Interval Walking Improves Glycemic Control and Body Composition After Cancer Treatment
A Randomized Controlled Trial

Christensen, Jesper F.; Sundberg, Anna; Osterkamp, Jens; Thorsen-Streit, Sarah; Nielsen, Anette B.; Olsen, Cecilie K.; Djurhuus, Sissal S.; Simonsen, Casper; Schauer, Tim; Ellingsgaard, Helga; Østerlind, Kell; Krarup, Peter Martin; Mosgaard, Camilla; Vistisen, Kirsten; Tolver, Anders; Pedersen, Bente K.; Hojman, Pernille

Published in:
The Journal of clinical endocrinology and metabolism

DOI:
10.1210/jc.2019-00590

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Interval Walking Improves Glycemic Control and Body Composition After Cancer Treatment: A Randomized Controlled Trial

Jesper F. Christensen,1,2 Anna Sundberg,1 Jens Osterkamp,2 Sarah Thorsen-Streit,1 Anette B. Nielsen,1 Cecilie K. Olsen,1 Sissal S. Djurhuus,1 Casper Simonsen,1 Tim Schauer,1 Helga Ellingsgaard,1 Kell Østerlind,3 Peter-Martin Krarup,4,5 Camilla Mosgaard,6 Kirsten Vistisen,6 Anders Tolver,7 Bente K. Pedersen,1 and Pernille Hojman1

1Centre of Inflammation and Metabolism, Rigshospitalet, Copenhagen 2100, Denmark; 2Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen 2100, Denmark; 3Department of Oncology, Rigshospitalet, Copenhagen 2100, Denmark; 4Digestive Disease Center, Bispebjerg Hospital, Copenhagen 2400, Denmark; 5Center for Surgical Science, Zealand University Hospital, Roskilde 4000, Denmark; 6Department of Oncology, Herlev and Gentofte Hospital, Copenhagen University, Herlev 2730, Denmark; and 7Data Science Laboratory, Department of Mathematical Sciences, University of Copenhagen, Copenhagen 2100, Denmark

ORCID numbers: 0000-0003-4858-1505 (J. F. Christensen).

Context: Patients with colorectal cancer have increased risk of metabolic diseases including diabetes. Exercise training may counteract metabolic dysregulation, but the impact of exercise training on glycemic control, including postprandial glycemia, has never been explored in patients with colorectal cancer.

Objective: To examine the effects of home-based interval walking on aerobic and metabolic fitness and quality of life in patients with colorectal cancer.

Design: Randomized controlled trial.

Setting: Clinical research center.

Participants: Thirty-nine sedentary (<150 minutes moderate-intensity exercise per week) patients with stage I to III colorectal cancer who had completed primary treatment.

Intervention: Home-based interval walking 150 min/wk or usual care for 12 weeks.

Main Outcome Measures: Changes from baseline to week 12 in maximum oxygen uptake (VO2peak) by cardiopulmonary exercise test, glycemic control by oral glucose tolerance test (OGTT), body composition by dual-energy x-ray absorptiometry scan, blood biochemistry, and quality of life.

Results: Compared with control, interval walking had no effect on VO2peak [mean between-group difference: −0.32 mL O2 · kg−1 · min−1 (−2.09 to 1.45); P = 0.721] but significantly improved postprandial glycemic control with lower glucose OGTT area under the curve [−126 mM · min (−219 to −33); P = 0.009], 2-hour glucose concentration [−1.1 mM (−2.2 to 0.0); P = 0.056], and improved Matsuda index [1.94 (0.34; 3.54); P = 0.01]. Also, interval walking counteracted an increase in fat mass in the control group [−1.47 kg (−2.74 to −0.19); P = 0.025].

Abbreviations: AUC, area under the curve; CCS, colorectal cancer subscale; CON, control; CRC, colorectal cancer; DXA, dual-energy x-ray absorptiometry; EWB, emotional well-being; FACT-C, Functional Assessment of Cancer Treatment-colorectal; FACT-G, Functional Assessment of Cancer Treatment-general; FWB, functional well-being; HOMA-IR, homeostatic model assessment of insulin resistance; IWALK, interval-walking; OGTT, oral glucose tolerance test; PWB, physical well-being; SWB, social well-being; VO2peak, maximum oxygen uptake.
Concentration: A home-based interval-walking program led to substantial improvements in postprandial glycemic control and counteracted fat gain in posttreatment patients with colorectal cancer, possibly providing an effective strategy for prevention of secondary metabolic diseases. (J Clin Endocrinol Metab 104: 3701–3712, 2019)

