

Longitudinal Associations of Sedentary Behavior and Physical Activity with Quality of Life in Colorectal Cancer Survivors

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ABSTRACT

KENKHUIS, M. F., E. H. VAN ROEKEL, J. J. L. BREEDVELD-PETERS, S. O. BREUKINK, M. L. G. JANSSEN-HEIJNEN, E. T. P. KEULEN, F. J. B. VAN DUIJNHOFEN, F. MOLS, M. P. WEIJENBERG, and M. J. L. BOURS. Longitudinal Associations of Sedentary Behavior and Physical Activity with Quality of Life in Colorectal Cancer Survivors. *Med. Sci. Sports Exerc.*, Vol. 53, No. 11, pp. 2298–2308, 2021. **Introduction:** Given the growing population of colorectal cancer (CRC) survivors, identifying ways to enhance health-related quality of life (HRQoL) and alleviate complaints of fatigue and chemotherapy-induced peripheral neuropathy (CIPN) is essential. **Purpose:** We aimed to assess longitudinal associations of sedentary behavior (SB) and moderate to vigorous physical activity (MVPA) independently, as well as their joint association, with HRQoL, fatigue, and CIPN in CRC survivors. **Methods:** In a prospective cohort among stage I–stage III CRC survivors ($n = 396$), five repeated home visits from diagnosis up to 24 months posttreatment were executed. SB was measured using triaxial accelerometers, and MVPA, HRQoL, fatigue, and CIPN were measured by validated questionnaires. We applied confounder-adjusted linear mixed models to analyze longitudinal associations from 6 wk until 24 months posttreatment. **Results:** Average time in prolonged SB (accumulated in bouts of duration ≥ 30 min) was 5.3 ± 2.7 h·d⁻¹, and approximately 82% of survivors were classified as sufficiently active (≥ 150 min·wk⁻¹ of MVPA) at 6 wk posttreatment. Decreases in SB and increases in MVPA were independently associated with better HRQoL and less fatigue over time. No associations were found for CIPN complaints. A synergistic interaction was observed between prolonged SB and MVPA in affecting functioning scales. Relative to CRC survivors with low prolonged SB and high MVPA, survivors with high prolonged SB and low MVPA reported a stronger decrease in physical functioning and role functioning over time than expected based on the independent associations of prolonged SB and MVPA. **Conclusion:** Our longitudinal results show that less SB and more MVPA are beneficial for CRC survivors' HRQoL and fatigue levels. Our findings regarding interaction underscore that joint recommendations to avoid prolonged sitting and accumulate MVPA are important. **Key Words:** COLORECTAL CANCER SURVIVORSHIP, PHYSICAL ACTIVITY, SEDENTARY BEHAVIOR, HEALTH-RELATED QUALITY OF LIFE, FATIGUE, CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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Colorectal cancer (CRC) diagnosis and subsequent treatments lead to considerable detriments in physical and mental health (1). Two common physical complaints affecting health-related quality of life (HRQoL) of CRC survivors include fatigue and chemotherapy-induced peripheral neuropathy (CIPN) (2–4). Given the growing population of CRC survivors, identifying ways to enhance their HRQoL is essential (5–7). Favorable HRQoL outcomes among CRC survivors are increasingly being attributed to modifiable lifestyle factors such as physical activity (8).

In the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report on cancer prevention, recommendations are included for cancer survivors to increase moderate to vigorous physical activity (MVPA) and decrease sedentary behavior (SB) (9). This is in line with the

recently published World Health Organization 2020 guidelines on physical activity and SB, which also address people living with chronic conditions or disability (10,11). MVPA consists of activities that expend ≥ 3 METs, including for example brisk walking, swimming, or cycling (12). SB refers to any waking behavior of low energy expenditure (≤ 1.5 METs) in a sitting or reclining posture (13,14). The distinction between SB and physical inactivity (i.e., not adhering to MVPA guidelines) is important because it implies that physical activity guidelines can be achieved while simultaneously leading a sedentary lifestyle or the other way around (15,16).

Engaging in more MVPA has been shown in many cross-sectional and prospective cohort studies to be beneficially associated with HRQoL and fatigue outcomes in CRC survivors up to 10 yr posttreatment (8). By contrast, a meta-analysis of six studies failed to reach statistical significance on the effect of exercise interventions on HRQoL and fatigue (17) in CRC survivors. The interventions lasted from 6 to 12 wk, and one of these studies was followed up for 6 months. A systematic review on the influence of exercise on CIPN found that HRQoL was ameliorated after exercise sessions (18). However, most studies in this review focused on exercise during chemotherapy and were of short duration; no study investigated posttreatment associations between MVPA or SB and CIPN. Prospective and cross-sectional studies showed mixed results for associations between postdiagnosis SB and HRQoL and fatigue in different types of cancers (19). Some did not identify associations between SB and HRQoL, whereas others found statistically significantly lower HRQoL or lower HRQoL subscores in survivors who were more sedentary (20). Furthermore, the joint associations of (i.e., interaction between) SB and MVPA have not been examined in CRC survivors so far. The National Health and Nutrition Examination Survey examined the interaction between SB and MVPA in the general U.S. population (age ≥ 20 yr) and found that a combination of higher SB and lower MVPA was associated with poor HRQoL (21). In addition, high MVPA had a more favorable association with HRQoL, whereas prolonged SB played a role in weakening the protective association of high MVPA on HRQoL.

Independent associations of SB and MVPA have been observed for a range of health outcomes, indicating the relevance of both behaviors for human health and well-being (8,19). However, there is a need for more longitudinal research on the association of, especially, SB with HRQoL, fatigue, and CIPN in CRC survivors, as well as on the joint associations of SB and MVPA with these outcomes. Our research group has previously observed that MVPA is generally decreased 6 wk after treatment completion and increases afterward in the 2 yr after treatment to levels similar to those observed at diagnosis (22). With regard to HRQoL, a similar reduction is generally observed shortly after treatment followed by a gradual improvement in the yr thereafter (22,23). Therefore, we aim to examine the longitudinal association of SB and MVPA independently, as well as their joint association (i.e., interaction), with HRQoL, fatigue, and CIPN in CRC survivors from 6 wk up to 24 months after the end of the cancer treatment.

METHODS

Study design and population. Data were collected as part of the Energy for Life after Colorectal Cancer (EnCoRe) study, an ongoing prospective cohort study of CRC survivors. From April 2012 onward, all patients diagnosed with stage I–stage III CRC at three Dutch hospitals were eligible for the study. Patients were excluded when having stage IV CRC, being younger than 18 yr, living outside the Netherlands, unable to understand the Dutch language, and having comorbidities obstructing successful participation (e.g., Alzheimer’s disease). The Medical Ethics Committee of the University Hospital Maastricht and Maastricht University approved the study (Netherlands Trial Register no. NL6904) (24). All participants provided written informed consent.

