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Original article

Effect of a one-year personalized intensive dietary intervention on body composition in colorectal cancer patients: Results from a randomized controlled trial

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SUMMARY

Background & aims: Changes in body composition may affect colorectal cancer (CRC) patient's risk of cancer recurrence, secondary cancer, and other chronic diseases. The suggested interventions for changes in body composition such as low muscle mass or high fat mass, are diet and physical activity. Nevertheless, there is limited evidence of how dietary intervention alone can impact body composition. This study aimed to investigate the effect of a 6 and 12 month dietary intervention with a focus on healthy eating according to Norwegian food-based dietary guidelines on weight and body composition in patients with CRC stage I-III, post-surgery.

Methods: This study included participants from the randomized controlled trial CRC-NORDIET study 2–9 months after surgery. The intervention group received an intensive dietary intervention, while the control group underwent similar measurements, but no dietary intervention. Body composition was measured with Lunar iDXA, and the results were analyzed using linear mixed models.

Results: A total of 383 participants were included, 192 in the intervention group and 191 in the control group. After 6 months, the intervention group showed a 0.7 kg lower mean weight gain ($p = 0.020$) and 0.6 kg lower fat mass gain ($p = 0.019$) than the control group, but no difference at 12 months. Moreover, the fat mass increase was 0.5 percentage points lower at 6 months ($p = 0.012$), and 0.7 percentage points lower at 12 months ($p = 0.011$) in the intervention group compared to the controls. At 6 months, the intervention group had 63 g lower gain of visceral adipose tissue compared to the control group ($p = 0.031$). No differences were seen for fat-free mass or subcutaneous adipose tissue at any time point. The intervention group showed a lower increase in the ratio between fat mass and fat-free mass at both 6 months ($p = 0.025$) and 12 months ($p = 0.021$).

Conclusion: The dietary intervention reduced the increases in total weight and fat masses, without changing fat-free mass. Although the individual changes are small, the dietary intervention may have resulted in an overall more favourable body composition profile. These findings suggest that dietary

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intervention may be part of a treatment strategy for prevention of weight and fat mass gain in CRC survivors.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer globally and second in terms of cancer-related deaths [1]. Over 1.8 million new CRC incidents were estimated globally in 2020, and Norway have among the highest rates in the world [2]. Together with the last years' decrease in mortality rates, there is a growing number of CRC survivors [2]. These subjects have a risk of cancer recurrence, in addition to an increased risk of secondary cancers [3] and other chronic diseases [4].

Increasing evidence shows that the amount and distribution of fat and muscle may have prognostic implications for patients with CRC. A progressive loss of muscle mass is a natural part of ageing [5]. However, in CRC patients, the muscle loss may accelerate due to immobilization, treatment and the disease itself [6]. Low muscle mass is often referred to as sarcopenia, and is an independent risk factor for both disease-free survival and overall survival [7–9]. Moreover, low muscle mass is also associated with treatment toxicity during chemotherapy [10]. High fat mass (FM) is a risk factor for developing several cancers including CRC [11], and visceral adipose tissue (VAT) is associated with lower survival in CRC patients [12]. The combination of low muscle mass and high fat mass, represents a worst-case scenario often named sarcopenic obesity and is not detected by the measurement of weight [9].

Dietary and physical activity interventions are main strategies in the treatment of both low muscle mass and excessive FM [13,14]. However, the impact of dietary interventions on body composition is not well understood due to a limited number of studies, various nutritional strategies, and a lack of precise body composition methods [14]. Dual-Energy X-ray Absorptiometry (DXA), is a low-cost, easily applicable tool for the measurement of body composition and quantifies compartments such as fat-free mass (FFM), FM, VAT and subcutaneous adipose tissue (SAT) [15]. Most dietary interventions aiming to improve body composition have a short intervention period ranging from 3 to 6 months [16] with a focus on single components or supplements, such as intake of protein, certain amino acids, fish oil etc. [14,16]. These interventions do not comply with evidence-based dietary guidelines and are not tailored to the individual patients' needs and preferences. The CRC-NORDIET study is a randomized controlled trial (RCT) aiming to explore the effect of a personalized dietary intervention based on Norwegian food-based dietary guidelines on survival [17].

To the best of our knowledge, no previous RCT has investigated the effect of a long individualized dietary intervention on body composition in non-metastatic CRC patients after surgery. Therefore, the aim of this study was to investigate the effect of a 6 and 12 months personalized dietary intervention on total body weight and body composition (FFM, FM, FM%, VAT, SAT, and FM/FFM) in patients with CRC stage I-III, post-surgery.

