Longitudinal associations of fiber, vegetable, and fruit intake with quality of life and fatigue in colorectal cancer survivors up to 24 months posttreatment

Marlou-Floor Kenkhuis,[1] Fränzel JB van Duijnhoven,[2] Eline H van Roekel,[1] José JL Breedveld-Peters,[1] Stéphanie O Breukink,[3] Maryska L Janssen-Heijnen,[1,4] Eric TP Keulen,[5] Floortje Mols,[6] Matty P Weijenberg,[1] and Martijn JL Bours[1]

[1]Department of Epidemiology, GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands; [2]Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands; [3]Department of Surgery, GROW School for Oncology and Developmental Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, The Netherlands; [4]Department of Clinical Epidemiology, Viecuri Medical Center, Venlo, The Netherlands; [5]Department of Internal Medicine and Gastroenterology, Zuyderland Medical Centre, Sittard-Geleen, The Netherlands; and [6]Department of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands

ABSTRACT

Background: The increasing colorectal cancer (CRC) survivor population highlights the need for dietary recommendations in order to enhance health-related quality of life (HRQoL) and alleviate symptoms of fatigue, chemotherapy-induced peripheral neuropathy (CIPN), and gastrointestinal problems.

Objectives: Because of the therapeutic potential of dietary fiber on the gut, we aim to assess longitudinal associations of post-diagnostic dietary fiber, fruit, and vegetable intake, a major source of dietary fiber, with HRQoL, fatigue, CIPN, and gastrointestinal symptoms in CRC survivors from 6 wk to 24 mo posttreatment.

Methods: In a prospective cohort among stage I–III CRC survivors ($n = 459$), 5 repeated study measurements between diagnosis and 24 mo posttreatment were executed. Dietary fiber intake and fruit and vegetable intake were measured by 7-d dietary records. HRQoL, fatigue, CIPN, and gastrointestinal symptoms were measured by validated questionnaires. We applied confounder-adjusted linear mixed models to analyze longitudinal associations from 6 wk until 24 mo posttreatment and used hybrid models to disentangle the overall association into intraindividual changes and interindividual differences over time.

Results: Higher dietary fiber intake and fruit and vegetable intake were longitudinally associated with statistically significant better physical functioning and less fatigue. Intraindividual analyses showed that an increase of 10 g/d in dietary fiber within individuals over time was associated with better physical functioning (β: 2.3; 95% CI: 0.1, 4.4), role functioning (ability to perform daily activities; 5.9; 1.5, 10.3), and less fatigue (−4.1; −7.7, −0.5). An average increase in fruit and vegetable intake of 100 g/d between individuals over time was predominantly associated with less fatigue (−2.2; −4.2, −0.3). No associations were found with CIPN and gastrointestinal symptoms.

Conclusions: Our results suggest that increasing dietary fiber, fruit, and vegetable intake is related to better physical and role functioning and less fatigue in the first 2 y after the end of treatment for CRC. *Am J Clin Nutr* 2022;115:822–832.

Keywords: colorectal cancer survivorship, dietary recommendations, diet, health-related quality of life, fatigue, chemotherapy-induced peripheral neuropathy

Introduction

More people are surviving colorectal cancer (CRC) because of earlier detection due to screening programs and increasing success of treatment for CRC. Besides increasing survival rates, the aging population also contributes to more CRC diagnoses; consequently, the population of CRC survivors continues to rise (1–3). Many cancer survivors are highly motivated to seek self-care strategies, particularly dietary counseling, to enhance their treatment and recovery (4).

The most recent expert report of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concludes that evidence is convincing for the consumption of dietary fiber and of foods containing fiber such as vegetables, fruit, whole grains, beans, and nuts, protecting against CRC development (5). Consequently, to prevent recurrence, the WCRF/AICR recommends CRC survivors to meet the guideline of 30 g of dietary fiber per day and consume 5 portions of fruit and vegetables combined (400 g/d) (5). However, evidence on the influence of dietary fiber, fruit, and vegetable intake on health-related quality of life (HRQoL) in CRC survivors and symptoms after treatment is mostly lacking.

Dietary fiber has many physicochemical characteristics (e.g., solubility, fermentability) (6) that determine its functionality in the gastrointestinal tract, including its effects on, for example, gut transit time and stool formation (6). These functionalities can be of a specific interest for CRC survivors, who often report gastrointestinal symptoms, such as frequent and irregular bowel movements and fecal incontinence (7), affecting HRQoL. Next to prevention of CRC (5) or recurrence (8), dietary fiber has the potential to be used as a therapeutic intervention aimed at reducing gastrointestinal symptoms, which is already happening in, for example, patients with irritable bowel syndrome (9, 10) and inflammatory bowel disease (11).

Only a few studies have evaluated the potential role of dietary fiber or fiber-rich sources on HRQoL, fatigue, and chemotherapy-induced peripheral neuropathy (CIPN) in the specific population of CRC survivors. We previously found cross-sectional associations between increased fruit and vegetable intake and better physical functioning and between increased vegetable intake and better global quality of life (QoL), physical functioning, and less fatigue in CRC survivors 2–10 y posttreatment (12) but not for dietary fiber. A similar association for fruit and vegetable intake with HRQoL was also found by 2 other cross-sectional studies that assessed fruit and vegetable intake in CRC survivors up to 10 y posttreatment (13, 14). We found no associations of fiber and fruit and vegetable intake with CIPN in the previous cross-sectional analyses (12).

There is a need for more prognostic dietary research among cancer survivors, particularly longitudinal studies. Because of the therapeutic potential of dietary fiber on the gut, we aim to examine the longitudinal association of dietary fiber, as well as fruit and vegetable consumption, a major source of dietary fiber, which is part of the WCRF nutrition guidelines (5, 15), with HRQoL, fatigue, CIPN, and gastrointestinal symptoms in CRC survivors from 6 wk to 24 mo posttreatment.

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Supplemental Tables 1 and 2are available from the "Supplementary data" link in the online posting of the article at https://academic.oup.com/ajcn/.

Address correspondence to M-FK (e-mail: m.kenkhuis@maastrichtuniversity.nl).

Abbreviations used: CIS, Checklist Individual Strength; CIPN, chemotherapy-induced peripheral neuropathy; CRC, colorectal cancer; EnCoRe, Energy for Life after Colorectal Cancer; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HRQoL, health-related quality of life; QoL, quality of life; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

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Methods

Study design and population

Since 2012, the Energy for Life after Colorectal Cancer (EnCoRe) study is an ongoing prospective cohort investigating lifestyle in CRC survivors. In 3 Dutch hospitals, patients with stage I–III CRC are recruited at diagnosis. Trained dietitians visit participants during 5 repeated home visits: at diagnosis and at 6 wk, 6 mo, 12 mo, and 24 mo posttreatment. For the current analysis, data collected up until July 2018 were used. **Figure 1** shows a flow diagram describing recruitment and follow-up of participants in the study (16). The decrease in number of participants during the follow-up measurements was mainly caused by participants who had not yet reached all posttreatment time points in July 2018.