Colorectal cancer (CRC) is part of the diseasome of physical inactivity linking abdominal adiposity and low-grade inflammation to the co-occurring risk of metabolic and cardiovascular diseases, several cancers, and neurocognitive impairments (1). Accordingly, it is well established that individuals with type 2 diabetes have an ~30% increased risk of CRC (2) and that these conditions negatively influence CRC prognoses (3). Moreover, new findings suggest that patients with CRC without pre-existing metabolic conditions may have increased risk of developing metabolic diseases and type 2 diabetes following their anticancer treatment. A recent observational study compared the risk of onset of diabetes in patients with CRC with age- and sex-matched control subjects and found that patients with CRC had ~50% increased risk of being diagnosed with secondary diabetes within the first year of their diagnoses and maintained a 19% increased risk up to 5 years after diagnosis (4). Given the continued advances in early detection, diagnostic precision, and more effective anticancer therapies, CRC prognosis is steadily improving, with current 5-year relative survival rates ranging between 70% and 90% in nonmetastatic patients (5), creating much warranted attention toward secondary prevention of metabolic dysregulation after a CRC diagnosis.

Over the last decade, several clinical trials have been conducted to explore if physical exercise may effectively protect against metabolic dysregulation in CRC patients during and after treatment (6–8). Although some data support exercise-dependent metabolic improvements, this has been exclusively examined through changes in fasting levels of various circulating factors, including fasting insulin, glucose, and lipids (9–11). However, the effect of exercise training on glycemic control, including postprandial glycemia, which is critical in the regulation of metabolic homeostasis, has never been examined in patients with CRC. Furthermore, studies in patients with CRC have reported that structured, hospital-based exercise-programs struggle with patient recruitment and program compliance (12, 13), questioning the clinical application of such programs.

Against this background, we conducted a randomized controlled trial to explore if a pragmatic 12-week home-based interval-walking program comprising 3-minute cycles of alternating fast- and slow-pace walking for a total of 150 min/wk could improve cardiometabolic health profile in patients with early stage CRC after cessation of primary anticancer treatment. In this study, we present the primary analyses showing the effects of interval walking on aerobic fitness by cardiopulmonary exercise test, glycemic control by oral glucose tolerance test (OGTT), whole-body and regional adiposity by dual-energy x-ray absorptiometry (DXA) scans, systemic lipid profile and markers of low-grade inflammation, and health-related quality of life.

Methods

The I-WALK-CRC study was a prospective, randomized controlled trial conducted at the Centre for Physical Activity Research at Rigshospitalet and was approved by the Committees of Biomedical Research Ethics of the Capital Region of Denmark and registered with www.clinicaltrials.gov (NCT02403024). The overall design and recruitment results of the trial has been previously reported (12).

Participants and study visits

Patients with CRC who had completed surgery for local stage disease (Union for International Cancer Control stage I to Ila) and patients who had completed surgery and any adjuvant chemotherapy for locally advanced stage disease (Union for International Cancer Control stage IIb to III) were eligible for inclusion. Major exclusion criteria were: age <18 years; major surgery scheduled within 24 weeks from inclusion; pregnancy; other current malignancy; performance status >1; self-reported physical activity level >150 minutes of moderate intensity per week; and inability to read and understand Danish.

For baseline and week 12 study visits, participants met at the laboratory after an 8-hour overnight water-only fast. At baseline, patients underwent a thorough medical screening by a study physician. After physician approval to continue, the participants performed study assessments, including evaluation of fasting blood biochemistry, OGTT for assessment of glycemic control, body composition, cardiopulmonary exercise test, and self-reported questionnaires. Week 12 follow-up visits were conducted by staff members who were blinded for group allocation.

Randomization and group allocation

A computer-generated list of random group assignments was created by the trial statistician using a permuted block design with allocation weight of 1:1 and stored on a password-protected web server. Following successful baseline assessment, participants were randomly allocated to either an interval-walking (IWALK) intervention group or control (CON) group, who were instructed to maintain their prestudy level of physical activity. Allocation was stratified by prior treatment (adjuvant chemotherapy/no adjuvant chemotherapy), and participants remained in the same group for the duration of the intervention.
Intervention group

Participants randomized into the IWALK group were prescribed interval walking for 150 min/wk. It was optional how the interval-walking exercise was planned and executed over any given week. On the day of the baseline test, participants were introduced to the InterWalk smartphone application as a training device (14, 15). The InterWalk application consists of two primary functions: an individual adaptation test function and a training function. The individual adaptation test comprises an incremental-walking test of the following steps by audio instruction: “stand still” for 30 seconds; “walk slow” for 2 min; “walk at medium pace” for 2 min; “walk fast” for 2 min; and “walk very fast” for 1 min. The InterWalk training function thereafter instructs repeating cycles of 3 minutes slow walking and 3 minutes fast walking, according to the individual paces for fast and slow walking, respectively. Participants were instructed to perform a new individual adaptation test at least every third week to ensure progression in the program.