2. Materials and methods

2.1. Subjects and study design

The present study included subjects participating in the CRC-NORDIET study [17]. The recruited subjects were men and women aged 50–80 with newly diagnosed primary adenocarcinoma CRC (ICD 10: C18–C20) with tumour, node and metastasis (TNM) stage I-III from Oslo University Hospital and Akershus University Hospital from 2012 to 2020 [17]. Subjects were excluded if they had colorectal adenoma, carcinoid, abdominal carcinomatosis or sarcoma. They were also excluded if they were unable to read and understand Norwegian, unable to understand or perceive information due to dementia or altered mental status, or unable to follow dietary interventions due to medical/clinical conditions (such as subjects that are permanently institutionalized or receives total parenteral nutrition). Patients that participated in other studies in conflict with the CRC-NORDIET study were also excluded. In total, 503 CRC patients were recruited at baseline in the CRC-NORDIET study [17]. The primary aim of the CRC-NORDIET study is to investigate if a healthy diet in line with the Norwegian food based dietary guidelines can improve disease-free survival and overall survival in CRC patients after 5 and 10 years [17].

The CRC-NORDIET is a food-based multicentre parallel RCT with two study arms. The patients were randomized to either the intervention or the control group in blocks of four, ratio 1:1. All study subjects were enrolled to baseline of the study 2–9 months after tumour surgery. The first intensive year included three study visits for both groups: at baseline (also called V2 in the CRC-NORDIET study), at 6 months (V3), and at 12 months (V4). Both the intervention and the control group underwent similar measurements during all visits to the study centre at the University of Oslo [17]. Both groups received general advice on physical activity.

Eligible subjects to the present study were all subjects from the CRC-NORDIET study with available measurement of body composition by DXA at either baseline, 6- or 12 months follow-up.

2.2. The dietary intervention

The intervention group received a personalized intensive dietary intervention the first year. First, the dietary counselling targeted treatment of nutrition-related symptoms, progressive weight loss and malnutrition. When this was managed, eating healthy in accordance with the Norwegian food-based dietary guidelines was the next focus, emphasizing on elements such as: daily intake of fruit, vegetables and berries (≥500 g/day), weekly intake of fish (300–450 g), daily intake of wholegrains (70–90 g), limiting red and processed meat (max. 500 g/week), keeping a body weight within normal BMI, reduce intake of added sugar (<10 E%) and reduce salt intake (max. 6 g/day) [17,18]. The one-year intensive dietary intervention period consisted of tailored individual counselling by a registered dietitian at every study visit (baseline, 6 months, and 12 months) and dietary counselling by telephone 1, 3, and 9 months after baseline. In addition, the intensive intervention included a 25% discount card on healthy foods from the grocery stores, delivery of free food items, invitation to attend an inspiration day, a cooking course, and access to a website with healthy recipes and printed materials. The intervention is described in detail elsewhere [17].

2.3. Anthropometrical measurements

Body weight was measured using the Marshden M−420 Digital Portable Floor Scale (Marshden, Rotherham, South Yorkshire,

United Kingdom) or Seca 285 (Seca, Birmingham, United Kingdom). Height was measured using a digital wireless stadiometer (Seca 285). The measurements were performed with light clothes and no shoes.

2.4. Dual-Energy X-Ray Absorptiometry (DXA)

Body composition was assessed using Lunar iDXA (GE Healthcare Lunar, Buckinghamshire, UK) with enCORE v18. The Lunar iDXA had previously been tested in sub-populations in the CRC-NORDIET study and showed high precision and valid measurements of body composition [19,20]. The system was calibrated daily prior to the scans, and trained personnel conducted the scans according to the manufacturer's procedures [21]. All the subjects fasted before the scan.

The following body compartments were used from the whole-body DXA scans: FM, FM%, FFM, abdominal VAT and abdominal SAT. VAT and SAT were both derived from the abdominal region, defined as 20% of the distance from iliac crest to the mandible. FM was divided by FFM to calculate the ratio (FM/FFM). Fat-free mass index (FFMI) was defined as FFM divided by the square of height in meters (kg/m^2). Low FFMI was defined as below 15 kg/m^2 for females and below 17 kg/m^2 for males, in accordance with the European Society for Clinical Nutrition and Metabolism (ESPEN) Consensus Statement [22].

2.5. Clinical data and questionnaires

Data concerning cancer type, TNM stage, type of surgery, and additional treatment was collected from the electronic patient records. A validated Norwegian version of the Patient-Generated Subjective Global Assessment (PG-SGA) was used to record the overall nutritional status [23]. A comorbidity questionnaire and the demographic questionnaire were used to describe the disease and education level of the subjects, also described elsewhere [17]. Dietary intake for the previous 1–2 months was measured at baseline using a semi-quantitative short food frequency questionnaire named NORDIET-FFQ, previously validated on a sub-population in the CRC-NORDIET study [24].

2.6. Statistical methods

We used linear mixed models for repeated measurements, with patient IDs defining random effects, to examine if there were differences in body composition between the intervention and control group (reference) at 6 and 12 months. Separate models were fitted for each of the dependent variables: weight, FFM, FM, FM%, VAT, SAT, FM/FFM. The treatment effect (difference between intervention and control groups) was investigated from baseline to 6 months and from baseline to 12 months, modelled as two-way interactions between treatment and the time points 6 and 12 months, see **pseudo code A** below. The model thus assumed that there was no treatment effect at baseline, according to Twisk et al. [25]. An unstructured covariance matrix was assumed. STATA version 17.0 was used for the linear mixed model analysis.