Men and women aged a minimum of 18 y diagnosed with stage I–III CRC were eligible, whereas individuals with stage IV CRC or comorbidities obstructing successful study participation (e.g., Alzheimer disease) were excluded. The Medical Ethics Committee of the University Hospital Maastricht and Maastricht University approved the study (METC 11–3-075; Netherlands Trial Register number NL6904) (17). The study was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Dietary intake

To obtain quantitative data on food and beverage consumption, participants filled out a 7-d structured dietary record at all posttreatment time points. In the dietary record, participants reported consumed meals, foods, and beverages with details on brand names, portion sizes, and preparation. Participants received detailed oral and written instructions on how to fill out the dietary record. Additionally, the dietitians checked all completed dietary records upon receipt.

Daily dietary intake was calculated using food calculation software (Compl-eat; Wageningen University) based on the Dutch Food Composition database (NEVO-2011), using existing or specifically created dietary food groups in the software based on the 2018 WCRF/AICR dietary subrecommendations, that is, consume a diet that provides at least 30 g/d of fiber from food and eat a diet high in all types of plant foods, including at least 5 portions or servings (at least 400 g) of a variety of nonstarchy vegetables and fruit every day. Fruit and vegetable consumption (g/d) was calculated from the reported use of all fresh, frozen, dried, and canned fruit and vegetables without added sugar. Calculation of total dietary fiber intake (g/d) was based on the nutrient value from the food calculation table for the reported overall dietary intake. Additional information regarding methods and procedures applied for the assessment and coding of dietary records is extensively explained in Kenkhuis et al. (12).

HRQoL, gastrointestinal symptoms, fatigue, and CIPN

To obtain data on HRQoL, gastrointestinal symptoms, and fatigue, participants filled out several questionnaires at all posttreatment time points. The well-validated cancer-specific European Organization for the Research and Treatment of Cancer

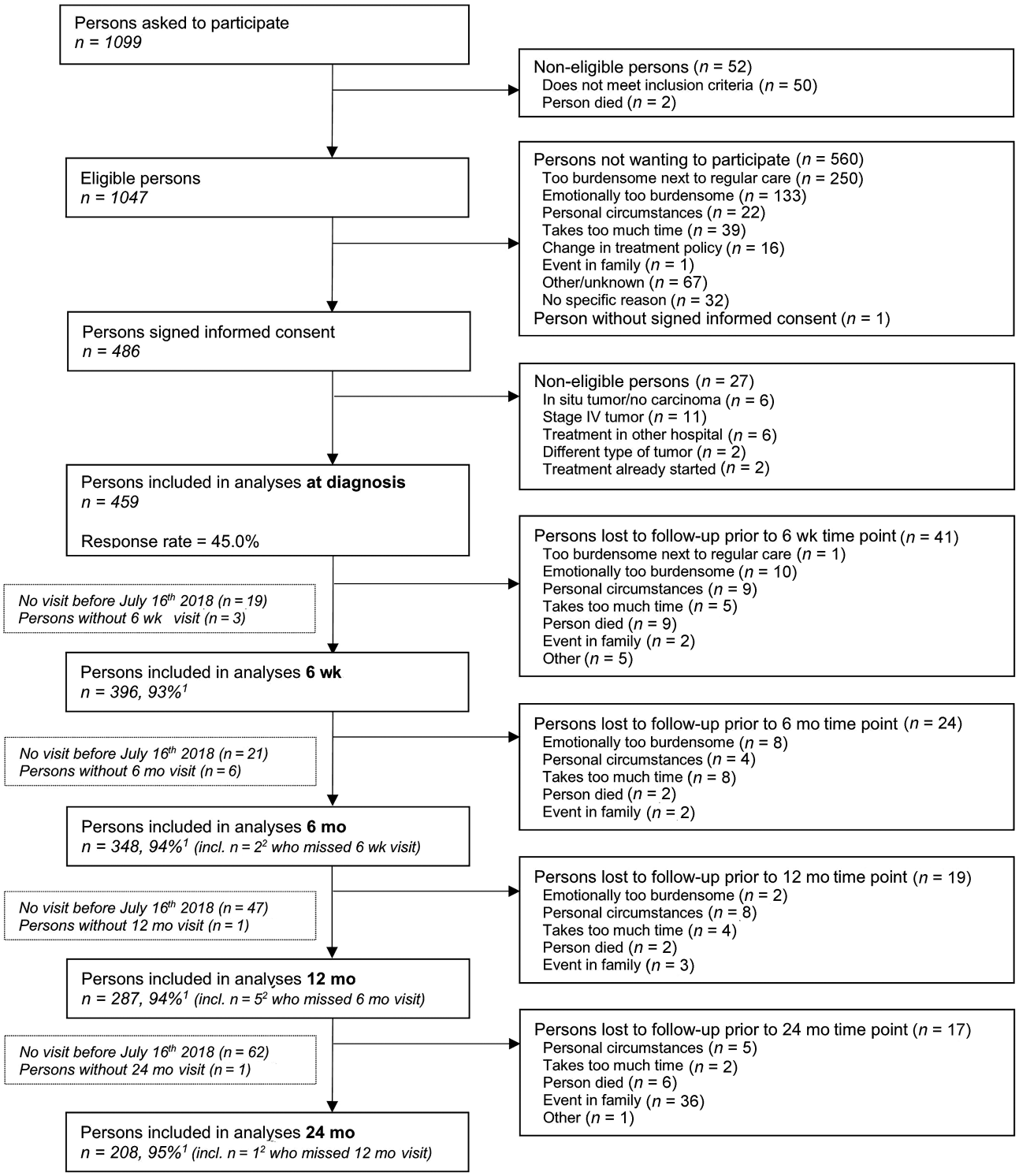

FIGURE 1 Flow diagram of inclusion of individuals within the Energy for Life after Colorectal Cancer study and included in the analyses presented in this article. Data of home visits performed before July 16, 2018, were included in the analyses. [1]Response rate posttreatment = (persons included) / (persons included + persons lost to follow-up – persons died). [2]Of the 3 persons without 6-wk follow-up visits, 1 person did not have a 6-mo follow-up visit before July 16, 2018. Of the 6 persons without 6-mo follow-up visits, 1 person did not have a 12-mo follow-up visit before July 16, 2018. This figure previously appeared in Kenkhuis et al. (16).

Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) (18, 19) assesses HRQoL outcomes, including global quality of life; physical, role, and social functioning; and cancer-specific symptoms such as fatigue, appetite, nausea and vomiting, constipation, and diarrhea. Role functioning assesses a patient's ability to perform daily activities, leisure-time activities, and/or work. Additionally, a summary score can be calculated based on the mean of 13 of the 15 QLQ-C30 scores (excluding the

TABLE 1 Demographic, lifestyle, and clinical characteristics of colorectal cancer survivors at all time points[1]

Characteristic	Diagnosis ($n = 459$)	6 wk posttreatment ($n = 396$)	6 mo posttreatment ($n = 348$)	12 mo posttreatment ($n = 287$)	24 mo posttreatment ($n = 208$)
Sex (male), *n* (%)	303 (66.0)	270 (68.2)	236 (67.8)	196 (68.3)	142 (68.3)
Age, mean ± SD, y	66.9 ± 9.1	67.0 ± 9.1	67.2 ± 9.23	67.4 ± 9.2	68.1 ± 9.2
Education, *n* (%)					
Low	130 (29.0)	107 (27.1)	91 (26.2)	73 (25.5)	45 (21.6)
Medium	168 (37.4)	149 (37.7)	137 (39.5)	114 (39.9)	89 (42.8)
High	151 (33.6)	139 (35.2)	119 (34.3)	99 (34.6)	74 (34.6)
Comorbidities, *n* (%)					
0 comorbidities	—	91 (23.0)	88 (25.4)	71 (25.1)	46 (22.6)
1 comorbidity	—	102 (25.8)	87 (25.1)	64 (22.6)	49 (24.0)
≥2 comorbidities	—	202 (51.1)	172 (49.6)	148 (52.3)	109 (53.4)
Smoking, *n* (%)					
Never	139 (31.0)	118 (30.5)	98 (28.7)	76 (27.6)	57 (29.1)
Former	255 (56.8)	235 (60.7)	213 (62.5)	172 (62.6)	120 (61.2)
Current	55 (12.3)	34 (8.8)	30 (8.8)	27 (9.8)	19 (9.7)
BMI, mean ± SD, kg/m^2	28.3 ± 4.7	27.8 ± 4.6	28.3 ± 4.7	28.7 ± 4.8	28.3 ± 4.6
Underweight: <18.5	2 ± 0.4	2 ± 0.5	0 ± 0.0	1 ± 0.4	1 ± 0.5
Healthy weight: 18.5–24.9	111 ± 24.3	117 ± 29.6	90 ± 25.9	62 ± 21.9	49 ± 24.0
Overweight: 25–29.9	201 ± 44.0	173 ± 43.8	151 ± 43.5	130 ± 45.9	85 ± 41.7
Obese: ≥30	143 ± 31.3	103 ± 26.1	106 ± 30.6	90 ± 31.8	69 ± 33.8
Moderate-to-vigorous physical activity, median (IQR), min/wk	660 (780)	420 (645)	570 (660)	600 (750)	600 (760)
Adherence to physical activity recommendation (yes), *n* (%)	408 (90.9)	320 (82.0)	302 (87.5)	255 (90.1)	181 (90.5)
Prolonged sedentary time, mean ± SD, h/wk	—	5.3 ± 2.7	4.2 ± 1.9	4.4 ± 1.9	4.5 ± 1.9
Tumor stage, *n* (%)					
Stage I	141 (30.7)	124 (31.3)	109 (31.3)	97 (33.8)	71 (34.1)
Stage II	108 (23.5)	100 (25.3)	86 (24.7)	69 (24.0)	52 (25.0)
Stage III	210 (45.8)	172 (43.4)	153 (44.0)	121 (42.2)	85 (40.9)
Cancer type, *n* (%)					
Colon	290 (63.2)	250 (63.1)	222 (63.8)	181 (63.1)	126 (60.6)
Rectosigmoid and rectum	169 (36.8)	146 (36.9)	126 (36.2)	106 (36.9)	82 (39.4)
Treatment, *n* (%)					
Surgery (yes)	412 (89.8)	354 (89.4)	317 (91.1)	259 (90.2)	186 (89.4)
Chemotherapy (yes)	184 (40.1)	155 (39.1)	134 (38.5)	107 (37.3)	79 (38.0)
Radiotherapy (yes)	116 (25.3)	101 (25.5)	88 (25.3)	73 (25.4)	55 (26.4)
Stoma (yes), *n* (%)	3 (0.7)	110 (28.4)	68 (19.8)	43 (15.2)	26 (13.1)

[1]Percentages may not add to 100 due to rounding. Adherence to physical adherence recommendation was based on at least 150 min of moderate-to-vigorous physical activity per week (29). This table previously appeared in Kenkhuis *et al.* (16).

financial difficulties and global QoL questions) (19). Besides gastrointestinal symptom scales from the EORTC QLQ-C30, we used the complementary module to EORTC QLQ-C30, designed for use among patients with CRC (EORTC QLQ-CR29) (20). The EORTC QLQ-C29 assesses CRC-specific symptoms such as stool frequency, bloating, abdominal pain, flatulence, and fecal incontinence. All scale scores were linearly transformed to a 0–100 scale, with higher scores on the functioning scales, global QoL, and the summary score reflecting better functioning or HRQoL, whereas higher symptom scale scores indicate more symptoms (e.g., worse fatigue or more constipation). To describe the prevalence of symptoms in our population, we made use of the EORTC QLQ-C30 symptom cutoff points (21).

Besides the fatigue symptom scale from the EORTC QLQ-C30, which is often used in cancer research, the 20-item Checklist Individual Strength (CIS) was also used to enable a more comprehensive multidimensional assessment of fatigue (22, 23). The CIS consists of 4 subscales: subjective fatigue (range: 8–56), concentration problems (range: 5–35), reduced motivation (range: 4–28), and activity-related fatigue (range: 3–21). In addition, a total fatigue score was derived by the summation of all subscales (range: 20–140). Higher scores indicate worse fatigue on all scales.

CIPN symptoms were measured with the EORTC QLQ-CIPN20 at every time point, including at diagnosis. This 20-item questionnaire consists of sensory, motor, and autonomic subscales and a summary score (24). All scale scores were linearly converted to a 0–100 scale (25), with higher scores indicating more CIPN symptoms.

Lifestyle, clinical, and sociodemographic factors

Sociodemographic characteristics, including age and 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 education level (at diagnosis), current smoking status, and presence of a stoma at all time points. Comorbidities were assessed with the Self-Administered Comorbidity Questionnaire at all time points (26). BMI (in kg/m^2) was assessed by trained dietitians at every time point and categorized according to the WHO guidelines (27). Moderate-to-vigorous physical activity was calculated (28) by adding up activities exceeding a metabolic equivalent (MET) value of ≥3 during commuting, household, work, and leisure-time activities in the past week, as assessed by the Short Questionnaire to Assess Health-Enhancing Physical Activity. Adherence to physical activity guidelines was set at having >150 min of moderate-to-vigorous physical activity per week (29). For objective measurement of sedentary time, the validated triaxial MOX activity meter was used (Maastricht Instruments B.V.), as described previously by van Roekel et al. (30). Habitual dietary intake in the year prior to the diagnosis (or prior to experiencing symptoms) was assessed retrospectively with a 253-item semiquantitative FFQ at diagnosis (31).