Participants were visited by trained dietitians during five repeated measurements: at diagnosis and at 6 wk, 6 months, 12 months, and 24 months posttreatment. Data collected until July 2018 were used for the current analysis. A flow diagram describing recruitment to and participation in the study is shown in Figure 1. At baseline, the response rate was 45%, and follow-up response rates were all above 92%. The decrease in number of participants during the follow-up measurements was mainly due to the fact that most participants had not yet reached all posttreatment time points in July 2018.

SB and MVPA. Objective data on SB ($\text{h}\cdot\text{d}^{-1}$) were collected using the validated triaxial MOX activity meter (Maastricht Instruments B.V., Maastricht, Netherlands), which was worn on the anterior upper thigh 10 cm above the knee by the participants for 7 consecutive days ($24 \text{ h}\cdot\text{d}^{-1}$) at every posttreatment time point (25). Data on total SB ($\text{h}\cdot\text{d}^{-1}$) and prolonged SB ($\text{h}\cdot\text{d}^{-1}$) of sedentary time accrued in uninterrupted sedentary bouts with a duration of at least 30 min (26) were used in the current analyses. Accelerometer data were deemed valid with ≥ 10 h of waking wear time per day; only participants with ≥ 4 valid days were included in the analyses. A customized Matlab program (version R2012a; The MathWorks, Inc., Natick, MA) was used to classify sedentary, standing, or total physical activity time. Further processing of worn waking data was performed in SAS (version 9.3; SAS Institute Inc., Cary, NC), using a customized program with bout scoring adapted from approaches by the National Cancer Institute (27,28). The device was shown to have moderate to high reproducibility and high validity to assess SB (29). Although the device also measures total physical activity (all activities with an energy expenditure >1.5 METs), the monitor unfortunately has limited reproducibility for estimating time in activities at a moderate to vigorous intensity (29). In this manuscript, we chose to focus on MVPA and not total physical activity, as MVPA is included in the WCRF physical activity recommendation (9).

Physical activity at every time point from diagnosis until 24 months after treatment was assessed using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) (30,31). Participants reported time spent on commuting, household, work, and leisure time activities in the past week. Based on Ainsworth’s Compendium of Physical Activities, all activities were assigned MET values; ≥ 3 MET values were categorized

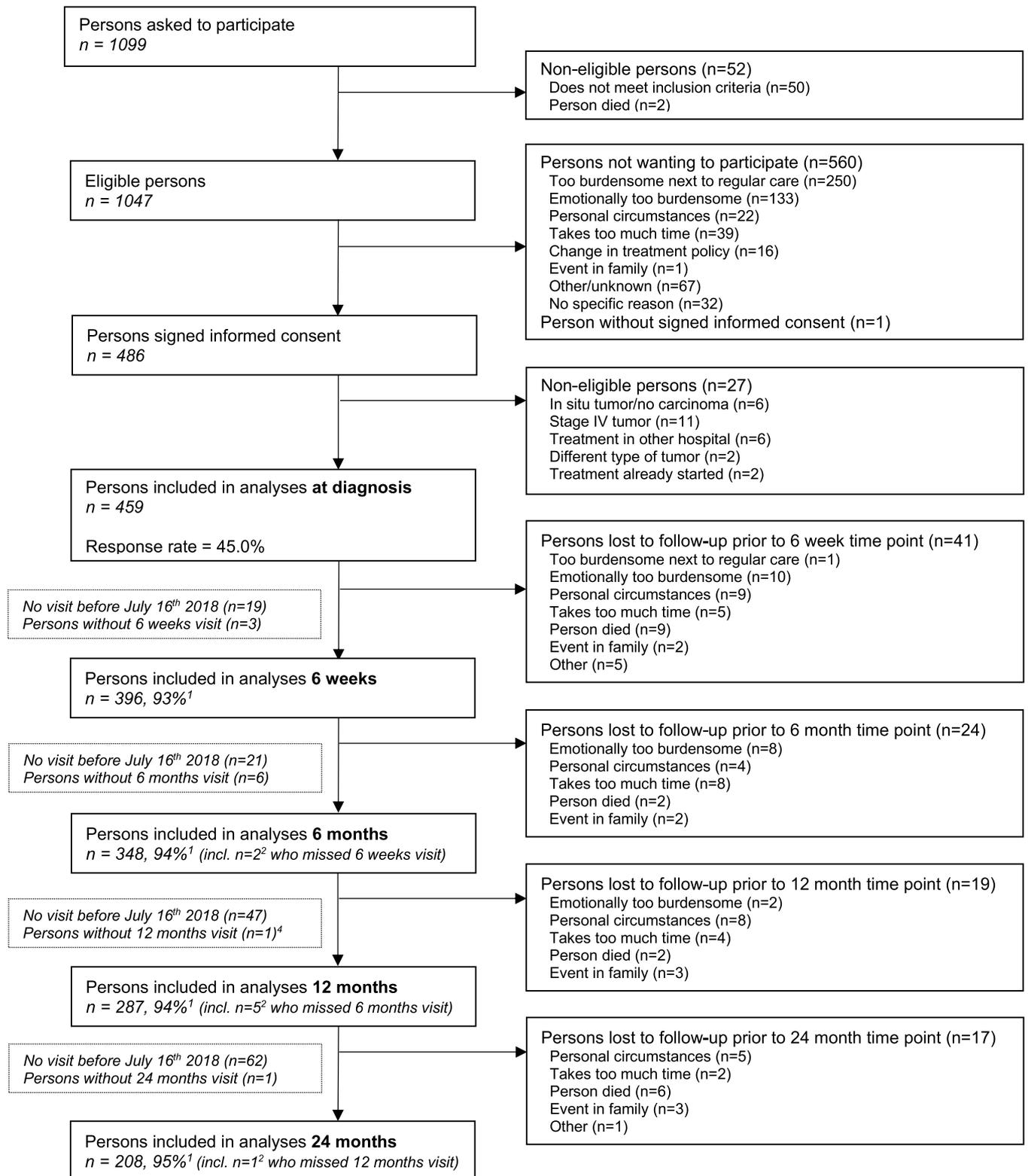


FIGURE 1—Flow diagram of inclusion of individuals within the EnCoRe study and included in the analyses presented in this article. Data of home visits performed before July 16, 2018, were included in the analyses. ¹ Response rate posttreatment = (persons included) / (persons included + persons lost to follow – persons died). ² Of the three persons without 6 wk follow-up visits, one person did not have a 6-month follow-up visit before July 16, 2018. Of the six persons without 6 months follow-up visits, one person did not have a 12-month follow-up visit before July 16, 2018.

as MVPA (e.g., vigorous household work, walking, and sports) (12). Total weekly MVPA (h·wk⁻¹) was calculated by summing the time spent in activities with a moderate to vigorous intensity.