If participants preferred not to use the InterWalk application or had repeated technological problems, they were instructed to use another device (e.g., another training application or a stopwatch) for time recording and were merely instructed to perform alternating cycles of 3 minutes fast pace and slow pace based on personal preferences.

Adherence

Participants in the IWALK group kept exercise logs for the duration of every session of interval walking. Total minutes of interval walking per week for each participant were summed. For participants using the InterWalk application, data on total walking time, steps, intensity, and Global Positioning System coordinates from the InterWalk application were transferred to a central server and downloaded after the last study visit for all participants, and minutes of interval walking per week for each participant were summed.

Control group

Participants randomized into the CON group were instructed to maintain their prestudy level of physical activity. After the week 12 follow-up visit, participants in this group were offered the same interval-walking program for 12 weeks.

Outcome measures

Cardiopulmonary fitness was determined as maximum oxygen uptake (VO2peak) during a cardiopulmonary exercise step-by-step incremental test on a stationary bicycle with direct measurement of oxygen uptake and carbon dioxide excretion with gas-exchange online measurement equipment (Quark; COSMED, Rome, Italy). The participants carried out 3 minutes of warm up by 70 Watts followed by a step-by-step incremental test with workload increasing by 20 Watts every minute until exhaustion. VO2peak (O2 mL ⋅ min⁻¹ ⋅ kg⁻¹) was determined as the maximum oxygen consumption rate over a 30-second period relative to body weight.

Glycemic control was assessed by a 2-hour OGTT. After a fasting blood sample had been drawn, participants consumed 83 g glucose suspended in 300 mL of water and had blood samples drawn after 30, 60, 90, and 120 minutes to measure responses in insulin, glucose, and C-peptide for calculation of area under the curve (AUC). Moreover, we calculated the following indices: Matsuda index = 10,000/square root of [(fasting glucose × fasting insulin) × (mean OGTT glucose × mean OGTT insulin)] (16); and homeostatic model assessment of insulin resistance (HOMA-IR) using the equation: HOMA-IR = (fasting glucose × fasting insulin)/22.5 (17). The insulinogenic index was used as a measure of β-cell function computed as: insulinogenic index = insulin30min − insulinfasting) / (glucose30min − glucosefasting), where insulin30min and glucose30min are the plasma concentration of insulin and glucose 30 minutes after the glucose load, respectively (18, 19).

Body composition was evaluated by whole-body DXA (DPX-IQ Lunar; Lunar Corporation, Madison, WI). Transverse scans at 1-cm intervals were made from head to toe measuring the absorption of X-ray beams at two different energy levels absorbed at a different intensity by different chemical compounds (bone, fat, and fat-free mass) allowing for valid determination of bone mass, fat mass, fat percentage, and fat-free (lean) mass.

Blood biochemistry involved blood samples for determination of: (1) lipid concentrations (total, high-density lipoprotein, and low-density lipoprotein cholesterol and triglycerides), blood glucose, insulin, C-peptide, and hemoglobin A1c by standard laboratory analyses, (2) plasma leptin by Meso Scale Discovery’s Human Leptin Kit (Meso Scale Discovery, Rockville, MD), and (3) cytokine levels (TNF-α and IL-6) by Meso Scale Discovery’s Human Proinflammation 4-plex Panel (Meso Scale Discovery). Plasma analyses for leptin and cytokine levels were performed in duplicates and blinded, according to the manufacturer’s protocol. Intra-assay coefficient of variation was <5%.

Finally, health-related quality of life was evaluated by Functional Assessment of Cancer Treatment-colorectal (FACT-C) questionnaire (20) comprising the four domains of the FACT-general (FACT-G) questionnaire (21): physical well-being (PWB), emotional well-being (EWB), functional well-being (FWB), and social well-being (SWB), as well as a disease-specific CRC subscale (CCS). From these five subscales, FACT-C Trial Outcome index (PWB + FWB + CCS), FACT-G total score (PWB + SWB + EWB + FWB), and FACT-C total score (PWB + SWB + EWB + FWB + CCS) were calculated according to the questionnaire manual.