Statistical analyses

To describe main sample characteristics, we performed descriptive analyses for sociodemographic, lifestyle, and clinical variables at every time point. To describe changes in dietary fiber, fruit, and vegetable intake and gastrointestinal symptoms, descriptive analyses were performed overall and stratified by sex (for dietary fiber, fruit, and vegetables) or by stoma (gastrointestinal changes). Confounder-adjusted linear mixed models were used to analyze longitudinal associations of dietary fiber, fruit, and vegetables in relation to HRQoL, fatigue, CIPN, and gastrointestinal symptoms between 6 wk and 24 mo posttreatment. Dietary fiber, fruit, and vegetable intake was modeled continuously, with relevant units based on the recommended portion per day and on relevant differences in portion sizes (e.g., 10 g of dietary fiber and 100 g of fruit and vegetables is 1 portion). All confounders were identified using causal reasoning. Based on literature on lifestyle and HRQoL in CRC survivors, we adjusted regression models for an a priori defined set of relevant confounders that included fixed (time-invariant) confounders, including age at enrollment (years), sex, and chemotherapy (yes, no), as well as time-variant confounders (measured at all posttreatment time points) such as BMI, number of comorbidities (0, 1, ≥2), moderate-to-vigorous physical activity (min/wk), sedentary behavior (h/d), stoma (yes/no), total energy intake (kcal/d), and time since diagnosis (months). We further applied the 10% change-in-estimate method (32) for assessing an additional set of potential confounders, including habitual dietary fiber intake in the year before diagnosis, habitual fruit and vegetable consumption in the year before diagnosis, protein intake (total intake in grams), education level (low, medium, high), radiotherapy (yes, no), and smoking (yes, no); none of these variables led to a >10% change in β estimates of the dietary exposure variables and were, therefore, not included in the main model. The use of random slopes was tested with a likelihood ratio test; random slopes were added when the model improved statistically significantly. CIPN outcomes were only analyzed for the subgroup of patients who received chemotherapy (33). 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) (34). Because dietary fiber has the potential to reduce gastrointestinal symptoms as mentioned in the Introduction, we performed a secondary analysis to gain insight into whether gastrointestinal symptoms could be a reason for changes in dietary fiber intake. We performed an exploratory confounder-adjusted linear mixed-models analysis with gastrointestinal symptoms as the independent variable and dietary fiber as the dependent variable.

Potential interaction between dietary fiber and fruit and vegetable intake with sex and with stoma was explored by including interaction terms in linear mixed models. Sex-stratified or stoma-stratified analyses were performed when interaction terms were statistically significant.

Statistical analyses were performed using Stata 15.0 (StataCorp LLC) with statistical significance set at $P < 0.05$ (2-sided).

Results

Of the 1047 CRC survivors who were invited to participate, 459 (response rate at diagnosis: 45%) were included at diagnosis (Figure 1) and 396 were included in the analysis (6 wk to 24 mo). At diagnosis, 66% of the participants were men, and the mean ± SD age was 66.9 ± 9.1 y (**Table 1**). Further sociodemographic and disease-related characteristics are shown in Table 1 (16).

Changes in HRQoL, gastrointestinal symptoms, fatigue, CIPN, and dietary fiber, fruit, and vegetable intake up to 24 mo posttreatment

At 6 wk, mean ± SD dietary fiber intake was 21.0 ± 5.8 g/d, and only 7.3% (28 participants) adhered to the WCRF/AICR recommendation of ≥30 g/d of dietary fiber. Dietary fiber remained relatively stable over time, and on average, men had a higher intake of dietary fiber in comparison to women (**Table 2**); no difference in dietary fiber intake was found for participants with or without a stoma. At 6 wk posttreatment, mean ± SD vegetable and fruit intake was 130.8 ± 71.7 g/d and 120.3 ± 88.5 g/d, respectively. In total, 13.6% (52 participants) and 18.9% (72 participants) adhered to the vegetable and fruit recommendation of WCRF/AICR, respectively. Vegetable and fruit intake also remained stable over time; on average, between 6 wk and 24 mo posttreatment, women had higher intakes of both vegetables and fruit than men (Table 2), and participants with a stoma on average had lower intakes of both vegetables and fruit than participants without a stoma.

Mean QoL scores improved over the course of 6 wk until 24 mo posttreatment, whereas fatigue followed a linear decline. Among CRC survivors who received chemotherapy, CIPN summary and subscale scores changed over time. Highest mean scores were observed at 6 wk posttreatment, followed by a steep decrease to 6 mo posttreatment and thereafter a more gradual decrease up to 24 mo posttreatment (Table 2).

Table 3 shows that the proportion of participants having a stoma decreased from 110 participants (28%) at 6 wk to 26

TABLE 2 Descriptive analysis on dietary exposures (dietary fiber, fruit, and vegetables) and outcomes (health-related quality of life, fatigue, and chemotherapy-induced peripheral neuropathy) of colorectal cancer survivors from 6 wk to 24 mo posttreatment