The SQUASH was shown to be fairly reliable (test–retest: Spearman’s $\rho = 0.57$ – 0.58) (30,32). Relative validity, determined by an accelerometer, was found to be comparable with other

physical activity questionnaires (Spearman's $\rho = 0.40$ for moderate-intensity activities) (30).

HRQoL, fatigue, and CIPN. The widely used and well-validated European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (33) is a 30-item cancer-specific HRQoL questionnaire composed of functioning scales (physical functioning, 5 questions; role functioning, 2 questions; social functioning, 2 questions), symptom scales (fatigue, 3 questions), global health/QoL scale (2 questions), and summary score (SumSc, 23 questions) (34). All scale scores were linearly transformed to a 0–100 scale, with higher scores on the functioning scales, global QoL, and SumSc reflecting better functioning or HRQoL, whereas higher symptom scale scores indicate more symptoms (i.e., worse fatigue).

Besides the fatigue symptom scale from the EORTC QLQ-C30, which is often used in cancer research, fatigue was also assessed by the Checklist Individual Strength (CIS) to enable a comprehensive multidimensional assessment by providing scores for overall fatigue and subdomains of fatigue. The CIS is a validated 20-item questionnaire that has been previously used in cancer survivors as well (35,36). A total fatigue score was derived by the summation of all items (range, 20–140). In addition, we included the CIS subscales subjective fatigue (range, 8–56) and reduced physical activity (range, 3–21) in the present analyses because we expected MVPA and SB to be associated with the physical and subjective dimensions of fatigue. Higher scores indicate worse fatigue on all scales.

To measure complaints related to CIPN, the EORTC QLQ-CIPN20 was used. This 20-item questionnaire consists of sensory, motor, and autonomic subscales and a summary score (37). All scale scores were linearly converted to a 0–100 scale (38). Higher scores on the CIPN20 scales indicate more CIPN-related complaints. To describe the prevalence of CIPN complaints in our population, we made use of the CIPN-20 symptom classification system. This classification system classifies participants into three groups: no symptoms (total score = 0), mild CIPN symptoms (total score ≤ 20), and moderate to severe CIPN symptoms (total score > 20) (39).

Lifestyle, clinical, and sociodemographic factors.

Age, sex, and clinical information (i.e., cancer stage, chemotherapy/radiotherapy, and tumor site) were retrieved from medical records. Self-reported data were collected on other factors, including current smoking status and presence of stoma at all time points. Comorbidities were assessed with the Self-Administered Comorbidity Questionnaire at all time points (40). Body mass index (BMI) was calculated as weight (kg) divided by squared mean height (m^2); trained research dietitians measured weight in duplicate at every time point and height in duplicate only at diagnosis. Dietary intake was measured through 7-d food diaries collected at each posttreatment time point (41). A diet quality score was calculated based on the five nutrition recommendations of the WCRF/AICR guidelines (9,42,43).

Statistical analyses. Descriptive statistics, including means and SD, medians and interquartile ranges (IQR), or frequencies and percentages, were calculated to describe main

sample characteristics, overall and by categories of prolonged SB (with the median used as cutoff), and compared with participants who did not wear the accelerometer.

Longitudinal analyses were performed by linear mixed regression models, which included modeling of changes in SB and MVPA over time and modeling of the associations between SB and MVPA and HRQoL, fatigue, and CIPN over time. The use of random slopes was tested with a likelihood-ratio test; random slopes were added when the model improved statistically significantly.

For describing longitudinal changes over time in total SB, prolonged SB, and MVPA, time was modeled as a categorical variable, represented by dummy variables. Longitudinal analyses of associations of SB (per $2 \text{ h}\cdot\text{d}^{-1}$), prolonged SB (per $2 \text{ h}\cdot\text{d}^{-1}$), and MVPA (per $150 \text{ min}\cdot\text{wk}^{-1}$) with HRQoL, fatigue, and CIPN outcomes between 6 wk and 24 months posttreatment were adjusted for *a priori*-defined confounders. Fixed (time-invariant) confounders included age at enrolment (yr), sex, chemotherapy (yes, no), and MVPA at diagnosis ($\text{h}\cdot\text{wk}^{-1}$). Time-variant confounders (measured at all posttreatment time points) included BMI ($\text{kg}\cdot\text{m}^{-2}$), number of comorbidities (0, 1, ≥ 2), stoma (yes/no), and time since diagnosis (months). To assess independent associations of SB and MVPA with outcomes, models for SB were adjusted for MVPA and *vice versa*. In addition, for the models including SB variables, adjustment for waking wear time ($\text{h}\cdot\text{d}^{-1}$) was done by including this time variable as an additional covariate. We further applied the 10% change-in-estimate method (44) for assessing an additional set of potential confounders, including education level (low, medium, high), radiotherapy (yes, no), dietary score (0–5 points) (42,43), and smoking (yes, no); none of the variables led to $>10\%$ change in beta estimates of SB or MVPA and were, therefore, not included in the main model. CIPN outcomes were only analyzed for the subgroup of patients who received chemotherapy (45). Inter- and intraindividual associations were disaggregated by adding centered person-mean values to the model to estimate interindividual associations (i.e., average differences between participants over time) and individual deviations from the person-mean value to estimate intraindividual associations (i.e., within-participant changes over time) (46).

To assess the interaction between prolonged SB and MVPA in relation to HRQoL, fatigue, and CIPN, participants were categorized in four groups based on dichotomized prolonged SB and MVPA variables using median values as cutoff: 1) high MVPA, low prolonged SB ($n = 69$); 2) high MVPA, high prolonged SB ($n = 62$); 3) low MVPA, low prolonged SB ($n = 115$); and 4) low MVPA, high prolonged SB ($n = 78$). Confounder-adjusted linear mixed model analyses were repeated with three dummy variables of the combined groups, using group 1 (i.e., most favorable SB and MVPA behavior) as reference category. Statistical significance of the interaction was tested by means of an interaction term of median-based dichotomous variables for prolonged SB and MVPA.

As a sensitivity analysis, to obtain more insight into the possible direction of the longitudinal associations, time-lag models

were used in which SB and MVPA variables at earlier time points were coupled with HRQoL, fatigue, and CIPN variables at subsequent time points to simulate a more natural direction of associations.