Statistical analyses

Sample size was based on the power calculation for changes in VO2peak. Assuming an SD of 2 mL O2 min⁻¹ ⋅ kg⁻¹, 16 patients in each group provided 80% power to detect a between group difference of 2 mL O2 min⁻¹ ⋅ kg⁻¹ in VO2peak. To account for a potential attrition rate of up to 20%, we aimed to include 20 patients in each group. The primary analysis compared difference in changes in study outcomes from baseline to week 12 between the two treatment arms. The primary analysis was based on a mixed-effect model with study outcomes as dependent variables and group (IWALK/CON), time (baseline/12 weeks), and their interaction as fixed effects. A random effect of patients was included to account for subject-specific variation of the levels of each outcome. For all study outcomes, the raw mean and SD for each group at baseline and week 12 were reported, along with the estimated in-group changes and between-group difference with 95% CIs extracted from the mixed-effect model. Some variables were log-transformed to improve model compliance, in which case the estimated in-group changes and between-group differences were analyzed on a log-scale and reported as back-transformed relative ratio.
with 95% CIs. Thus, for example, a back-transformed estimate of 0.85 corresponds to a median relative change of −15%. All analyses were performed as intention-to-treat analyses, thus all patients remained in the originally allocated treatment arms regardless of compliance to the intervention. Because of a relatively low number of returned training logs (n = 8) and available InterWalk records (n = 11) in the IWALK group (i.e., missing data for training adherence), we performed subgroup analyses to examine if there were differences in study outcomes among subjects with or without training logs or InterWalk records. All statistical tests were two-tailed, and significance level was set at 0.05.

Results

Study participants

Between 1 October 2015 and 1 February 2017, a total of 83 subjects were screened for eligibility (Fig. 1). From these, 42 patients (51%) accepted participation and completed baseline assessments. Three patients were excluded prior to randomization due to medical or motivational reasons. Thus, a total of 39 patients were randomly allocated to either the interval-walking intervention group (IWALK group; n = 19) or usual care control (CON group; n = 20) (Table 1). During the study period, 5 participants dropped out; thus, follow-up data were available in 34 patients (IWALK: n = 16; CON: n = 18).

Interval-walking adherence

Training logs were available from 8 out of the 16 IWALK participants, and tracking data from the InterWalk application were available from 11 IWALK participants. Five subjects recorded adherence data using both training logs and the InterWalk application, and five subjects did not have any adherence data registered. On average, participants reported that they performed 154 ± 23 minutes interval walking per week, equivalent to 102 ± 16% of the dose prescribed, and tracking data from the InterWalk application on average registered 119 ± 15 minutes (79 ± 10%) of usage per week (Fig. 2). Based on available data, 5 out of 8 subjects reported on average to perform at least 150 minutes interval walking per week from training logs, and 1 out of 11 subjects with InterWalk data registered >150 min/wk, as the InterWalk application generally registered lower volumes than the training logs. For all study outcomes, we found no differences between subjects with or without available adherence data (data not shown).

Cardiopulmonary fitness

The primary end point was change in VO₂peak from baseline to week 12. We found no remarkable changes in the IWALK group or CON group, and no between-group difference was observed (Table 2). There were no differences for measures of blood pressure or resting heart rate.

Glycemic control

Next, we examined the effects of interval walking on glycemic control as evaluated by OGTT (Fig. 3). For the IWALK group, we found a small reduction in fasting glucose concentration [mean in-group change −0.3 mM (−0.6 to −0.1); P = 0.01] concurrent with significant improvements in postprandial glycemic control as determined by reduced glucose AUC [mean in-group change −93 mM × min (−156 to −27); P = 0.007] and 2-hour glucose concentration [mean in-group change −1.0 mM (−1.8 to −0.2); P = 0.015]. For glucose AUC, the reduction in the IWALK group was superior to the change in the CON group [mean between-group difference: −126 mM × min (−219 to 33), P = 0.009]. For the corresponding insulin measures, we found no differences from baseline to week 12, except for an in-group reduction in 2-hour insulin and C-peptide concentrations in the IWALK group. There were no significant changes in either group for HOMA-IR index or insulinogenic index, but the IWALK group increased the Matsuda index [mean in-group change 2.90 (1.81; 4.00); P < 0.001], which was a significant improvement compared with the CON group [mean between-group difference 1.94 (0.34; 3.54); P = 0.019].
Body composition

Changes in body composition are presented in Fig. 4. In the IWALK group, there were no significant changes in body composition, but we found increased total fat mass in the CON group [mean in-group change 1.12 kg (0.24; 1.99); \( P = 0.014 \)], which resulted in a significant between-group difference [mean between-group difference: 2.14 kg (2.74 to 0.19); \( P = 0.025 \)]. Compartment analyses showed significant increased android, but not gynoid, fat mass in the CON group [mean in-group change 0.12 kg (0.00; 0.23); \( P = 0.048 \)]. No patients in either group were reported to be diagnosed with lymphedema before or during the study.