	6 wk posttreatment, mean ± SD		6 mo posttreatment, mean ± SD		12 mo posttreatment, mean ± SD		24 mo posttreatment, mean ± SD	
Characteristic	Women	Men	Women	Men	Women	Men	Women	Men
Dietary exposures	($n = 122$)	($n = 260$)	($n = 110$)	($n = 222$)	($n = 89$)	($n = 185$)	($n = 62$)	($n = 132$)
Dietary fiber, g/d	18.8 ± 5.4	22.0 ± 5.8	18.9 ± 5.3	21.7 ± 6.4	19.0 ± 6.2	21.9 ± 5.8	18.3 ± 5.9	21.6 ± 5.9
Fruit and vegetables, g/d	271.2 ± 121.6	241.6 ± 125.5	278.5 ± 133.9	233.7 ± 133.7	256.9 ± 130.1	244.1 ± 135.1	252.2 ± 151.4	267.3 ± 184.4
Vegetables, g/d	131.6 ± 64.0	130.4 ± 74.4	140.2 ± 72.0	123.6 ± 76.2	127.7 ± 67.4	131.7 ± 71.5	122.0 ± 77.3	136.3 ± 93.0
Fruit, g/d	139.6 ± 89.9	111.2 ± 86.5	138.3 ± 91.2	109.9 ± 97.8	131.2 ± 89.1	112.4 ± 98.7	130.2 ± 96.8	131.0 ± 126.4
Health-related quality of life: EORTC-QLQ C30 (range: 0–100)[1]	($n = 123$)	($n = 266$)	($n = 112$)	($n = 232$)	($n = 90$)	($n = 193$)	($n = 63$)	($n = 136$)
Global quality of life	75.5 ± 17.8	75.2 ± 18.4	75.0 ± 18.1	77.6 ± 18.5	75.5 ± 17.8	78.8 ± 17.3	77.1 ± 19.9	79.4 ± 19.0
Physical functioning	72.7 ± 19.4	80.4 ± 18.9	75.9 ± 19.5	85.7 ± 16.2	76.0 ± 20.7	87.5 ± 16.0	79.4 ± 19.6	87.6 ± 16.3
Role functioning	71.4 ± 27.1	73.4 ± 27.6	78.0 ± 24.2	83.3 ± 23.6	80.4 ± 23.5	84.8 ± 22.4	81.0 ± 25.0	88.2 ± 21.5
Social functioning	82.9 ± 19.7	83.8 ± 21.8	89.0 ± 19.6	89.9 ± 18.1	90.9 ± 16.4	91.6 ± 17.6	90.7 ± 18.6	91.5 ± 18.1
Summary score	83.5 ± 11.9	85.8 ± 12.6	85.4 ± 11.0	88.8 ± 11.3	85.0 ± 14.2	90.0 ± 11.3	85.5 ± 14.3	90.0 ± 11.7
Fatigue	30.3 ± 22.3	26.3 ± 23.1	24.3 ± 19.7	21.5 ± 21.6	26.0 ± 23.7	17.9 ± 21.0	21.3 ± 22.0	18.3 ± 22.4
Fatigue: Checklist Individual Strength	($n = 123$)	($n = 265$)	($n = 112$)	($n = 232$)	($n = 90$)	($n = 193$)	($n = 63$)	($n = 136$)
Total fatigue (range: 20–140)[1]	64.5 ± 27.2	61.2 ± 25.7	60.1 ± 26.4	55.9 ± 26.0	56.6 ± 27.2	52.6 ± 25.2	54.9 ± 27.6	53.4 ± 26.0
Subjective fatigue (range: 8–56)	28.1 ± 13.2	25.7 ± 13.1	25.5 ± 12.9	23.2 ± 12.0	24.1 ± 12.1	21.5 ± 11.9	23.7 ± 13.4	21.6 ± 12.1
Motivation-related fatigue (range: 4–28)	12.2 ± 5.7	12.4 ± 7.4	11.9 ± 6.3	11.1 ± 5.5	11.3 ± 6.8	10.6 ± 5.6	10.7 ± 5.9	10.8 ± 5.8
Activity-related fatigue (range: 3–21)	10.5 ± 5.4	10.8 ± 5.0	9.3 ± 5.1	9.3 ± 5.2	8.6 ± 5.4	8.8 ± 5.0	8.1 ± 5.2	8.5 ± 5.1
Concentration-related fatigue (range: 5–35)	13.5 ± 7.6	12.3 ± 7.1	13.4 ± 7.2	12.4 ± 7.4	12.4 ± 6.6	11.8 ± 7.0	12.4 ± 7.4	12.4 ± 7.3
Chemotherapy-induced peripheral neuropathy: EORTC CIPN20[2] (range: 0–100)[1]	($n = 38$)	($n = 94$)	($n = 36$)	($n = 82$)	($n = 28$)	($n = 76$)	($n = 23$)	($n = 54$)
Summary score	15.5 ± 13.1	14.2 ± 16.0	14.3 ± 12.6	10.6 ± 12.8	11.9 ± 11.2	11.3 ± 14.6	9.3 ± 11.0	10.2 ± 14.5
Motor scale	17.4 ± 14.2	11.7 ± 15.4	15.6 ± 13.0	8.0 ± 12.6	10.9 ± 8.4	9.1 ± 14.8	9.3 ± 10.8	8.0 ± 15.2
Sensory scale	15.2 ± 17.1	17.8 ± 20.6	14.9 ± 17.4	13.7 ± 16.5	14.6 ± 17.7	13.8 ± 18.2	10.5 ± 15.3	12.3 ± 16.0
Autonomic scale	10.1 ± 15.3	7.1 ± 11.6	6.9 ± 13.4	5.5 ± 9.5	3.6 ± 7.0	7.0 ± 12.8	4.3 ± 9.0	8.3 ± 15.8

EORTC, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

[1]Higher scores on the functioning scales, global quality of life, and the summary score reflect better functioning or health-related quality of life, whereas higher symptom scale scores indicate more symptoms (i.e., worse fatigue or chemotherapy-induced peripheral neuropathy symptoms).

[2]Chemotherapy-induced peripheral neuropathy outcomes were only described for the subgroup of patients who received chemotherapy.

TABLE 3 Prevalence of gastrointestinal symptoms and symptom levels such as appetite loss, nausea and vomiting, constipation, diarrhea, stool frequency, abdominal pain, bloating, flatulence, and fecal incontinence after colorectal cancer treatment

	6 wk posttreatment		6 mo posttreatment		12 mo posttreatment		24 mo posttreatment	
	No stoma ($n = 278$)	Stoma ($n = 110$)	No stoma ($n = 276$)	Stoma ($n = 68$)	No stoma ($n = 240$)	Stoma ($n = 43$)	No stoma ($n = 173$)	Stoma ($n = 26$)
Symptoms EORTC QLQ-C30 scores,[1] mean ± SD, range: 0–100[2]								
Appetite loss	7.0 ± 19.6	10.6 ± 22.5	2.7 ± 11.4	2.5 ± 8.3	3.9 ± 13.8	2.3 ± 11.3	5.2 ± 15.4	5.1 ± 12.3
Nausea and vomiting	2.2 ± 9.4	3.0 ± 7.5	1.7 ± 7.7	4.4 ± 12.8	2.6 ± 9.6	0.4 ± 2.5	2.7 ± 8.8	1.9 ± 7.2
Constipation	6.7 ± 16.8	2.4 ± 9.8	6.0 ± 16.2	2.0 ± 9.8	5.0 ± 15.6	0.8 ± 5.1	5.4 ± 16.0	1.3 ± 6.5
Diarrhea	10.6 ± 22.0	7.5 ± 19.6	11.7 ± 22.5	5.9 ± 17.2	10.5 ± 21.8	7.8 ± 19.0	10.0 ± 21.3	1.3 ± 6.5
Categories of symptoms (yes),[3] *n* (%)								
Appetite loss (threshold: 50)	15 ± 5.4	7 ± 6.4	4 ± 1.5	1 ± 1.5	6 ± 2.5	1 ± 2.3	5 ± 2.9	0 ± 0
Nausea and vomiting (threshold: 8)	22 ± 7.9	17 ± 15.5	21 ± 7.6	6 ± 8.8	24 ± 10.0	1 ± 2.3	18 ± 10.4	2 ± 7.7
Constipation (threshold: 50)	9 ± 3.2	1 ± 0.9	6 ± 2.2	1 ± 1.5	7 ± 2.9	0 ± 0	6 ± 3.5	0 ± 0
Diarrhea (threshold: 17)	64 ± 23.0	16 ± 15.0	73 ± 26.5	8 ± 11.8	53 ± 22.2	7 ± 16.3	37 ± 21.4	1 ± 3.85
Symptoms EORTC QLQ-CR29 scores, mean ± SD, range: 0–100[2]								
Stool frequency	19.7 ± 21.1	19.7 ± 22.7	20.1 ± 21.8	16.9 ± 21.6	16.7 ± 20.2	10.9 ± 14.9	15.9 ± 20.6	12.7 ± 16.9
Abdominal pain	14.0 ± 23.9	14.0 ± 23.2	11.1 ± 20.4	8.3 ± 15.6	9.5 ± 19.9	7.0 ± 13.7	9.6 ± 20.9	3.8 ± 14.4
Bloating	17.0 ± 23.3	13.3 ± 21.7	15.2 ± 22.6	14.7 ± 21.1	11.9 ± 20.4	14.0 ± 19.6	12.3 ± 20.1	10.3 ± 18.3
Flatulence	32.4 ± 28.1	27.0 ± 26.5	33.6 ± 28.1	25.0 ± 24.7	34.6 ± 28.5	27.1 ± 23.3	32.0 ± 30.9	22.7 ± 26.7
Fecal incontinence	6.5 ± 17.2	24.5 ± 31.6	7.1 ± 15.8	14.2 ± 26.0	8.1 ± 19.0	12.4 ± 24.2	7.9 ± 30.9	12.0 ± 21.3