Statistical analyses were performed using Stata 15.0 (StataCorp. 2017, College Station, TX) with statistical significance set at $P < 0.05$ (two-sided).

RESULTS

Participant characteristics. Characteristics of included study participants ($n = 396$) at 6 wk posttreatment, stratified according to the median value of prolonged SB ($4.9 \text{ h}\cdot\text{d}^{-1}$, IQR = 3.6) and availability of accelerometer data ($n = 71$ missing), are presented in Table 1. About two-thirds of the participants were men (68%), and the mean age at diagnosis was 67 yr (SD = 9.1). Most participants were colon cancer survivors (63%), whereas 37% were rectum cancer survivors. The majority of participants received surgery (90%), and 39% and 26% received chemotherapy and radiotherapy, respectively. Those with high prolonged SB ($\geq 4.9 \text{ h}\cdot\text{d}^{-1}$) were more often older, overweight, and obese compared with those with low prolonged SB ($< 4.9 \text{ h}\cdot\text{d}^{-1}$). The participants without accelerometer data had higher BMI and reported lower levels of MVPA in comparison with those with low prolonged SB. Those with low prolonged SB reported a median of $8.8 \text{ h}\cdot\text{wk}^{-1}$ (IQR = 11.5) in MVPA, those with high prolonged SB reported 6.0 (8.6)

$\text{h}\cdot\text{wk}^{-1}$ in MVPA, and those with no accelerometer data spent 6.3 (9.6) $\text{h}\cdot\text{wk}^{-1}$ in MVPA.

Changes in HRQoL, fatigue, and CIPN up to 24 months posttreatment. As described previously (22,47), mean scores of global quality of life, physical functioning, role functioning, and social functioning increased from the 6 wk to 24 months posttreatment time point. Mean fatigue scores (EORTC subscale and CIS total scale), as well as the CIS subscales subjective fatigue and reduced activity, followed a decline between 6 wk and 24 months posttreatment. Among CRC survivors who received chemotherapy, peripheral neuropathy symptoms (EORTC CIPN-20 summary score and subscale scores) changed over time from diagnosis up to 24 months posttreatment. Peripheral neuropathy symptoms were highest at 6 wk posttreatment and gradually declined thereafter. At 6 wk, more than half (60%) of the participants who received chemotherapy reported mild CIPN symptoms and 27% reported moderate to severe CIPN symptoms. The proportion of people reporting mild CIPN symptoms remained relatively stable over time, whereas the proportion of people reporting moderate to severe CIPN symptoms gradually declined to 14% at 24 months.

Changes in SB and MVPA up to 24 months post-treatment. At 6 wk posttreatment, highest levels of total SB (mean \pm SD, $10.8 \pm 1.8 \text{ h}\cdot\text{d}^{-1}$) and prolonged SB ($5.3 \pm 2.7 \text{ h}\cdot\text{d}^{-1}$) were observed. Total SB and prolonged SB showed a statistically significant decline between 6 wk and 6 months posttreatment and thereafter remained relatively

TABLE 1. Sociodemographic, lifestyle, and clinical characteristics of included participants at 6 wk, by low and high prolonged SB and for those without accelerometer data.

	Total, N = 396	Low Prolonged SB (<4.9 h·d ⁻¹), n = 162	High Prolonged SB (≥4.9 h·d ⁻¹), n = 163	No Accelerometer Data, n = 71
Gender (male), n (%)	270 (68.2)	115 (71.0)	105 (64.4)	50 (70.4)
Age (yr), mean (SD)	67.0 (9.1)	64.6 (8.0)	69.5 (9.4)	66.8 (9.2)
BMI ^a (kg m ⁻²), mean (SD)	27.8 (4.6)	26.9 (4.1)	28.1 (4.8)	29.0 (4.7)
Underweight ^b and healthy weight: ≤24.9	119 (31.1)	60 (37.0)	41 (25.3)	18 (25.4)
Overweight: 25.0–29.9	173 (43.8)	69 (42.6)	75 (46.3)	29 (40.9)
Obese: ≥30.0	103 (26.1)	33 (20.4)	46 (28.4)	24 (33.8)
MVPA (h·wk ⁻¹), median (IQR)	7 (10.8)	8.8 (11.5)	6.0 (8.6)	6.3 (9.6)
Adherence to MVPA recommendation, n (%)				
Yes	320 (82.0)	143 (88.3)	123 (75.9)	54 (81.8)
No	70 (18.0)	19 (11.7)	39 (24.1)	12 (18.2)
Total SB, mean (SD)	10.8 (1.8)	9.9 (1.5)	11.7 (1.5)	–
Prolonged SB, mean (SD)	5.3 (2.7)	3.2 (1.1)	7.4 (2.1)	–
Smoking, ^d n (%)				
Current	34 (8.8)	15 (9.3)	14 (8.6)	5 (7.8)
Former	235 (60.7)	106 (65.8)	93 (57.4)	36 (56.3)
Never	118 (30.5)	40 (24.8)	55 (34.0)	23 (35.9)
Education, ^d n (%)				
Low	107 (27.1)	37 (22.8)	49 (30.1)	21 (30.0)
Medium	149 (37.7)	69 (42.6)	58 (35.6)	22 (31.4)
High	139 (35.2)	56 (34.6)	56 (34.4)	27 (38.6)
Comorbidities, n (%)				
0	91 (23.0)	36 (22.2)	34 (20.9)	21 (30.0)
1	102 (25.8)	52 (32.1)	35 (21.5)	15 (21.4)
≥2	202 (51.1)	74 (45.7)	94 (57.7)	34 (48.6)
Stoma (yes), n (%)	110 (28.4)	46 (28.6)	42 (25.9)	22 (33.9)
Cancer type, n (%)				
Colon	250 (63.1)	98 (60.5)	107 (65.6)	45 (63.4)
Rectosigmoid and rectum	146 (36.9)	64 (39.5)	56 (34.4)	26 (36.6)
Tumor stage, n (%)				
Stage I	124 (31.3)	54 (33.3)	51 (31.3)	19 (26.8)
Stage II	100 (25.3)	45 (27.8)	37 (22.7)	18 (25.4)
Stage III	172 (43.4)	63 (38.9)	75 (46.0)	34 (47.9)
Cancer treatment n (%)				
Surgery	354 (89.4)	142 (87.7)	143 (87.7)	69 (97.2)
Chemotherapy (yes)	155 (39.1)	58 (35.8)	62 (38.0)	35 (49.3)
Radiotherapy (yes)	101 (25.5)	39 (24.1)	40 (24.5)	22 (31.0)

stable up to 24 months posttreatment (Figs. 2A and 2B). In addition, Figures 2A and 2B show that men and women followed a similar trend over time for both total SB and prolonged SB. However, men had higher levels of total SB in comparison with women at all time points, whereas prolonged SB was similar for both men and women. Lowest levels of MVPA were observed at 6 wk posttreatment (median = 7, IQR = 10.8 h·wk⁻¹), which were significantly decreased relative to MVPA levels measured at diagnosis (Fig. 2C). From the 6-wk posttreatment time point onward, MVPA significantly increased again up to 24 months after treatment (β , i.e., difference in MVPA h·wk⁻¹ at 24 months posttreatment vs 6 wk posttreatment, 2.6; 95% confidence interval [CI] = 1.2–3.9) but remained significantly lower in comparison with levels at diagnosis