Blood biochemistry

In Table 3, we present changes in plasma lipids, leptin, and inflammatory cytokines. In this study, we observed a significant 15% in-group reduction in systemic triglyceride concentrations in the IWALK group and a tendency toward increased IL-6 concentration in the CON group, but no between-group differences were observed.

Health-related quality of life

Finally, we examined the effect of interval walking of self-reported health-related quality of life assessed by the FACT-C questionnaire (Table 4). We found no significant between-group differences, but within the IWALK group, FACT-C total score and FACT-C trial outcome index were improved. These improvements were largely attributed to improvements in the FWB domain.

Discussion

In the current study, we demonstrate that a pragmatic home-based interval-walking program was feasible in patients with CRC and effectively improved metabolic fitness in the form of lower fasting glucose levels, improved postprandial glycemic control, and prevention of posttreatment gain in fat mass. In contrast, interval walking had no effect on cardiopulmonary fitness, which has been found in previous studies in middle-aged/elderly healthy individuals (22, 23) and patients with type 2 diabetes (24). Improvements in aerobic fitness levels require a marked load on the cardiopulmonary system and are generally considered to be driven by improvements in
cardiac stroke volume. Despite the alternating intensities, the present intervention did not appear strenuous enough to improve the central components of the oxygen cascade. It is possible that the high-intensity component of our intervention did not reach the required target level (70% to 85% of VO2peak intensity level) or volume (up to 300 min/wk), as prescribed and monitored by accelerometers in the prior studies. Also, these diverse findings may be explained by differences in study design. The previous studies performed unblinded VO2peak assessments and strict per-protocol analyses, excluding a large proportion of subjects. In contrast, we had blinded assessors and performed intention-to-treat analyses including all subjects regardless of adherence and/or contamination.

Figure 2. Interval-walking adherence. (A and B) Available data from 11 subjects in the WALK group using the InterWalk smartphone application for time in minutes and mean (± SD) intensity as the vector magnitude calculated as the square root of the summed squared acceleration from the x-, y-, and z-axes averaged over 30 s. A depicts individual adaptation test (total of 28 adaptation test for 11 subjects) comprising a total 7 min (after standing still for 30 s) as follows: “walk slow” for 2 min; “walk at medium pace” for 2 min; “walk fast” for 2 min; and “walk very fast” for 1 min. B shows interval-walking sessions performed of at least 6 and up to 30-min duration (total of 196 sessions from 11 subjects) using the InterWalk training function instructing repeating cycles of 3 min “slow walking” and 3 min “fast walking,” according to the individual paces for fast and slow walking from the individual adaption test, respectively. C presents the average interval walking training dose performed minutes per week (± SD) based on self-reported training logs from 8 subjects (white bars) and registered InterWalk usage from 11 subjects (gray bars). Dashed line denotes the prescription of 150 min/wk. All available data are included in C. It is not possible to compare individual weeks between training logs and InterWalk data, as they are not from same subjects, and the number of missing observations varied from week to week.
The current study demonstrates improved postprandial glycemic control following an exercise program in patients with CRC. Considerable reductions in blood glucose and insulin levels during the last part of the OGTT, resulting in highly improved Matsuda index, clearly indicate that the early adaptive response after 12 weeks of interval walking is driven by improved peripheral insulin sensitivity. This finding is in accordance with the physiological understanding that peripheral adaptations in insulin sensitivity occur as a rapid response to exercise (25). This may be of particular importance in patients with CRC without pre-existing metabolic disorders in whom the window for rapid adaptations/improvements is substantial.

Although it is well known that impaired glycemic control and type 2 diabetes are risk factors for CRC, less is known about the possible opposite association that CRC may predispose to type 2 diabetes (4). Erhmann-Josko et al. (26) proposed that CRC is a diabetogenic factor, especially in younger, nonoverweight individuals, and showed significantly higher incidence of impaired glycemic control and type 2 diabetes in patients with CRC compared with controls without cancer irrespective of age and body mass index (26). In that study, no differences were observed between CRC and control subjects in fasting glucose, insulin, and C-peptide levels, indicating that fasting blood samples do not capture early metabolic deficiencies and highlighting the need for glucose challenges in both risk assessments and for the evaluation of lifestyle interventions.