Independent samples t-test and Mann–Whitney U-test were used for normally distributed and skewed distributed continuous data, respectively. Chi-square test was used for categorical data. The abovementioned tests were done in SPSS (IMB SPSS Statistics 27). As this study addresses a secondary endpoint in the original CRC-NORDIET study, no sample size estimation was performed for this exploratory sub-study. The sample size estimation for the primary endpoint in the CRC-NORDIET study is described in a previous article [17].

Due to the late introduction of DXA to the CRC-NORDIET study (three years after initiating recruitment), the included subjects in this study presents with missing values for body composition at various time points (total missing is 16%). The pattern of the missing values is described in greater detail in Supplementary Table 1. The independent variables age and sex had no missing data. The missing data were not imputed before running linear mixed model analysis as the literature suggests that the linear mixed model for longitudinal data handles missing data well [26]. As a sensitivity analysis, the linear mixed models were ran both on the "all data" series which included subjects with missing DXA data and on the "non-missing" complete case dataset including only subjects will all three DXA measurements. As a secondary analysis, we investigated treatment effects among obesity (BMI>30 and <30 kg/m^2), sex and patients with low muscle mass (low FFMI) by modelling pairwise interactions of treatment group, time points, and obesity, sex or low FFMI, respectively (see **pseudo-code B**, example provided for BMI_over30).

Stata pseudo-code A: mixed [depvar] t2 t3 c.TreatmGr#c.t2 c.TreatmGr#c.t3 c.Sex c.Age || ParticipantID: time, var cov (un).

Stata pseudo-code B: mixed [depvar] BMI_over30 t2 t3 c.TreatmGr#c.t2 c.TreatmGr#c.t3 c. BMI_over30#c.t2 c. BMI_over30#c.t3 c. TreatmGr#c.t2#c.BMI_over30 c. TreatmGr#c.t3#c.BMI_over30 c. Sex c. Age || ParticipantID: time, var cov (un).

Variable explanations: t2 is 6 months, t3 is 12 months, TreatmGr is treatment group, ParticipantID is ID, depvar is body composition variable: weight, FFM, FM, FM%, VAT, SAT or FM/FFM.

3. Results

Of the 503 subjects participating at baseline in the CRC-NORDIET study, 383 subjects had performed at least one DXA scan at baseline, 6 or 12 months follow-up, and were included in this study (Fig. 1). While the results are based on statistical models using the total data (n = 383) including participants with missing data points, each model were also performed on the non-missing dataset (n = 247, see Supplementary Table 2) showing similar results.

3.1. Baseline characteristics

Baseline took place on average 6 months after surgery. The mean (±SD) age at baseline was 66 [7] and 67 [8] years in the intervention and control groups, respectively (Table 1). The average BMI was around 27 kg/m^2 for both groups. Most of the patients were classified as well-nourished according to the PG-SGA. Low FFMI was identified in 25% and 23% of the intervention and control groups, respectively (Table 2). Both the intervention and the control groups had a similar distribution of cancer diagnoses, TNM stages and neoadjuvant and adjuvant treatment. Musculoskeletal diseases (i.e. osteoarthritis, fibromyalgia, osteoporosis, ankylosing spondylitis and rheumatoid arthritis) and other previous cancers were the most prevalent comorbidities (Table 1). Baseline weight and body composition were similar for the intervention and control groups (Table 2).

3.2. Weight and FFM

After 6 months of follow-up, the intervention group increased 0.74 kg (p = 0.020) less in weight than the control group (Fig. 2, Table 3). No difference was observed at 12 months (0.41 kg, p = 0.364). Both the intervention and the control groups increased significantly in total body weight at both 6 and 12 months compared to baseline (Fig. 2, Supplementary Table 3).