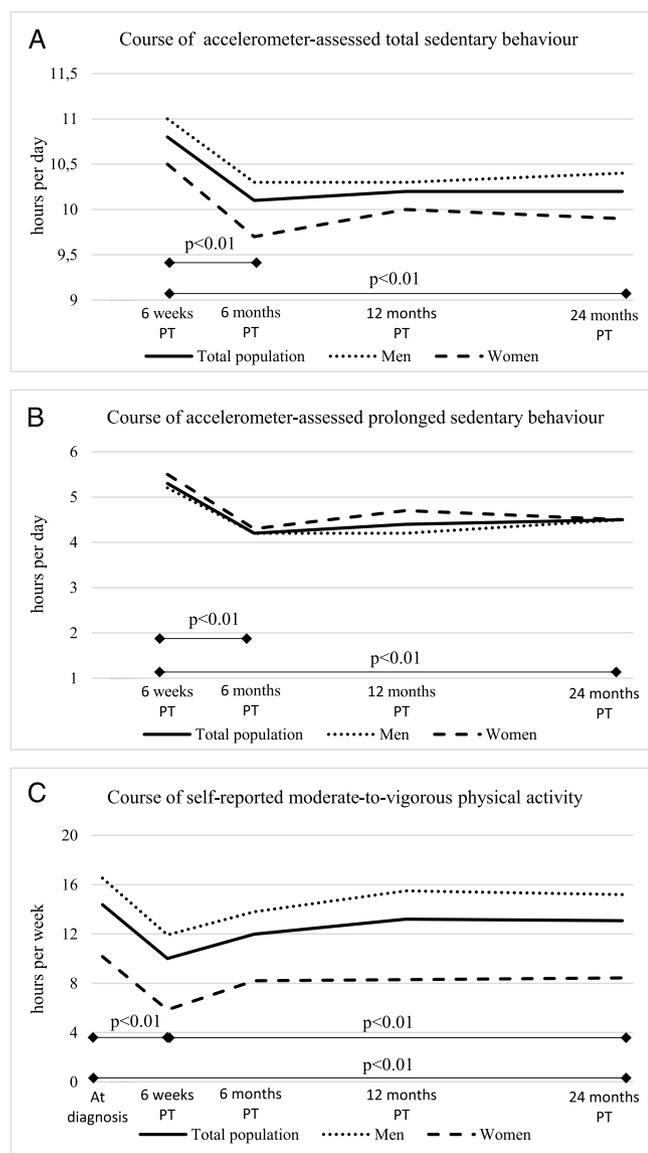


FIGURE 2—Course of accelerometer-assessed total SB (A), accelerometer-assessed prolonged SB, i.e., in bouts of duration ≥ 30 min (B), self-reported MVPA (C) from 6 wk up to 24 months posttreatment (PT) in CRC survivors in the EnCoRe study. Time was modeled as categorical variable, represented by dummy variables to obtain *P* values for differences between different time points for the total population.

TABLE 2. Linear mixed models between total SB, prolonged SB, and MVPA in relation to HRQoL and fatigue.

	EORTC QLQ-C30				CIS											
	Physical functioning (0–100)		Role functioning (0–100)		Social functioning (0–100)		Summary score (0–100)		Fatigue (EORTC) (0–100)		Total fatigue (CIS) (20–140)		Subjective fatigue (CIS) (8–56)		Activity fatigue (CIS) (3–21)	
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	
Total SB (per 2 h·d ⁻¹) ^b	Unadjusted -2.3* (-3.7 to -0.9)	-3.3* (-4.5 to -2.1)	-4.2* (-6.2 to -2.2)	-2.8* (-4.3 to -1.3)	-2.0* (-2.8 to -1.2)	3.2* (1.5 to 4.9)	5.1* (3.2 to 7.0)	1.9* (1.0 to 2.9)	1.6* (1.2 to 2.0)							
	Adjusted ^{a,b} -3.6* (-5.1 to -2.1)	-3.9* (-5.2 to -2.6)	-5.3* (-7.5 to -3.1)	-3.2* (-5.0 to -1.4)	-2.7* (-3.7 to -1.8)	3.8* (2.0 to 5.7)	6.0* (3.9 to 8.0)	2.2* (1.2 to 3.2)	1.8* (1.3 to 2.2)							
	Intra ^c -3.0* (-4.9 to -1.0)	-2.7* (-4.1 to -1.2)	-4.9* (-7.9 to -2.0)	-4.2* (-6.4 to -2.1)	-2.6* (-3.6 to -1.6)	4.9* (2.7 to 7.2)	6.7* (4.3 to 9.1)	2.6* (1.4 to 3.8)	1.8* (1.3 to 2.4)							
Prolonged SB (per 2 h·d ⁻¹) ^b	Unadjusted -1.4* (-2.4 to -0.4)	-2.9* (-3.8 to -2.1)	-3.2* (-4.6 to -1.8)	-2.1* (-3.2 to -1.0)	-1.4* (-2.0 to -0.8)	2.3* (1.1 to 3.5)	4.2* (2.8 to 5.5)	1.6* (1.0 to 2.3)	1.3* (1.0 to 1.5)							
	Adjusted ^{a,b} -1.3* (-2.3 to -0.3)	-2.3* (-3.2 to -1.4)	-3.0* (-4.6 to -1.3)	-2.0* (-3.1 to -0.9)	-1.1* (-1.7 to -0.5)	2.1* (0.6 to 3.5)	3.8* (2.4 to 5.2)	1.4* (0.7 to 2.1)	1.2* (0.9 to 1.4)							
	Intra ^c -1.2 (-2.5 to 0.1)	-1.4* (-2.4 to -0.5)	-3.0* (-5.0 to -0.9)	-2.7* (-4.2 to -1.2)	-1.3* (-2.0 to -0.5)	3.3* (1.8 to 4.9)	4.8* (3.2 to 6.5)	2.1* (1.3 to 2.9)	1.4* (1.0 to 1.7)							
MVPA (per 150 min·wk ⁻¹) ^b	Unadjusted 0.9* (0.6 to 1.1)	0.9* (0.7 to 1.1)	1.3* (1.0 to 1.7)	0.9* (0.6 to 1.2)	0.6* (0.5 to 0.7)	-0.9* (-1.2 to -0.6)	-1.2* (-1.6 to -0.9)	-0.6* (-0.7 to -0.4)	-0.3* (-0.4 to -0.2)							
	Adjusted ^{a,b} 0.7* (0.5 to 1.0)	0.5* (0.3 to 0.7)	1.0* (0.6 to 1.4)	0.7* (0.4 to 1.1)	0.4* (0.3 to 0.6)	-0.7* (-1.1 to -0.4)	-0.8* (-1.2 to -0.4)	-0.4* (-0.6 to -0.2)	-0.2* (-0.3 to -0.1)							
	Intra ^c 0.7* (0.4 to 1.0)	0.5* (0.2 to 0.7)	1.1* (0.6 to 1.6)	0.8* (0.4 to 1.1)	0.5* (0.3 to 0.6)	-0.8* (-1.2 to -0.4)	-0.7* (-1.1 to -0.3)	-0.3* (-0.5 to -0.1)	-0.1* (-0.2 to 0.0)							
	Inter ^d 0.8* (0.3 to 1.4)	0.9* (0.4 to 1.5)	1.0* (0.3 to 1.7)	1.0* (0.3 to 1.7)	0.4* (0.0 to 0.8)	-0.6* (-1.3 to 0.1)	-0.9* (-1.8 to -0.1)	-0.5* (-0.9 to -0.1)	-0.3* (-0.4 to -0.1)							