EORTC, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

[1]Reported gastrointestinal symptoms were divided into 2 groups: participants having a stoma and not having a stoma at that time point posttreatment.

[2]Higher scores on the symptom scales indicate more symptoms.

[3]Based on previously published cut-off scores for the subscales of the EORTC QLQ-C30 (24).

participants (13%) at 24 mo. Of all the gastrointestinal symptoms, diarrhea was the most prevalent symptom measured by the EORTC QLQ-C30. At 6 wk, 23% of the participants without a stoma and 15% of the participants with a stoma experienced this problem. For the participants without a stoma, diarrhea increased at 6 mo and remained relatively high, with 21% still experiencing problems regarding diarrhea at 24 mo. In participants with a stoma, the proportion of participants experiencing diarrhea decreased to 4% at 24 mo. Gastrointestinal symptoms measured by the EORTC QLQ-CR29 were similar across the participants without a stoma and with a stoma. Stool frequency, abdominal pain, and bloating scores slowly decreased after 6 mo, whereas scores for flatulence and fecal incontinence remained high, especially in participants without a stoma.

Longitudinal associations of dietary fiber, fruit, and vegetable intake with HRQoL, fatigue, gastrointestinal symptoms, and CIPN

In confounder-adjusted models assessing overall longitudinal associations from 6 wk to 24 mo post-CRC treatment (**Table 4**), higher dietary fiber intake was statistically significantly associated with better physical functioning (β per 10 g/d: 2.1; 95% CI: 0.2, 4.0) over time. In addition, a higher intake of dietary fiber was also associated with less activity-related fatigue measured by the CIS (−0.9; −1.6, −0.1), although not statistically significantly with the EORTC fatigue subscale (−1.7; −4.7, 1.3). Separate models testing inter- and intraindividual associations (Table 4) showed that the associations for dietary fiber intake were mostly driven by the intraindividual component, indicating that an increase in dietary fiber intake over time within individuals, and not a difference in average dietary fiber intake between individuals, was predominantly associated with better HRQoL outcomes and less fatigue over time. In particular, intraindividual analyses showed that an increase of 10 g/d in dietary fiber within individuals over time was statistically significantly associated with better physical functioning (2.3; 0.1, 4.4) and role functioning (5.9; 1.5, 10.3), as well as with less fatigue (EORTC: −4.2; −7.6, −0.9), total fatigue (CIS: −4.1; −7.7, −0.5), subjective fatigue (−2.2; −4.0, −0.4), and activity-related fatigue (−1.1; −1.9, −0.3).

A higher fruit and vegetable intake was associated with better physical functioning (β per 100 g/d: 0.7; 0.0, 1.3) and role functioning (1.2; 0.1, 2.3) and with less total fatigue (CIS: −1.2; −2.3, −0.2) and subjective fatigue (−0.6; −1.1, −0.1). This association appeared to be mostly driven by vegetable intake and not fruit intake. Interestingly, in contrast to dietary fiber intake, the separate models testing inter- and intraindividual associations showed that the associations for fruit and vegetable intake were mostly driven by the interindividual component. A difference on average in fruit and vegetable intake of 100 g/d between individuals over time was predominantly associated with less total fatigue (CIS: −2.2; −4.2, −0.3) and subjective fatigue (−1.3; −2.2, −0.4).

In confounder-adjusted models assessing overall longitudinal associations from 6 wk to 24 mo post-CRC treatment (**Supplemental Table 1**), changes in dietary fiber intake were not associated with gastrointestinal symptoms for all subscales. In addition, when exploring whether gastrointestinal symptoms could have led to changes in dietary fiber intake, mixed models with dietary fiber as the dependent variable and gastrointestinal symptoms as independent variables showed no longitudinal associations of gastrointestinal symptoms with dietary fiber.

Two statistically significant associations were found for fruit and vegetable intake and vegetable intake separately with the autonomic CIPN subscale in participants who received chemotherapy (**Supplemental Table 2**).

Interaction analyses

Statistically significant interactions between dietary fiber and sex were found for subjective fatigue ($P = 0.02$) and between dietary fiber and stoma with physical functioning ($P = 0.01$) and social functioning ($P = 0.03$). In addition, statistically significant interactions between fruit and vegetable intake and sex ($P < 0.01$) and stoma ($P = 0.03$) were found for social functioning. Subsequent stratified analysis by sex and stoma showed no clear patterns (results not shown).

Discussion

Within this longitudinal study of stage I–III CRC survivors, we described changes over time in the intake of dietary fiber, fruit, and vegetables from 6 wk to 24 mo after treatment. On average, dietary fiber, fruit, and vegetable intake remained relatively stable over time. In confounder-adjusted analyses, we observed that higher dietary fiber, fruit, and vegetable intake was longitudinally associated with increases in physical and role functioning and decreases in fatigue from 6 wk to 24 mo posttreatment. Associations for dietary fiber appeared to be mainly driven by within-person changes over time, indicating that posttreatment increases in dietary fiber over time within individuals, instead of a difference in dietary fiber intake between individuals, were associated with better functioning and with less fatigue over time. In contrast, longitudinal associations of fruit and particularly vegetable intake appeared to be mainly driven by between-person differences, indicating that individuals with higher fruit and vegetable intake reported less fatigue over time than individuals with lower intakes. No meaningful associations were found for dietary fiber, fruit, and vegetable intake and CIPN and gastrointestinal symptoms.