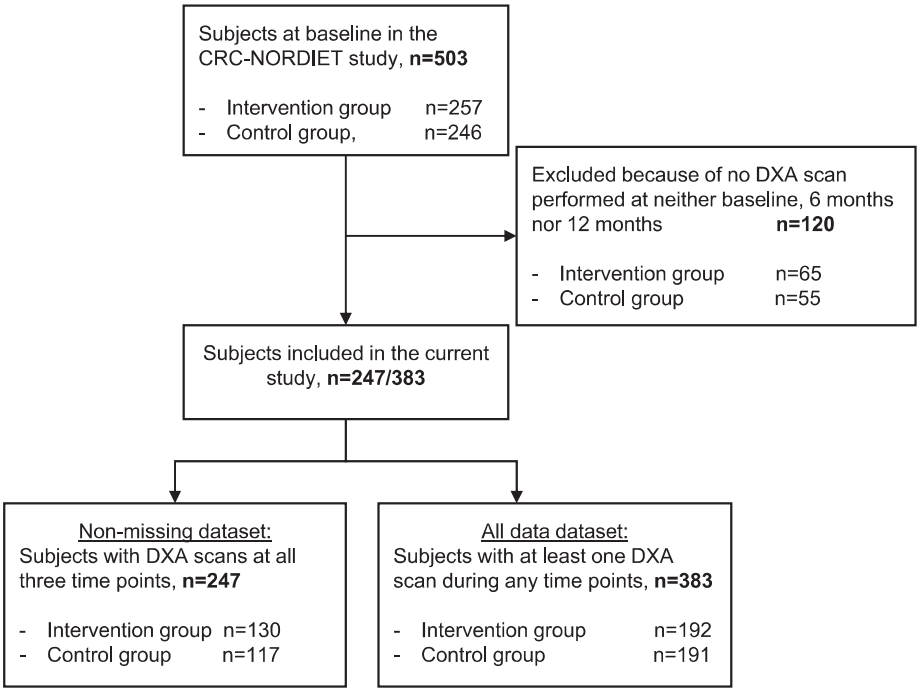

Fig. 1. Flow chart with number of subjects included in the current study from the CRC-NORDIET study and the management of datasets in the current study.

No significant differences in FFM were seen between the groups at neither 6 nor 12 months (Fig. 2, Table 3). Both the intervention and the control groups had overall stable FFM throughout the study period (Fig. 2, Supplementary Table 3). Mean (SD) unadjusted FFM change from baseline to 12 months were 0.4% (3.1), n = 265.

3.3. Total FM and FM%

At 6 months, a smaller increase in average FM was seen in the intervention group compared to the control group (0.59 kg, p = 0.019). This could not be seen at 12 months (0.66 kg less, p = 0.067) (Fig. 2, Table 3). The control group had a significant increase in FM at 6 months (0.90 kg, p=<0.001). At 12 months, both the intervention and the control groups showed significantly increased FM (intervention: 0.61 kg, p = 0.021, and control: 1.28 kg, p < 0.001) (Fig. 2, Supplementary Table 3).

In total, the intervention group had 0.50 percentage points lower increase at 6 months (p = 0.012) and a 0.69 percentage points lower increase in FM% at 12 months (p = 0.011) compared to the control group (Fig. 2, Table 3). The intervention group showed no significant increases in FM% at any time. The control group increased FM% with 0.68 and 1.02 percentage points at 6 months (p < 0.001) and 12 months (p < 0.001) (Fig. 2, Supplementary Table 3).

3.4. Abdominal VAT and SAT

At 6 months, the intervention group increased 63 g less than the intervention group (p = 0.031) in VAT, but no difference were observed at 12 months (Fig. 2, Table 3). The control group had a mean increase in VAT of 46 g from baseline to 6 months (p = 0.032), whereas the intervention group showed no significant change at any point (Fig. 2, Supplementary Table 3).

For SAT, no significant differences were found between the groups at any time point (Fig. 2, Table 3). However, SAT increased in both groups. The intervention group gained 46 g and 70 g at 6 months (p = 0.016) and 12 months (p = 0.003), respectively. The control group increased with 70 g and 126 g (both p < 0.001) after 6 and 12 months, respectively (Fig. 2, Supplementary Table 3).

3.5. FM/FFM

The intervention group had a lower increase in the FM/FFM ratio at both 6 months (0.011, p = 0.025) and 12 months (0.015, p = 0.021) compared to the control group (Fig. 2, Table 3). The control group presented an increased ratio of FM/FFM at 6 months (0.016, p < 0.001) and at 12 months (0.025, p < 0.001), while no changes were seen in the intervention group (Fig. 2, Supplementary Table 3). The overall changes in all body compartments after 6 and 12 months in the groups are illustrated in Fig. 3.

3.6. Secondary analysis - effect of the dietary intervention on obesity (BMI above and below 30), sex, and low FFMI

The difference in weight gain in subjects with BMI above 30 compared to BMI below 30 was significantly higher in the intervention group compared to the control group (1.39 kg, CI: 0.11–2.68, p = 0.034) at 6 months. This was also observed for SAT (149 g, CI: 28–270, p = 0.016) and FM/FFM (0.0212, CI: 0.001–0.416, p = 0.041) at 6 months, but not for FFM, FM, FM% or VAT. No differences in the effect of the intervention on weight or body composition could be found between the sexes at any time point.

The difference in the FM/FFM gain in subjects with low muscle mass (low FFMI) compared to normal/high muscle mass was significantly different between the intervention and control groups at 12 months (difference: −0.034, p = 0.018). In the intervention group, the gain in FM/FFM was lower in the subjects with low muscle mass (0.475) compared to the subjects with normal/high muscle mass (0.491) (Δ = −0.016). Opposite, subjects with low

Table 1
Baseline characteristics for the intervention and control group.