Another interesting, but somewhat unexpected, finding was that interval walking attenuated a notable posttreatment gain in fat mass, in particular in android fat, in the CON group. Abdominal adiposity is a source of low-grade inflammation (1, 27), and we did observe that systemic IL-6 levels tended to increase in the CON group. Posttreatment weight gain is well established in several populations with cancer [i.e., early stage breast (28) and prostate cancer (29)] and has also been reported in patients with CRC, but has largely been attributed to adjuvant chemotherapy or simply re-established equilibrium after surgery-induced weight loss (30, 31). In the current study, however, the gain in fat mass in the CON group was not confined to patients with adjuvant chemotherapy nor moderated by time from surgery (data not shown), which questions these as main drivers of posttreatment fat accumulation. It is possible that tumor resection per se may lead to fat accumulation due to the loss of specific incretin hormone-secreting cells from different colonic segments. For instance, left/distal colonic tumor resections by left hemicolectomy, sigmoid colectomy, or low anterior resection may lead to the loss of high numbers of L-cells responsible for the secretion of incretin hormones, such as GLP-1, peptide YY, oxyntomodulin, and GLP-2 (32). Conversely, proximal resections by right hemicolectomy may predominantly lead to loss of K-cells and subsequent higher loss of the secretory capacity of other hormones including GIP (33). Our sample size did not allow for subgroup analyses based on type of surgery; thus, we can only speculate whether resection of specific colonic segments may determine posttreatment energy balance in CRC and hence whether exercise have diverse potential to rescue this late effect in different subpopulations.

Engaging patients with CRC in exercise intervention studies has previously been undertaken to improve psychosocial parameters and physical performance, but several studies have displayed poor recruitment rates and/or program compliance resulting in prolonged trial
periods or premature study termination (13, 34, 35). In this study, we used a simple, home-based interval-walking program, which could be supported by a smartphone-based application but could also be prescribed by simply instructing subjects to walk in fast/slow pace for 3-minute intervals. From a dissemination

Figure 3. Data for postprandial glycemic control assessed by OGTT, with 83 g oral glucose administered to time 0, and blood samples drawn immediately before (time 0) and to time 30, 60, 90, and 120 min. Data for OGTT glucose concentrations for (A) the CON group, (B) the IWALK group, (C) changes in AUC, and (D) changes in 2-h (2H) concentration. Data for OGTT insulin concentration for (E) the CON group, (F) the IWALK group, (G) changes in AUC, and (H) changes in 2H concentration. Data for OGTT C-peptide concentration for (I) the CON group, (J) the IWALK group, (K) changes in AUC, and (L) changes in 2H concentration. Data for (M) HOMA-IR, (N) insulinogenic index, (O) Matsuda index, and (P) fasting hemoglobin A1c (HbA1c). Data are presented as means ± SEM. *P < 0.05 for in-group change; **P < 0.05; ***P < 0.01 for between-group difference.
perspective, it is promising that due to the simplicity of the intervention, even patients, who simply performed interval walking with the fast-slow paces based on personal preferences, improved metabolic fitness.

The current study has important limitations. Our findings are based on a small samples size, and most outcomes in the current study were secondary, explorative analyses, thus the risk of type 1 errors should be considered. Some of our findings (e.g., the effect on glycemic control by improved peripheral insulin sensitivity) are highly concordant with existing knowledge and prior reports, whereas the protection from fat accumulation was unexpected and may have been a consequence of other factors, such as type of tumor resection, for which we could not control. Also, body composition assessment by DXA scans are highly influenced by soft-tissue water retention, which can occur in postsurgical survivors with cancer with lymph node removal. No subjects reported this, but we cannot rule out if some subjects experienced swelling or subclinical/early

![Figure 4. Changes for baseline to week 12 in body composition for (A) lean body mass, (B) total fat mass, (C) android fat mass, and (D) gynoid fat mass. Data are presented as means ± SEM. *P < 0.05 for in-group change; *P < 0.05 for between-group difference.](https://academic.oup.com/jcem/article/104/9/3701/5436995)

