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Dose–response effects of aerobic exercise on body composition among colon cancer survivors: a randomised controlled trial

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Background: Physical activity is associated with a lower risk of disease recurrence among colon cancer survivors. Excess visceral adipose tissue is associated with a higher risk of disease recurrence among colon cancer survivors. The pathways through which physical activity may alter disease outcomes are unknown, but may be mediated by changes in visceral adipose tissue.

Methods: Thirty-nine stage I–III colon cancer survivors were randomised to one of three groups: usual-care control, 150 min wk^{-1} of aerobic exercise (low dose) and 300 min wk^{-1} of aerobic exercise (high dose) for 6 months. The prespecified key body composition outcome was visceral adipose tissue quantified using dual energy X-ray absorptiometry.

Results: Exercise reduced visceral adipose tissue in dose–response fashion ($P_{trend} = 0.008$). Compared with the control group, the low- and high-dose exercise groups lost 9.5 cm^2 (95% CI: –22.4, 3.5) and 13.6 cm^2 (95% CI: –27.0, –0.1) in visceral adipose tissue, respectively. Each 60 min wk^{-1} increase in exercise predicted a 2.7 cm^2 (95% CI: –5.4, –0.1) reduction in visceral adipose tissue.

Conclusions: Aerobic exercise reduces visceral adipose tissue in dose–response fashion among patients with stage I–III colon cancer. Visceral adipose tissue may be a mechanism through which exercise reduces the risk of disease recurrence among colon cancer survivors.

Each year 83 000 people are diagnosed with stage I–III colon cancer in the United States (Siegel *et al*, 2014). Despite efficacious surgical and chemotherapeutic interventions, 25–40% of patients will experience recurrent and metastatic disease within 3 years of diagnosis (André *et al*, 2004), and 91% of those who recur within 3 years, die by 5 years (Sargent *et al*, 2005). Therefore, it is critical to identify additional therapies that may reduce the risk of recurrent disease and promote long-term survival in this population.

Participation in physical activity after diagnosis of colon cancer is associated with a lower risk of recurrence and mortality (Meyerhardt *et al*, 2006). This observation is independent of various demographic, clinico-pathologic and treatment-related

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prognostic factors. A consistently reported observation is that post-diagnosis physical activity is associated with disease outcomes in a dose–response fashion, such that larger doses of physical activity or exercise, up to approximately 300 min per week (min wk^{-1}), are associated with more favourable disease outcomes (Schmid and Leitzmann, 2014).

The biologic or biobehavioural pathways through which exercise may favourably alter disease outcomes among colon cancer survivors are unknown. One plausible pathway includes exercise-induced alterations in body composition (Park *et al*, 2011, 2014). Excess visceral adipose tissue is associated with a higher risk of disease recurrence and mortality among colon cancer survivors (Xiao *et al*, 2016). In addition, waist circumference (an anthropometric proxy for visceral adipose tissue) is associated with cancer-specific and all-cause mortality among colon cancer survivors (Haydon *et al*, 2006). These observations are further strengthened by evidence that the visceral adipose tissue of colon cancer survivors exhibits extensive metabolomic activity (Liesenfeld *et al*, 2015; Del Corno *et al*, 2016; Donninelli *et al*, 2017), polymorphisms within adiposity-related genes predict disease recurrence among colon cancer survivors (Sebio *et al*, 2015) and adipocytes promote the proliferation of colon cancer cells *in vivo* (Amemori *et al*, 2007).

Exercise reduces visceral adipose tissue among non-diabetic persons with obesity in a dose–response fashion (Slentz *et al*, 2009); however, the dose–response effects of exercise on visceral adipose tissue and other body composition measures, such as waist circumference, have not been examined among colon cancer survivors. Understanding how exercise may favourably alter pathways that are hypothesised to influence disease outcomes and the sensitivity of such pathways to respond to different doses of exercise will help to improve the specificity of exercise prescriptions in this population, and provide experimental evidence to support observational studies that document the beneficial effects of exercise among colon cancer survivors.

The COURAGE trial was a randomised controlled trial with the primary aim of examining the safety, feasibility and biological efficacy of 150 and 300 min wk^{-1} of aerobic exercise *vs* usual care control over 6 months among men and women with a history of stage I–III colon cancer (Brown *et al*, 2016). The primary outcomes of this study are published, demonstrating that exercise is feasible, safe and induces reductions in soluble intercellular adhesion molecule-1 (Brown *et al*, 2017). Here we report body composition outcomes. Visceral adipose tissue quantified using dual-energy X-ray absorptiometry (DXA) was prespecified as the key body composition outcome of this trial. Our hypothesis was that exercise would reduce visceral adipose tissue in a dose–response fashion.