	Intervention group	n	Control group	n
Age, years	66.1 (7.0)	192	66.8 (8.1)	191
Men, n (%)	100 (52)	192	111 (58)	191
Height, cm	172.6 (9.0)	192	173.1 (9.0)	191
BMI, kg/m^2	26.8 (4.6)	192	27.2 (4.6)	191
Underweight (<18.5 kg/m^2) n (%)	0		2 (1.0)	
Normal (18.5–24.9 kg/m^2) n (%)	70 (37)		61 (32)	
Overweight (25–29.9 kg/m^2) n (%)	86 (45)		81 (42)	
Obese (>30 kg/m^2), n (%)	36 (19)		47 (25)	
PG-SGA status, n (%)		184		183
A – well nourished	157 (85)		164 (90)	
B – moderately malnourished or suspected malnourished	27 (15)		19 (10)	
C – severely malnourished	0		0	
Cancer site, n (%)		192		191
Colon	121 (63)		109 (57)	
Rectosigmoid	5 (3)		15 (8)	
Rectum	65 (34)		65 (34)	
Colon and rectosigmoid	1 (1)		1 (1)	
Colon and rectum	0 (0)		1 (1)	
TNM stage, n (%)		192		191
I	69 (36)		64 (34)	
II	70 (36)		62 (32)	
III	53 (28)		65 (34)	
Additional treatment, n (%)[a]	76 (40)	192	76 (40)	191
Neoadjuvant	15 (8)		15 (8)	
- Radio chemotherapy	13 (7)		14 (7)	
- Radiation therapy	2 (1)		1 (1)	
Adjuvant chemotherapy	47 (25)		46 (24)	
No additional treatment	116 (60)		115 (60)	
Days between surgery and baseline	175.8 (56)	192	182.3 (54)	191
Comorbidities				
Any comorbidity, n (%)	118 (67)	175	118 (66)	180
Musculoskeletal diseases, n (%)[c]	51 (29)	178	44 (24)	185
Skin diseases, n (%)[d]	19 (11)	180	30 (16)	186
Kidney diseases, n (%)	27 (4)	181	7 (4)	187
Heart diseases, n (%)[e]	20 (11)	180	30 (16)	186
Stroke, n (%)	11 (6)	181	4 (2)	187
Diabetes, n (%)	18 (10)	181	20 (11)	187
Other cancers, n (%)	46 (25)	182	48 (26)	185
Highest completed education, n (%)		189		189
Primary school	18 (10)		19 (10)	
Lower/secondary/high school	74 (39)		81 (43)	
College/University	97 (51)		89 (47)	
Dietary intake[b]		186		188
Processed meat, g/day[f]	42 (20, 58)		35 (21, 57)	
Total red meat, g/day[g]	56 (42, 87)		53 (42, 74)	
Fruits, berries and vegetables, g/day[h]	355 (262, 456)		332 (219, 483)	
Whole grains g/day[i]	95 (56, 123)		86 (50, 123)	
Alcohol, g/day[j]	6 (1, 13)		6 (1, 15)	
Dairy products, g/day[k]	157 (54, 258)		132 (40, 236)	

Mean and SD unless otherwise specified. The number varies because of missing data in the different data sets.
Abbreviations: DXA, Dual-Energy X-Ray Absorptiometry; PG-SGA, Patient-Generated Subjective Global Assessment; TNM, Tumour Node Metastasis.
[a] Patients may have received more than one of the treatments listed.
[b] Median and 25th and 75th percentile.
[c] Osteoarthritis, fibromyalgia, osteoporosis, ankylosing spondylitis and rheumatoid arthritis.
[d] Hand eczema and psoriasis.
[e] Angina pectoris, myocardial infarction, heart failure and other heart disease.
[f] Both processed red and processed white meat.
[g] Processed and non-processed red meat.
[h] Including one portion of fruit juice.
[i] Calculation of whole grains in grams (not the entire whole grain product itself).
[j] Grams of ethanol calculated from beer, wine and spirits.
[k] All high- and low-fat dairy products, including milk.

muscle mass (0.517) had a higher gain in FM/FFM compared to the subjects with normal/high muscle mass (0.499) in the control group ($\Delta = 0.018$). No statistical difference was observed in FM/FFM at 6 months, nor for weight, FFM, FM, FM%, VAT or SAT at any time point.

4. Discussion

The main finding of this RCT is that CRC patients undergoing a dietary intervention after surgery had lower weight, FM and VAT gain after 6 months and lower FM% gain after 6 and 12 months

Table 2
Weight and body composition for the subjects at baseline.

	Intervention group	n	Control group	n	p-value
Weight, kg	80.2 (16.6)	192	81.6 (16.0)	191	0.394
FFM, kg	52.8 (10.5)	157	53.3 (10.4)	162	0.981
LBM, kg	50.0 (10.0)	157	50.5 (9.9)	162	0.656
FM, kg	27.5 (9.7)	157	28.4 (9.3)	162	0.211
FM%	35.0 (7.7)	157	35.6 (7.6)	162	0.461
Abdominal VAT, g[a]	1334.9 (781.0, 1957.2)	157	1328.6 (784.7, 2256.2)	162	0.514
Abdominal SAT, g[a]	1389.0 (960.8, 1781.7)	157	1432.0 (1130.3, 1959.4)	162	0.183
FM/FFM ratio[a]	0.50 (0.41, 0.64)	157	0.51 (0.42, 0.67)	162	0.414
Low FFMI kg/m^2, n (%)[b]	39 (24.8)	157	37 (22.8)	162	0.695

Mean, SD and Independent samples T-test are used unless otherwise specified.
FFM, fat-free mass; LBM, lean body mass; FM, fat mass; FM%, fat mass in percentage; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FFMI, fat-free mass index.
[a] Median, 25th and 75th percentile and Mann Whitney U-test are used.
[b] Count, % of total and chi-square test are used.

compared to the controls. The intervention did not change SAT or FFM compared to the controls. The current report is the first to show that a dietary intervention can reduce increases in weight and FM post-surgery in CRC patients staged TNM I-III.