To our knowledge, this is the first study that assessed longitudinal relations between dietary fiber, fruit, and vegetable intake and HRQoL, fatigue, and CIPN in CRC survivors, from 6 wk to 24 mo posttreatment. Interestingly, we observed that the associations with dietary fiber were mainly driven by intraindividual changes, whereas those of fruit and vegetable intake were driven by interindividual differences. The between-person association observed for fruit and vegetable consumption might be explained by an overall healthier lifestyle pattern for people with high consumption of fruit and vegetables, despite thorough confounder adjustment. In contrast, our within-person findings for dietary fiber may suggest that changing intake of dietary fiber influences HRQoL and fatigue. A possible biological mechanism involved in this association could be inflammation. Higher consumption of dietary fiber has been associated with lower concentrations of serum inflammatory biomarkers (35, 36), and inflammation has been described in the literature as a major pathway related to several domains of HRQoL and fatigue (37,

TABLE 4 Overall longitudinal, intraindividual, and interindividual associations ($n = 396$) between dietary recommendations and health-related quality of life and fatigue

	EORTC QLQ-C30, β (95% CI)						CIS, β (95% CI)		
Characteristic	Global QoL (0–100)	Physical functioning (0–100)	Role functioning (0–100)	Social functioning (0–100)	Summary score (0–100)	Fatigue (EORTC) (0–100)	Fatigue (CIS) (20–140)	Subjective fatigue (CIS) (8–56)	Activity-related fatigue (CIS) (3–21)
Dietary fiber (10 g/d)									
Unadjusted	1.1 (−0.7, 3.0)	2.3* (0.7, 3.9)	3.5* (0.8, 6.2)	−0.2 (−2.2, 1.9)	1.1* (0.0, 2.3)	−1.5 (−3.7, 0.8)	−2.5 (−5.0, 0.0)	−1.4* (−2.7, −0.2)	−0.7 (−1.2, −0.1)
Adjusted[1,2,3]	0.4 (−1.9, 2.7)	2.1* (0.2, 4.0)	2.4 (−0.9, 5.6)	−0.2 (−2.8, 2.4)	1.1 (−0.4, 2.6)	−1.7 (−4.7, 1.3)	−3.1 (−6.6, 0.4)	−1.7 (−3.5, 0.0)	−0.9* (−1.6, −0.1)
Within[1,4]	1.7 (−1.2, 4.6)	2.3* (0.1, 4.4)	5.9* (1.5, 10.3)	−0.5 (−3.6, 2.7)	1.9* (0.3, 3.4)	−4.2* (−7.6, −0.9)	−4.1* (−7.7, −0.5)	−2.2* (−4.0, −0.4)	−1.1* (−1.9, −0.3)
Between[1,5]	−1.2 (−4.4, 2.0)	1.7 (−1.4, 4.8)	−0.7 (−4.8, 3.4)	−0.8 (−3.9, 2.3)	0.2 (−2.0, 2.4)	1.8 (−2.1, 5.8)	−0.8 (−5.7, 4.1)	−1.0 (−3.4, 1.3)	−0.2 (−1.2, 0.7)
Fruit and vegetables (per 100 g/d)									
Unadjusted	0.6 (−0.1, 1.4)	0.5 (−0.1, 1.2)	1.3 (0.2, 2.4)	0.4 (−0.4, 1.3)	0.5* (0.0, 0.9)	−0.6 (−1.5, 0.3)	−1.0* (−2.0, −0.0)	−0.5 (−1.0, 0.0)	−0.1 (−0.4, 0.1)
Adjusted[1,2,3]	0.6 (−0.2, 1.4)	0.7* (0.0, 1.3)	1.2* (0.1, 2.3)	0.3 (−0.7, 1.3)	0.5* (0.1, 1.0)	−0.5 (−1.5, 0.4)	−1.2* (−2.3, −0.2)	−0.6* (−1.1, −0.1)	−0.2 (−0.4, 0.0)
Within[1,4]	0.2 (−0.1, 0.5)	0.1 (−0.4, 0.4)	0.4 (0.0, 0.9)	0.1 (−0.3, 0.4)	0.2 (0.0, 0.3)	−0.1 (−0.5, 0.2)	−0.2 (−0.6, 0.1)	−0.1 (−0.2, 0.1)	0.0 (−0.2, 0.1)
Between[1,5]	0.6 (−0.7, 1.9)	1.2 (−0.0, 2.5)	1.0 (−0.6, 2.6)	0.2 (−1.0, 1.5)	0.6 (−0.3, 1.5)	−0.7 (−2.3, 0.9)	−2.2* (−4.2, −0.3)	−1.3* (−2.2, −0.4)	−0.3 (−0.7, 0.1)
Vegetables (per 50 g/d)									
Unadjusted	1.0* (0.4, 1.7)	0.6* (0.0, 1.1)	1.6* (0.6, 2.6)	0.3 (−0.5, 1.0)	0.5* (0.1, 0.9)	−1.1* (−1.9, −0.3)	−1.3* (−2.1, −0.4)	−0.6* (−1.0, 0.2)	−0.2 (−0.4, 0.0)
Adjusted[1,2,3]	0.8* (0.1, 1.5)	0.3 (−0.2, 0.9)	1.0* (0.0, 2.0)	0.2 (−0.7, 1.1)	0.4 (−0.0, 0.8)	−0.9 (−1.9, 0.1)	−1.1* (−2.0, −0.2)	−0.5* (−1.0, −0.1)	−0.1 (−0.3, 0.0)
Within[1,4]	0.8 (−0.0, 1.6)	0.2 (−0.4, 0.8)	0.9 (−0.4, 2.2)	−0.1 (−1.1, 0.8)	0.3 (−1.1, 0.8)	−0.6 (−1.6, 0.4)	−0.8 (−1.8, 0.2)	−0.3 (−0.8, 0.2)	−0.2 (−0.4, 0.0)
Between[1,5]	0.9 (−0.4, 2.1)	0.9 (−0.4, 2.1)	1.2 (−0.4, 2.7)	0.2 (−1.0, 1.4)	0.7 (−0.2, 1.5)	−0.8 (−2.3, 0.8)	−2.0* (−3.9, −0.1)	−1.2* (−2.1, −0.3)	0.0 (−0.4, 0.4)
Fruit (per 50 g/d)									
Unadjusted	0.0 (−0.6, 0.5)	0.1 (−0.3, 0.6)	0.3 (−0.5, 1.1)	0.2 (−0.3, 0.8)	0.1 (−0.2, 0.5)	0.1 (−0.6, 0.7)	−0.2 (−0.9, 0.5)	−0.1 (−0.5, 0.2)	0.0 (−0.2, 0.1)
Adjusted[1,2,3]	0.0 (−0.5, 0.6)	0.4 (−0.0, 0.9)	0.6 (−0.2, 1.4)	0.2 (−0.4, 0.8)	0.3 (−0.1, 0.6)	−0.1 (−0.8, 0.6)	−0.5 (−1.3, 0.3)	−0.3 (−0.6, 0.1)	−0.1 (−0.3, 0.2)
Within[1,4]	0.0 (−0.7, 0.7)	0.3 (−0.2, 0.9)	0.8 (−0.4, 1.9)	0.3 (−0.5, 1.1)	0.3 (−0.1, 0.7)	0.0 (−0.8, 0.8)	−0.2 (−1.1, 0.7)	−0.1 (−0.5, 0.4)	0.0 (−0.2, 0.2)
Between[1,5]	0.2 (−0.7, 1.1)	0.8 (0.1, 1.7)	0.4 (−0.8, 1.5)	0.1 (−0.8, 1.0)	0.3 (−0.4, 0.9)	−0.3 (−1.5, 0.8)	−1.2 (−2.6, 0.2)	−0.7* (−1.3, −0.0)	−0.3* (−0.5, −0.0)