β , beta-coefficient.

^aModel adjusted for sex (male/female), age enrollment (yr), comorbidities (0, 1, ≥ 2), weeks since end of treatment (wk), chemotherapy (yes/no), BMI (kg·m⁻²), and stoma (yes/no). Models for SB were adjusted for MVPA (min·wk⁻¹), and models for MVPA were adjusted for prolonged SB (h·d⁻¹ in bouts 30 per minute). For the SB variables, we also added total waking wear time (h·d⁻¹).

^bThe beta-coefficients represent the overall longitudinal difference in the outcome score.

^cThe beta-coefficients represent the change in the outcome score over time within individuals.

^dThe beta-coefficients represent the difference in the outcome score between individuals.

^eA random slope was added to the model for total SB with global QoL, physical functioning, role functioning, social functioning, summary score, and activity fatigue; prolonged SB with physical functioning, role functioning, and fatigue (EORTC); MVPA with Global QoL, physical functioning, role functioning, social functioning, summary score, total fatigue, subjective fatigue, and activity fatigue (see Methods).

*Indicates statistically significant longitudinal associations.

(β , i.e., difference in MVPA $\text{h}\cdot\text{wk}^{-1}$ at 24 months posttreatment vs at diagnosis, -2.1 ; 95% CI = -3.4 to -0.8).

Longitudinal associations of SB and MVPA with HRQoL, fatigue, and CIPN. Table 2 shows the independent overall associations of SB and MVPA with HRQoL, fatigue, and CIPN over time. When controlling for sociodemographic and disease-specific variables, time of assessment, and MVPA levels, total SB and prolonged SB were significantly unfavorably associated with all HRQoL and all fatigue outcomes (Table 2). For example, higher prolonged SB was longitudinally associated with lower physical functioning (β per $2 \text{ h}\cdot\text{d}^{-1} = -2.2$; 95% CI = -3.0 to -1.3) and higher total fatigue (3.8; 2.4–5.2). In addition, the observed associations were generally stronger for total SB than for prolonged SB. Table 2 also shows the intra- and interindividual associations of total and prolonged SB with HRQoL, fatigue, and CIPN. The overall associations appeared to be driven by both within-person changes over time as well as between-person differences. As an example of an intraindividual association, participants increasing their prolonged SB by $2 \text{ h}\cdot\text{d}^{-1}$ in the period from 6 wk to 24 months posttreatment reported decreasing levels of physical functioning over time (-1.4 ; -2.4 to -0.5) and increasing levels of total fatigue (4.8; 3.2–6.5). Interindividual associations indicated that, for example, participants spending, on average, $2 \text{ h}\cdot\text{d}^{-1}$ more in prolonged SB than others reported lower levels of physical functioning (-3.9 ; -5.4 to -2.4) and higher total fatigue levels (1.6; -0.8 to 4.0), although the latter was not statistically significant. Similar to the findings for SB, higher MVPA levels were independently associated with higher HRQoL and lower fatigue levels over time when adjusted for time spent in prolonged SB, both intra- and interindividually (Table 2). No associations of SB or MVPA with CIPN outcomes were found (Table 3).

Interaction between SB and MVPA over time. Participants with high prolonged SB (above median, $\geq 4.9 \text{ h}\cdot\text{d}^{-1}$) and low MVPA (below median, $< 7 \text{ h}\cdot\text{wk}^{-1}$) reported, on average, lowest HRQoL and highest fatigue levels over time compared with the most favorable reference group of participants with low prolonged SB ($< 4.9 \text{ h}\cdot\text{d}^{-1}$) and high MVPA ($\geq 7 \text{ h}\cdot\text{wk}^{-1}$; Table 4). For participants with high prolonged SB and low MVPA, the level of physical functioning relative to the reference group (β high SB and low MVPA vs low SB and high MVPA = -7.6 ; 95% CI = -9.9 to -5.2) was significantly lower than expected based on the independent associations of prolonged SB and MVPA. This suggests synergism between prolonged SB and MVPA in their longitudinal association with physical functioning, which was statistically significant (P for interaction < 0.01). A similar synergistic association was observed for role functioning (-11.6 ; -15.7 to -7.4 ; P for interaction < 0.01). Significant statistical interaction between prolonged SB and MVPA was also found for the EORTC summary score, but not for fatigue (Table 4).

Sensitivity analyses: time-lag model. In comparison with the results of the main analysis, the overall longitudinal associations of prolonged SB with HRQoL and fatigue were attenuated within time-lag analyses, and most betas were not

TABLE 3. Linear mixed models between total SB, prolonged SB, and MVPA in relation to CIPN in participants treated with chemotherapy ($n = 155$ at 6 wk).

