenn die letzte Woche nicht Ihrer normalen Lebensweise entsprach, antworten Sie für eine typische Woche.

1. **In den letzten 7 Tagen:** An wie vielen Tagen führten Sie intensive körperliche Aktivitäten durch, die mit größerer Anstrengung verbunden sind? Intensive Aktivitäten verstärken Ihre Atmung stark. Dazu gehören zum Beispiel stark anstrengende körperliche Aktivitäten bei der Arbeit, im und ums Haus und in der Freizeit, sportliche Aktivitäten wie schnelles Radfahren als Sport oder auf dem Hometrainer, Joggen, Aerobics oder Fitnesstraining.

   Denken Sie nur an diejenigen Aktivitäten, die Sie jeweils während **mindestens 10 Minuten** ohne Unterbrechung ausführten.

☐ **Gar nicht in den letzten 7 Tagen** → **Bitte weiter mit Frage 2**

	1-2 Tage	3-4 Tage	5-6 Tage	7 Tage
a. An wie vielen Tagen in den letzten 7 Tagen?	☐	☐	☐	☐

	ca. 10 Minuten	ca. 20 Minuten	ca. 30 Minuten	ca. 1 Stunde	ca. 2 Stunden	ca. 3 Stunden oder mehr
b. Wie viel Zeit wenden Sie **an einem dieser Tage** üblicherweise für **intensive körperliche Aktivitäten** auf?	☐	☐	☐	☐	☐	☐

2. **In den letzten 7 Tagen:** An wie vielen Tagen führten Sie körperliche Aktivitäten durch, die mäßig anstrengend sind? Mäßige körperliche Aktivitäten lassen Sie etwas stärker atmen. Dazu könnten mäßige körperliche Aktivitäten bei der Arbeit, im und ums Haus und in der Freizeit, sportliche Aktivitäten wie Radfahren mit normaler Geschwindigkeit, Nordic Walking, Wandern, Turnen/Gymnastik, Schwimmen oder Tanzen zählen.

   Noch einmal: Denken Sie nur an die Aktivitäten, die Sie während **mindestens 10 Minuten** ohne Unterbrechung ausübten.

☐ **Gar nicht in den letzten 7 Tagen** → **Bitte weiter mit Frage 3**

	1-2 Tage	3-4 Tage	5-6 Tage	7 Tage
a. An wie vielen Tagen in den letzten 7 Tagen?	☐	☐	☐	☐

	ca. 10 Minuten	ca. 20 Minuten	ca. 30 Minuten	ca. 1 Stunde	ca. 2 Stunden	ca. 3 Stunden oder mehr
b. Wie viel Zeit wenden Sie **an einem dieser Tage** üblicherweise für **mäßige körperliche Aktivitäten** auf?	☐	☐	☐	☐	☐	☐

3. **In den letzten 7 Tagen:** An wie vielen Tagen gingen Sie für **mindestens 10 Minuten** oder länger ohne Unterbrechung? Dazu zählen das Gehen während der Arbeit und zu Hause, Gehen um von einem Ort zu einem anderen zu gelangen und jedes weitere Gehen, das Sie vielleicht ausschließlich zur Erholung oder in der Freizeit ausübten (dazu zählen nicht: Wandern oder Nordic Walking).

☐ **Gar nicht in den letzten 7 Tagen** ➔ **Bitte weiter mit Frage 4**

	1-2 Tage	3-4 Tage	5-6 Tage	7 Tage
a. An wie vielen Tagen in den letzten 7 Tagen?	☐	☐	☐	☐

	ca. 10 Minuten	ca. 20 Minuten	ca. 30 Minuten	ca. 1 Stunde	ca. 2 Stunden	ca. 3 Stunden oder mehr
b. Wie viel Zeit wenden Sie üblicherweise **an einem dieser Tage** für **das Gehen** auf?	☐	☐	☐	☐	☐	☐

4. **In den letzten 7 Tagen:** Wie lange **saßen** Sie üblicherweise an einem Wochentag? Berücksichtigen Sie die Zeit bei der Arbeit, zu Hause oder während der Freizeit. Dazu können das Sitzen am Tisch, beim Besuch von Freunden, beim Lesen oder das Sitzen oder Liegen beim Fernsehen gehören.

+	ca. 10 Minuten	ca. 20 Minuten	ca. 30 Minuten	ca. 1 Stunde	ca. 2 Stunden	ca. 3 Stunden oder mehr
a. Wie viele Minuten / Stunden an einem Wochentag?	☐	☐	☐	☐	☐	☐

9. CURRICULUM VITAE

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11. EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

Physical activity and quality of life among long-term colorectal cancer survivors

handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt. Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

Heidelberg, 12.11.2018

(Ort und Datum) (Unterschrift)