### Table 3. Plasma Lipids, Leptin, and Low-Grade Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Baseline/Week 12</th>
<th>In-Group Change</th>
<th>Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Δ (95% CI)</td>
</tr>
<tr>
<td>Total cholesterol, mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>5.0 (1.0)</td>
<td>5.1 (0.8)</td>
<td>−0.1 (0.3; 0.2)</td>
</tr>
<tr>
<td>CON</td>
<td>5.3 (0.9)</td>
<td>5.3 (0.8)</td>
<td>−0.1 (0.3; 0.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.4)</td>
<td>0.0 (−0.1 to 0.2)</td>
</tr>
<tr>
<td>CON</td>
<td>1.7 (0.5)</td>
<td>1.7 (0.6)</td>
<td>0.0 (−0.1 to 0.2)</td>
</tr>
<tr>
<td>LDL cholesterol, mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>3.1 (0.9)</td>
<td>3.2 (0.8)</td>
<td>−0.1 (−0.3 to 0.2)</td>
</tr>
<tr>
<td>CON</td>
<td>3.2 (0.8)</td>
<td>3.2 (0.8)</td>
<td>−0.1 (−0.3 to 0.2)</td>
</tr>
<tr>
<td>Triglycerides, mM&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>1.72 (0.96)</td>
<td>1.42 (0.69)</td>
<td>0.85 (0.74; 0.97)</td>
</tr>
<tr>
<td>CON</td>
<td>1.27 (0.72)</td>
<td>1.27 (0.63)</td>
<td>0.95 (0.84; 1.09)</td>
</tr>
<tr>
<td>Leptin, pg/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>33,978 (34,911)</td>
<td>33,318 (34,709)</td>
<td>0.95 (0.77; 1.16)</td>
</tr>
<tr>
<td>CON</td>
<td>25,719 (32,353)</td>
<td>25,540 (27,201)</td>
<td>1.06 (0.88; 1.29)</td>
</tr>
<tr>
<td>IL-6, pg/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>0.53 (0.30)</td>
<td>0.52 (0.24)</td>
<td>1.05 (0.83; 1.32)</td>
</tr>
<tr>
<td>CON</td>
<td>0.54 (0.24)</td>
<td>0.66 (0.32)</td>
<td>1.23 (0.99; 1.55)</td>
</tr>
<tr>
<td>TNF-α, pg/mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>2.16 (0.75)</td>
<td>2.17 (0.84)</td>
<td>0.99 (0.93; 1.05)</td>
</tr>
<tr>
<td>CON</td>
<td>2.02 (0.55)</td>
<td>2.14 (0.59)</td>
<td>1.03 (0.96; 1.10)</td>
</tr>
</tbody>
</table>

Means (SD) are based on all available data (baseline and week 12) for CON (N = 20 and N = 18) and IWALK (N = 19 and N = 16, respectively). Within-group change may not reflect the numerical difference between baseline and wk 12, given that mean change is estimated based on mixed-model analysis.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

<sup>a</sup>Analyses for triglycerides, leptin, IL-6, and TNF-α are performed on log-transformed data and estimates for in-group changes and between group differences are back-transformed and should be interpreted as median relative changes/differences with back-transformed 95% CIs.
stage lymphedema. Another important limitation comprises our incomplete adherence registration, as we only had available InterWalk data from 11 and training logs from 8 subjects, respectively. Although some subjects successfully used the InterWalk application to individualize the walking intensities and logged comprehensive online-training records (Fig. 2A and 2B), we encountered considerable technological challenges and clearly underestimated the need for technological support and training in this population (36), resulting in several participants not being able to use the application. In these cases, we instructed participants to perform the walking program using other devices (e.g., stopwatch).

Subgroup analyses comparing the participants with available adherence data to the participants who did not register their interval walking did not show considerable differences for any of the study outcomes (data not shown), the lack of a valid training device may have resulted in a suboptimal training intensity. Another limitation is the lack of data for physical activity at baseline (beyond the inclusion criteria of 150 minutes moderate intensity exercise per week) and during the trial period in the CON group; thus, we cannot determine to which extend the CON group may have changed their physical activity level during the study period.

### Conclusion

In summary, free-living interval walking in patients with CRC is an effective intervention to improve metabolic fitness, in particular peripheral insulin sensitivity, but not to improve aerobic capacity. Based on a high adherence to the program and small improvements in health-related quality of life, we propose that this type of exercise prescription is an implementable strategy into clinical practice for prevention of secondary metabolic diseases with particular relevance for patients who by choice or logistical reasons are precluded from standard hospital-based programs.