4.1. The dietary intervention and fat masses

A minor, but statistically significant lower increase in FM was observed as a result of the dietary intervention. It is a matter of discussion whether a 0.6 kg lower increase in FM is clinically important. The American Cancer Society recommends to avoid obesity after completion of cancer treatment. They describe that avoiding obesity by being physically active and consuming healthy foods may increase the cancer survivors' long-term survival [27]. Our patients had a high average BMI of 27 kg/m^2 and slightly higher FM compared to a healthy Norwegian population from the Tromsø 7 study aged 40–80+ years [28].

In contrast to other dietary interventions on body composition targeting the acute treatment phase, our study was initiated after surgery, representing a recovery phase. Taking this into consideration, in addition to our subjects' high degree of fatness, a lower increase in weight, FM, and VAT along with the maintained FFM, indicates an improved body composition. By this, our results support the use of dietary intervention as a strategy to prevent excess fat mass gain. This is potentially clinically important because CRC patients in Norway have a relatively high CRC-specific survival rate [2], and an increased risk of comorbidities [4,29]. Hence, many CRC patients ultimately die from other diseases associated with excess fat deposits, such as cardiovascular disease, diabetes, and other cancers [11].

Also, the effect of the dietary intervention might have been larger if we compared the intervention effect with CRC patients in usual care, since participation in this study may have inspired lifestyle changes even in the control group.

4.2. The dietary intervention and fat-free mass

Although dietary intake influences body composition over time, our one-year dietary intervention did not alter FFM. The average lean body mass values at baseline in this study were similar to the Norwegian population aged 40–80+ from the Tromsø 7 study [28]. In contrast to a small study by Phillips et al. who showed a perioperative reduction in lean body mass after six weeks [30], our patients were stable in FFM. This may indicate that our recruitment (which took place in average 6 months after surgery) did not capture the largest changes in FFM, and that subjects were partly recovered at baseline. None of our subjects were categorized as severely malnourished according to PG-SGA, which supports the theory that the subjects were not in a catabolic phase at baseline.

After the age of 65, an annual muscle loss of 1–2% is expected in a healthy population [5]. However, in our study the two groups together showed stable FFM, with a mean unadjusted gain of 0.3%. According to ESPEN, a nutrition intervention that halts muscle depletion in cancer patients may be considered a positive outcome itself [6]. Another possible explanation for the absence of FFM change might be that very few of our patients experienced FFM loss during the course of treatment, reducing the potential FFM-enhancing effect of our intervention. This is supported by a study by Dolan et al., showing that less than 6% of their CRC patients had a muscle mass loss from the pre-operative state to 12 months after surgery, based on body composition measured by computed tomography (CT) [31]. In our study, both groups received similar general advice on physical activity. Even though no change in FFM was observed neither between groups nor within, we cannot exclude that physical activity may have influenced FFM.

4.3. Strengths and limitations

To the best of our knowledge, this study is the first RCT to study the effect of a personalized dietary intervention on CRC patients after surgery. Our results adds to the evidence for treatment strategies targeting body composition in cancer patients. Also, the RCT design of this study is a gold standard for determining potential cause–effect relationships [32]. Secondly, Lunar iDXA was used for the measurement of body composition under fasting and standardized conditions. This DXA device is shown to be valid and precise in the same CRC population as used in this study [19,20].

A limitation of our study is that the CRC-NORDIET was not designed to impact body composition, which was a secondary outcome. Consequently, no sample size estimation was performed as we included all available patients from the CRC-NORDIET who met our inclusion criteria. We therefore cannot control the rate of type II errors (false negatives). Further, our intervention did not include comprehensive physical activity and pharmacological interventions, which are known to be optimal for fat loss and the stimulation of muscle synthesis [14].

Other studies have observed that a dietary intervention may also cause higher levels of physical activity in subjects [33]. As the influence of physical activity and function were beyond the scope of this article, we did not control for potential interaction between the dietary intervention and change in physical activity. Because of limited access to advanced imaging methods, we could not include measurements of muscle quality. Like most RCTs, we cannot rule out that the study participants in the CRC-NORDIET study were more motivated and healthier than those that did not participate.