CIS, Checklist Individual Strength; EORTC, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; QoL, quality of life.

[1]Linear mixed models adjusted for sex (male/female), age at enrollment (years), comorbidities (0, 1, ≥2), weeks since end of treatment (weeks), chemotherapy (yes/no), BMI (kg/m^2), moderate-to-vigorous physical activity (min/wk), sedentary time (h/d), energy intake (kcal/d), and stoma (yes/no).

[2]The β-coefficients represent the overall longitudinal difference in the outcome score using linear mixed models.

[3]A random slope was added to the model for fruit and vegetables with social functioning; vegetables with social functioning and fatigue (EORTC); and fiber with social functioning, summary score, fatigue (EORTC), total fatigue, subjective fatigue, and activity-related fatigue; no random slope was added to the models for fruit (see Methods).

[4]The β-coefficients represent the change in the outcome score over time within individuals using a hybrid model within linear mixed models.

[5]The β-coefficients represent the difference in the outcome score between individuals using a hybrid model within linear mixed models.

*Indicates a statistically significant association.

38). Inflammation may also play a role in the mechanism of developing CIPN (39). However, we did not observe a relation between posttreatment dietary fiber and CIPN symptoms over time. Nevertheless, our findings underline the importance for the separate recommendations in the WCRF/AICR lifestyle recommendations for cancer survivors regarding fiber, fruit, and vegetable intake.

In this article, we also addressed gastrointestinal symptoms related to CRC survivorship. We hypothesized that CRC survivors may introduce lifestyle changes, such as increasing fiber intake, to take charge of their health and alleviate symptoms such as diarrhea, abdominal pain, bloating, and flatulence (4). Somewhat surprisingly, gastrointestinal symptoms were not associated with increased or decreased dietary fiber, fruit and vegetable intake, and increased dietary fiber, fruit, and vegetable intake was not associated with decreased or increased gastrointestinal symptoms. The number of participants reporting gastrointestinal symptoms over time was low (e.g., <10% for appetite loss and constipation at measurements 6 mo, 12 mo, and 24 mo), possibly explaining the lack of associations. In comparison to a study by Whistance et al. (20), our scores for gastrointestinal symptoms were slightly lower. Their study reported that participants receiving palliative treatment had the highest symptom scores, which are mostly stage IV participants who were excluded from our study. We observed small differences and changes in gastrointestinal symptoms over time between participants having a stoma and without a stoma. However, we could not confirm that gastrointestinal symptoms were more problematic for people without a stoma compared with those with a stoma, which was recently stated by a meta-synthesis of qualitative studies (7).

An important strength of the current study is the prospective nature and repeated-measures design. In addition, a major strength of this study is the availability of extensive measurements on dietary intake, which enabled quantitative assessment of fruit and vegetable consumption and absolute intake of dietary fiber, consequently being more accurate than commonly used FFQ data. Additionally, assessment on multiple days resulted in more reliable estimates (40). Also, memory limitations are not expected to be a source of error, because intakes are asked to be recorded at the time of intake (40). Still, participants may delay recording their intakes, alter their intake of food, or not record their true intake due to social desirability or the relatively high burden of keeping a dietary record (40). Because of social desirability, self-reported intake of, for example, fruit and vegetables may thus have been overestimated. However, we do not expect that social desirability played a role in dietary fiber intake, except for the dietary fiber part coming from fruit and vegetables. Other strengths of our study included the high response rates during follow-up (>90%), the limited number of missing data resulting from intensive data collection methods, and the availability of extensive data on potential confounders and effect modifiers. Furthermore, the mixed models enabled disentangling of inter- and intraindividual associations, thereby providing valuable insights into the nature of the longitudinal associations.

There are also limitations that should be considered. Based on these observational data, we cannot be sure of the direction of associations between dietary intake and HRQoL, fatigue, and CIPN. Because these are multifactorial outcomes, bidirectional associations between diet and these outcomes are likely; therefore, intervention studies will be necessary to infer causality. In addition, the limited response rate at diagnosis (45%) and potential for selective loss to follow-up might have resulted in a selection bias. We observed that participants with a high education appeared to be slightly more likely to stay in the study compared with participants with a low education (Table 1). This might indicate that participants with less favorable dietary conditions and lower HRQoL were possibly less likely to participate or keep participating, which may have led to an attenuation of associations. Moreover, because we had no information on HRQoL and fatigue at diagnosis or complete follow-up for recurrences during posttreatment follow-up, we were not able to adjust for these potential confounders. Finally, we cannot rule out the possibility of false-positive findings due to the large number of tests performed.

In conclusion, we showed that posttreatment dietary fiber, fruit, and vegetable intake is longitudinally associated with improved physical and role functioning and with less fatigue in CRC survivors. Our results suggest that survivors who increase their dietary fiber intake after treatment report better functioning and less fatigue and that survivors who eat more fruit and vegetables report less fatigue in the first 2 y after the end of treatment. So both dietary fiber and fruit and vegetable intake are probably relevant for several HRQoL outcomes and alleviate symptoms of fatigue. This research can ultimately contribute to more specific guidelines for CRC survivors in order to improve their health and well-being in the years after treatment.

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The authors' contributions were as follows—M-FK: analyzed data, interpreted the findings, and wrote paper; MPW and MJLB: designed research and had primary responsibility for final content; MJLB, MPW, EHvR, JJLB-P, SOB, MLJ-H, ETPK, FJBvD, and FM: reviewed and edited the manuscript. All authors read and approved the final manuscript.

Author disclosures: JJLB-P has been employed in the health information department and is currently consultant for the healthy information programs of Wereld Kanker Onderzoek Fonds (WCRF NL), the Netherlands. All other authors report no conflicts of interest.

Data Availability

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

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