	EORTC QLQ-CIPN20		
	SumScore β (95% CI)	Motric β (95% CI)	Sensoric β (95% CI)
Total SB (per $2 \text{ h}\cdot\text{d}^{-1}$) ^b	Unadjusted	1.1 (-0.6 to 2.9)	1.6 (-0.6 to 3.9)
	Adjusted ^{a,b}	1.4 (-0.5 to 3.3)	1.8 (-0.7 to 4.3)
	Intra ^c	0.8 (-1.2 to 2.9)	1.0 (-1.7 to 3.7)
Prolonged SB (per $2 \text{ h}\cdot\text{d}^{-1}$) ^b	Inter ^d	0.5 (-3.1 to 4.0)	0.0 (-4.7 to 4.7)
	Unadjusted	0.4 (-0.8 to 1.6)	0.1 (-1.4 to 1.7)
	Adjusted ^{a,b}	0.4 (-0.8 to 1.6)	0.2 (-1.4 to 1.7)
MVPA (per $150 \text{ min}\cdot\text{wk}^{-1}$) ^b	Intra ^c	0.5 (-0.9 to 1.9)	0.2 (-1.6 to 2.1)
	Inter ^d	0.1 (-2.1 to 2.3)	0.1 (-2.8 to 2.9)
	Unadjusted	0.1 (-0.2 to 0.3)	0.0 (-0.3 to 0.4)
	Adjusted ^{a,b}	0.1 (-0.2 to 0.4)	0.2 (-0.2 to 0.6)
	Intra ^c	0.1 (-0.3 to 0.4)	0.1 (-0.3 to 0.6)
	Inter ^d	0.3 (-0.5 to 1.1)	0.4 (-0.7 to 1.5)
			Autonomic β (95% CI)
			0.1 (-1.7 to 2.0)
			0.7 (-1.4 to 2.7)
			1.4 (-1.1 to 3.9)
			-0.7 (-4.0 to 2.5)
			0.1 (-1.3 to 1.1)
			-0.2 (-1.4 to 1.1)
			0.2 (-1.5 to 1.9)
			-0.6 (-2.6 to 1.4)
			0.1 (-0.2 to 0.4)
			0.1 (-0.3 to 0.4)
			-0.0 (-0.4 to 0.4)
			0.4 (-0.4 to 1.1)

β , beta-coefficient.

^aModel adjusted for sex (male/female), age enrollment (yr), comorbidities (0, 1, ≥ 2), weeks since end of treatment (wk), BMI ($\text{kg}\cdot\text{m}^{-2}$), and stoma (yes/no). Models for SB were adjusted for MVPA ($\text{min}\cdot\text{wk}^{-1}$), and models for MVPA were adjusted for prolonged SB ($\text{h}\cdot\text{d}^{-1}$ in bouts 30 per minute). For the SB variables, we also added total waking wear time ($\text{h}\cdot\text{d}^{-1}$).

^bThe beta-coefficients represent the overall longitudinal difference in the outcome score.

^cThe beta-coefficients represent the change in the outcome score over time within individuals.

^dThe beta-coefficients represent the difference in the outcome score between individuals.

^eA random slope was added to the model for total SB with summary score, motric score, and sensory score; no random slope was added to the models for prolonged SB and MVPA (see Methods).

TABLE 4. Linear mixed models between combined categories of prolonged SB and MVPA in relation to HRQoL and fatigue.

	EORTC QLQ-C30						CIS		
	Global QoL (0-100)	Physical Functioning (0-100)	Role Functioning (0-100)	Social Functioning (0-100)	Summary Score (0-100)	Fatigue (EORTC) (0-100)	Total Fatigue (CIS) (20-140)	Subjective Fatigue (CIS) (6-56)	Activity Fatigue (CIS) (3-21)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Median-based combination groups of prolonged SB (4.9 h·d ⁻¹) and MVPA (7 h·wk ⁻¹)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Low SB and high MVPA (most favorable; n = 69) ^a	-4.3* (-6.9 to -1.7)	-2.7 (-4.8 to -0.6)	-2.7 (-6.6 to -1.2)	-3.1* (-5.9 to -0.2)	-1.4 (-2.9 to 0.0)	4.6 (1.5 to 7.7)	5.7* (2.3 to 9.2)	3.2 (1.5 to 4.9)	1.3* (0.5 to 2.0)
High SB and low MVPA (n = 62)	-2.8* (-5.6 to -0.0)	-0.0 (-2.3 to 2.2)	0.3 (-3.8 to 4.3)	-1.3 (4.3 to 1.7)	-0.7 (-2.3 to 0.9)	3.0 (-0.3 to 6.4)	7.4* (3.7 to 11.1)	2.7* (0.9 to 4.5)	2.0* (1.2 to 2.8)
High SB and low MVPA (most unfavorable; n = 78) ^b	-8.5* (-11.3 to -5.6)	-7.6* (-9.9 to -5.2)	-11.6* (-15.7 to -7.4)	8.4* (-11.5 to -5.4)	-4.6* (-6.3 to -2.9)	7.7* (4.3 to 11.2)	11.4* (7.6 to 15.3)	5.2* (3.4 to 7.1)	3.0* (2.2 to 3.8)
P value interaction ^c	0.58	0.00*	0.00*	0.06	0.02*	0.95	0.40	0.48	0.47

β , beta-coefficient.

^aModel adjusted for sex (male/female), age enrolment (yr), comorbidities (0, 1, ≥ 2), weeks since end of treatment (wk), chemotherapy (yes/no), BMI (kg·m⁻²), and stoma (yes/no). For the SB variables, we also added total waking wear time (h·d⁻¹).

^bOur estimates exceeded thresholds of small minimally important differences (MIDs) for the EORTC QLQ-C30 (4, 5, 6, 5, and 5 for the global quality of life, physical, role, social, and fatigue subscales, respectively) (48). For the CIS, no guidelines for MIDs are available. The observed associations in fatigue did not exceed 0.5 times the SD within our population (6 wk SD total fatigue (CIS), 26; subjective fatigue, 13; activity fatigue, 5), which is generally regarded as MID in this case (49).

^cP value interaction term of median-based categories for both prolonged SB as MVPA.

*Indicates statistically significant longitudinal associations.

significant anymore (see Table, Supplemental Digital Content, Time-lag analysis of linear mixed models between total sedentary behaviour, prolonged sedentary behavior, and moderate-to-vigorous physical activity in relation to health-related quality of life and fatigue, <http://links.lww.com/MSS/C333>).