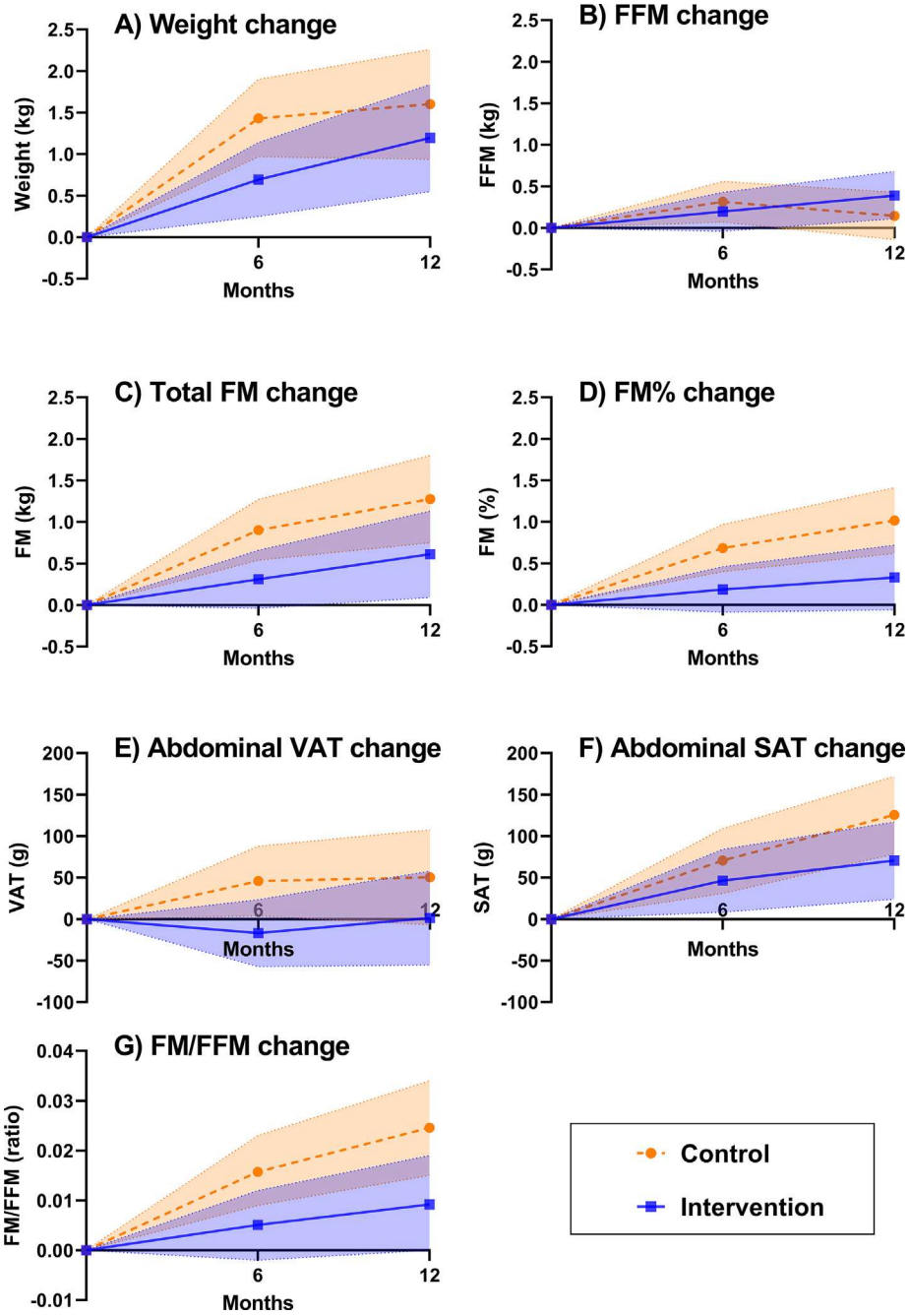

Fig. 2. Change in body composition in the intervention and control group from baseline to 6 and 12 months using linear mixed model adjusting for baseline values, age and sex. Orange dotted line represents the control group and the blue solid line is the intervention group. Filled area represents 95% confidence intervals. Abbreviations: FFM, Fat-free mass; FM, Fat mass; FM%, Fat mass in percentage; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FM/FFM, ratio between fat mass and fat-free mass.

Table 3
Difference between the intervention- and the control group from baseline to 6 and 12 months estimated as fixed effects in the linear mixed model, n = 383.

Change in variable		Average change (slope)[a]	95% Confidence interval	p-value
Weight, kg				
Δ (intervention minus control)	baseline to 6 m	−0.74	(-1.36, −0.12)	**0.020**
	baseline to 12 m	−0.41	(-1.28, 0.47)	0.364
FFM, kg				
Δ (intervention minus control)	baseline to 6 m	−0.12	(-0.45, 0.21)	0.483
	baseline to 12 m	0.25	(-0.14,0.63)	0.211
Total FM, kg				
Δ (intervention minus control)	baseline to 6 m	−0.59	(-1.09, −0.10)	**0.019**
	baseline to 12 m	−0.66	(-1.37, 0.05)	0.067

Table 3 (*continued*)