### Acknowledgments

We thank all of the clinicians from recruiting departments at Copenhagen University Hospitals for assistance; particularly, we thank Maj-Britt Ferm Petersen and Julia S. Johansen (Department of Oncology, Herlev Hospital), Lotte Jakobsen (Department of Gastric Surgery, Hvidovre Hospital), Sigríð Nikoline Bank Nielsen (Digestive Disease Center, Bispebjerg Hospital), and Olivia Johansen (Department of Oncology, Rigshospitalet) for excellent assistance in this study. We also thank Centre for Physical Activity Research (CFAS) affiliates Naja Zenius Jespersen, Kristian Karstoft, Grith Elster Legård, Ulrik Winning

---

**Table 4. Health-Related Quality of Life**

<table>
<thead>
<tr>
<th></th>
<th>Baseline/Week 12</th>
<th>In-Group Change</th>
<th>Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Δ (95% CI)</td>
</tr>
<tr>
<td>PWB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>23.3 (4.3)</td>
<td>24.8 (3.2)</td>
<td>0.7 (−0.6 to 2.0)</td>
</tr>
<tr>
<td>CON</td>
<td>22.8 (5.4)</td>
<td>23.6 (3.6)</td>
<td>0.4 (−0.9 to 1.6)</td>
</tr>
<tr>
<td>EWB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>20.1 (4.3)</td>
<td>21.6 (1.9)</td>
<td>0.5 (−0.4 to 1.4)</td>
</tr>
<tr>
<td>CON</td>
<td>20.0 (3.6)</td>
<td>19.9 (4.1)</td>
<td>0.0 (−0.8 to 0.8)</td>
</tr>
<tr>
<td>FWB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>22.0 (5.1)</td>
<td>25.0 (3.2)</td>
<td>1.9 (0.4; 3.3)</td>
</tr>
<tr>
<td>CON</td>
<td>21.8 (5.4)</td>
<td>22.7 (6.1)</td>
<td>0.7 (−0.7 to 2.1)</td>
</tr>
<tr>
<td>SWB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>24.4 (3.4)</td>
<td>25.5 (3.3)</td>
<td>0.5 (−1.5 to 2.5)</td>
</tr>
<tr>
<td>CON</td>
<td>21.9 (5.9)</td>
<td>21.4 (5.0)</td>
<td>−0.4 (−2.2 to 1.5)</td>
</tr>
<tr>
<td>CCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>22.6 (3.7)</td>
<td>24.1 (2.4)</td>
<td>1.1 (−0.3 to 2.4)</td>
</tr>
<tr>
<td>CON</td>
<td>21.8 (3.8)</td>
<td>22.1 (0.4)</td>
<td>0.4 (−0.9 to 1.7)</td>
</tr>
<tr>
<td>FACT-C-TOI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>68.0 (11.6)</td>
<td>73.8 (7.6)</td>
<td>3.4 (0.5; 6.4)</td>
</tr>
<tr>
<td>CON</td>
<td>66.4 (12.7)</td>
<td>68.4 (10.2)</td>
<td>1.4 (−1.4 to 4.2)</td>
</tr>
<tr>
<td>FACT-G-TOI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>89.8 (14.1)</td>
<td>96.9 (9.4)</td>
<td>3.1 (−0.1 to 6.4)</td>
</tr>
<tr>
<td>CON</td>
<td>86.6 (16.3)</td>
<td>87.7 (16.4)</td>
<td>0.7 (−1.4 to 4.2)</td>
</tr>
<tr>
<td>FACT-C-TOI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWALK</td>
<td>112 (17)</td>
<td>121 (11)</td>
<td>4.2 (0.1; 8.2)</td>
</tr>
<tr>
<td>CON</td>
<td>108 (19)</td>
<td>110 (18)</td>
<td>1.1 (−2.7 to 5.0)</td>
</tr>
</tbody>
</table>

Means (SD) are based on all available data (baseline and wk 12) for CON (N = 20 and N = 18) and IWALK (N = 19 and N = 16, respectively). Within-group change may not reflect the numerical difference between baseline and wk 12, given that mean change is estimated based on mixed-model analysis.

Abbreviation: TOI, Trial Outcome Index.
Iepsen, and Anita Herrstedt for the assistance in the medical screening and examination, Sarah Leggett and Maria Brinkløv for assistance in test assessments of participants, and Mathias Ried-Larsen for excellent assistance and feedback in preparation of the manuscripts.

**Financial Support:** CFAS is supported by a research grant from TrygFonden. J.F.C. is supported by research grants from Rigshospitalet, the Danish Cancer Society, the Capital Region of Denmark, and TrygFonden.

**Clinical Trial Information:** ClinicalTrials.gov no. NCT02403024 (registered 31 March 2015).


**Correspondence and Reprint Requests:** Jesper F. Christensen, PhD, Centre for Physical Activity Research, Department 7641, Rigshospitalet, Blegdamsvej 9, Copenhagen DK-2100, Denmark. E-mail: jesper.frank.christensen@regionh.dk.

**Disclosure Summary:** The authors have nothing to disclose.

**References and Notes**