DISCUSSION

We used data of the EnCoRe study to investigate longitudinal independent associations of SB and MVPA, as well as their joint association (i.e., interaction), with HRQoL, fatigue, and CIPN. Our main finding was that lower total and prolonged SB and higher MVPA, mutually adjusted, were all longitudinally associated with better HRQoL outcomes and lower fatigue from 6 wk up to 24 months posttreatment. These associations appeared to be driven by both within-person changes over time as well as between-person differences in SB and MVPA. No associations of SB or MVPA with CIPN outcomes were found. When we examined the joint association of prolonged SB and MVPA, we observed lowest levels of HRQoL and highest levels of fatigue in individuals with high prolonged SB and low MVPA when compared with those with the most favorable profile of low prolonged SB combined with high MVPA. We observed (Table 4) that in participants with low prolonged SB and low MVPA, HRQoL scores were significantly decreased over time when compared with those with high MVPA. In addition, high MVPA, even in participants with high prolonged SB, was able to attenuate the association with reduced HRQoL. Moreover, the joint associations of high prolonged SB and low MVPA with physical and role functioning were stronger than expected based on the independent associations of prolonged SB and MVPA with these outcomes, suggesting synergism between SB and MVPA. In addition, associations for the EORTC QLQ-C30 subscales in Table 4 appeared to be clinically relevant, according to previously published thresholds for interpreting changes (48,49).

The current study shows that both decreasing SB and increasing MVPA are favorably associated with better HRQoL and less fatigue up to 24 months after CRC treatment. Our findings add to the growing evidence that combining recommendations against prolonged SB and encouraging MVPA is beneficially associated with HRQoL and fatigue (9). Furthermore, the significant interaction observed for physical and role functioning provides evidence for a synergistic interaction of prolonged SB and MVPA on these functioning outcomes. To the best of our knowledge, no previous study has shown this synergistic interaction in CRC survivors. Importantly, our findings indicate that CRC survivors with low MVPA benefit more from decreasing prolonged SB than CRC survivors with high MVPA. This may be particularly relevant for those survivors who may not be able or willing to engage in sufficient amounts of MVPA because of their older age and/or presence of comorbidities (50). For those survivors, replacing SB by light physical activity (e.g., household activities, light walking) may be especially important and could therefore be a relevant target for lifestyle interventions. Findings from our own research group support this because

we have previously shown that substituting sedentary time with standing or physical activity was significantly associated with better physical functioning (51), and that increased light physical activity independent of MVPA was both cross-sectionally and longitudinally associated with better HRQoL and less complaints of fatigue in CRC survivors (22,52).

A possible biological mechanism that could explain the observed associations between SB and MVPA with HRQoL is inflammation (53–55). Observational studies in the general population observed that less SB and more physical activity were associated with lower levels of proinflammatory markers and higher levels of anti-inflammatory markers (56,57). A review published in 2014 identified inflammation as the key pathway that was related to several domains of HRQoL (58).

This study has several strengths. First, SB was objectively assessed using the thigh-mounted triaxial MOX activity monitor, which provides reliable and valid measurements of SB (29) and enabled us to quantify prolonged SB (29). In addition, we studied the interaction between prolonged SB and MVPA in their longitudinal associations with HRQoL and fatigue, which had not been done before in CRC survivors. In addition, fatigue was extensively measured by both the EORTC QLQ-C30 and the CIS, which enabled us to conclude that SB and MVPA were associated with different dimensions of fatigue (total, subjective, and activity). Other strengths of our study included the high response rates during follow-up (>92%), the limited number of missing data resulting from intensive data collection methods, and the availability of extensive data on potential confounders.

There are also limitations that should be considered. This study is an observational study, which limits our ability to make causal inferences, despite thorough confounder adjustment in our longitudinal analyses. In addition, we were not able to adjust for recurrence as a potential confounder because we did not have data available for all of the participants. In comparison with the results of the main analysis, the overall longitudinal associations of prolonged SB with HRQoL and fatigue were attenuated within time-lag analyses, and most betas were not significant anymore, indicating that the association found over time are likely reciprocal (see Table, Supplemental Digital Content, Time-lag analysis of linear mixed models between total sedentary behaviour, prolonged sedentary behavior, and moderate-to-vigorous physical activity in relation to health-related quality of life and fatigue, <http://links.lww.com/MSS/C333>). SB and MVPA may have affected HRQoL and fatigue, but at the same time HRQoL and fatigue may have independently altered SB and MVPA. Nevertheless, results from observational studies are necessary before significant investment is made on trials to further investigate the effectiveness of (combinations of) interventions. Future randomized controlled trials should further explore the associations of the combination of SB and MVPA to confirm whether the synergistic interaction between MVPA and SB observed in our study may be causal. An additional limitation was the use of a self-report questionnaire to assess MVPA. The questionnaire may be susceptible to recall bias or desirability, and it is likely that MVPA levels were overestimated by the participants (59). In addition, our study

may have included a selective sample. Although we did not have information on nonparticipants, nonparticipants may have differed from participants regarding certain characteristics (e.g., the more health conscious or healthier patients participated), possibly affecting the generalizability of our results. Also, our results for CIPN outcomes might suffer from limited statistical power. CIPN outcomes were only relevant for the subgroup of patients who received chemotherapy ($n = 155$), and analyses were thus performed within this relatively small group. Finally, we cannot rule out the possibility of false-positives due to the large number of tests performed. Nevertheless, the consistent significant longitudinal associations across both SB and MVPA and the HRQoL and fatigue outcomes underline the importance of our findings.

In summary, we observed that decreases in SB and increases in MVPA were independently associated with improved HRQoL and fatigue in the first 24 months posttreatment after CRC. When examined in combination, low prolonged SB and high MVPA demonstrated the largest positive association on increasing HRQoL and decreasing fatigue over time, with an especially large beneficial influence on physical and role functioning in the first 2 yr after CRC treatment. Overall, our results indicate that CRC survivors may benefit from the joint recommendation to avoid prolonged sitting and accumulate adequate MVPA, as recommended in the WCRF/AICR lifestyle recommendations for cancer survivors.

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The EnCoRe study has been approved by the Medical Ethics Committee of the Academic Hospital Maastricht and Maastricht University, The Netherlands (METC 11-3-075). The study was performed in accordance with the Declaration of Helsinki.

All participants gave written informed consent.

Registration: The EnCoRe study was registered at trialregister.nl as NL6904 (old ID: NTR7099).

Data described in the manuscript, code book, and analytic code will be made available upon request pending (e.g., application and approval, payment, other). Requests for data of the EnCoRe study can be sent to Dr. Martijn Bours, Department of Epidemiology, GROW School for Oncology and Developmental Biology, Maastricht University, the Netherlands (e-mail: m.bours@maastrichtuniversity.nl).

J. J. L. B.-P. has previously been used in the health information department and is currently consultant for the healthy information programs of Wereld Kanker Onderzoek Fonds (WCRF NL), the Netherlands. The authors declare that there are no conflicts of interest. In addition, the authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. Finally, the authors state that the results of the present study do not constitute endorsement by the American College of Sports Medicine.

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