Change in variable		Average change (slope)[a]	95% Confidence interval	p-value
Total FM %				
Δ (intervention minus control)[b]	baseline to 6 m	−0.50	(-0.89, −0.11)	**0.012**
	baseline to 12 m	−0.69	(-1.22, −0.16)	**0.011**
Abdominal VAT, g				
Δ (intervention minus control)	baseline to 6 m	−62.78	(-119.66, −5.90)	**0.031**
	baseline to 12 m	−49.03	(-126.73, 28.68)	0.216
Abdominal SAT, g				
Δ (intervention minus control)	baseline to 6 m	−24.13	(-77.91, 29.66)	0.379
	baseline to 12 m	−55.05	(-119.14, 9.04)	0.092
Total FM/FFM				
Δ (intervention minus control)	baseline to 6 m	−0.011	(-0.020, −0.001)	**0.025**
	baseline to 12 m	−0.015	(-0.029, −0.002)	**0.021**

Abbreviations: FFM, Fat-free mass; FM, Fat mass; FM%, Fat mass in percentage; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FM/FFM, ratio between fat mass and fat-free mass.

[a] All models are adjusted for baseline values, sex and age. Statistically significant ($p < 0.05$) values are marked in bold.

[b] Differences are percentage points.

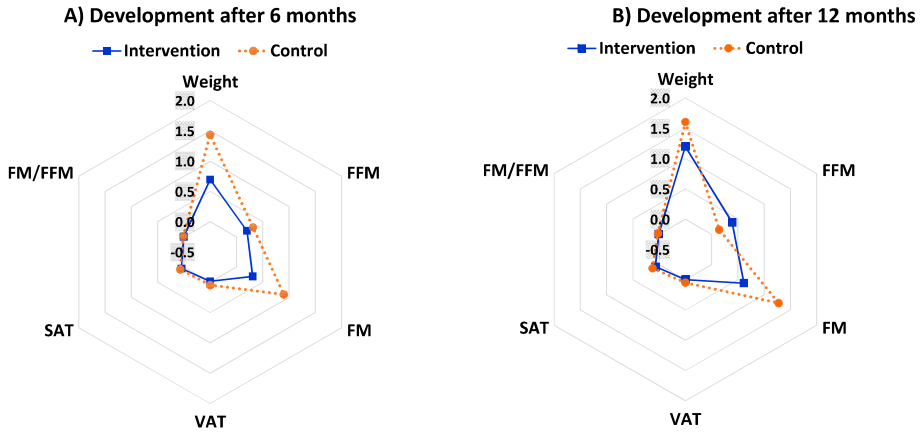

Fig. 3. Average change in body composition profile in intervention and control group from A) baseline to 6 months and B) baseline to12 months of dietary intervention. All components are mean values in kg. Orange dotted line represents the control group and the blue solid line is the intervention group. Abbreviations: FFM, Fat-free mass; FM, Fat mass; FM%, Fat mass in percentage; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FM/FFM, ratio between fat mass and fat-free mass.

This could potentially limit the transferability of these results to the general CRC population stage I-III in Norway. Also, we did not investigate body composition changes in relation to adherence to the dietary intervention, but we highly encourage future studies to explore these relationships further. At last, although the secondary analysis suggested there might be an obesity/low muscle mass effect of the intervention (above and below BMI 30/FFMI cut-off), we cannot conclude upon these results due to low power. Therefore, we suggest future powered trials to investigate the relationship between intervention effect and BMI/low muscle mass.

5. Conclusion

This one-year dietary intervention in CRC patients post-surgery resulted in a lower weight, total FM and VAT gain, but did not alter FFM and SAT. Additionally, the intervention reduced the increase in the ratio between FM and FFM. Although the differences observed between the groups were small, the dietary intervention may have led to an overall more favourable body composition profile. These findings suggest that a dietary intervention may not be sufficient to increase FFM alone, but should be a part of a treatment strategy to prevent weight and FM gain in CRC survivors.

Ethical statement

The study was approved by the Regional Committees for Medical and Health Research Ethics (REC Protocol Approval 2011/836) and by the data protection officials at Oslo University Hospital and Akershus University Hospital. All patients have provided written informed consents and the study was carried out in accordance with the Declaration of Helsinki. The CRC-NORDIET study is registered at the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010).

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Author contributions

DHA - Conceptualization, formal analysis, investigation, methodology, visualization, writing - original draft, writing — review and editing. HBH — Conceptualization, investigation, methodology, resources, supervision, writing — review and editing. PML - Conceptualization, methodology, supervision, writing — review and editing. MZ — Formal analysis, methodology, writing — review and editing. SKB - Conceptualization, resources, methodology, writing — review and editing. CH- Conceptualization, resources, methodology, writing — review and editing. IP - Conceptualization, resources, writing — review and editing. SS - Conceptualization, resources, writing — review and editing. RB — Conceptualization,

funding acquisition, investigation, methodology, project administration, resources, supervision, writing – review and editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the main author used ChatGPT and QuillBot in order to improve language and readability. After using this tool/service, the main author reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

RB is a shareholder of AS Vitas. DTA have received grants from the Norwegian Research Council and the University of Oslo Growth house for development of BodySegAI, however this is unrelated to this project. HBH, PML, MZ, SKB, CH, IP and SS declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.06.037.

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