PATIENTS AND METHODS

Participants. Detailed study methods of the COURAGE trial are published (Brown *et al*, 2016). Potentially eligible participants were recruited throughout the metropolitan Philadelphia region. Participants were eligible if they were diagnosed with histologically proven stage I–III colon cancer; completed surgical resection and adjuvant chemotherapy within 36 months of entering the study; self-reported participating in $\leqslant$150 min wk^{-1} of moderate or vigorous intensity physical activity using the Paffenbarger Physical Activity Questionnaire (Paffenbarger *et al*, 1978); were of age $\geqslant$18 years; provided written physician approval; had no additional surgery planned within the 6-month intervention period (including colostomy reversal); and had the ability to walk unaided for 6 min. Participants were ineligible if they had a history of another primary cancer (other than non-melanoma skin cancer); had evidence of distant metastases; were pregnant or breast feeding; were unable to provide a baseline blood sample; had a myocardial infarction or coronary revascularisation procedure within the past 3 months; had uncontrolled hypertension, defined as a systolic blood pressure $\geqslant$180 mm Hg or diastolic blood pressure $\geqslant$100 mm Hg; had high risk or uncontrolled heart arrhythmias (not including atrial fibrillation); had clinically significant heart valve disease; had decompensated heart failure; had a known aortic aneurysm; or had any other condition which, in the opinion of the investigator, may impede testing of study hypotheses or make it unsafe to engage in the exercise program.

Participants were stratified on cancer stage (AJCC 7th Edition: I *vs* II *vs* III) and randomised to one of three groups: low-dose aerobic exercise (150 min wk^{-1}), high-dose aerobic exercise (300 min wk^{-1}) or usual care control. This study was approved by the University of Pennsylvania Institutional Review Board and registered on clinicaltrials.gov as NCT02250053. Participants provided written informed consent and written approval from their physician prior to participation.

Intervention. Aerobic exercise was performed over 6 months using study-provided in-home treadmills (LifeSpan Fitness, TR1200i, Salt Lake City, UT, USA). Participants were provided with a heart rate monitor to objectively record heart rate during each exercise session. Participants also used paper logs to record exercise adherence. Participants met with a clinical exercise physiologist to introduce the exercise prescription, and familiarise the participant with use of the treadmill, completion of exercise logs, use of a heart rate monitor, appropriate warm-up and cool-down, stretches, and proper footwear for aerobic exercise. The exercise physiologist provided ongoing behavioural and clinical support and monitored exercise adherence to the study protocol throughout the duration of the study using weekly telephone and email communications. Exercise intensity was prescribed at 50–70% of the age-predicted maximum heart rate (equivalent to 3–6 METs (Ainsworth *et al*, 2000)). The low-dose and high-dose groups progressed towards of the goal of 150 or 300 min wk^{-1} of exercise, respectively. Participants were instructed to maintain their pre-study dietary patterns throughout the study. Detailed methods of the intervention are published (Brown *et al*, 2016).

Participants randomised to the usual-care control group were asked to maintain their pre-study levels of physical activity and/or follow the recommendations provided by their physician. After completing 6-month measures, control group participants were provided with an in-home treadmill and individualised exercise program, like that prescribed to the two exercise groups. Upon study completion, all participants could keep their study-provided treadmills.

Measurements. Baseline and follow-up measurements were obtained by trained staff members who were blinded to treatment assignment. Demographic characteristics including age and sex were self-reported. Daily caloric intake was quantified using 3-day food records that were analysed by a registered dietitian using the Nutrition Data System for Research software (v.2014). Clinical information including cancer stage and treatment were obtained from the state cancer registry, pathology reports or physician records.

Body composition outcomes. The prespecified key body composition outcome was visceral adipose tissue quantified using DXA. All other body composition outcomes were considered exploratory. Participants underwent whole-body DXA (Hologic Horizon, Bedford, MA, USA). Dual-energy X-ray absorptiometry scans were reviewed for quality assurance by a certified DXA technician who was blinded to the study group (Powers *et al*, 2014). The DXA scanner was calibrated daily using an anthropomorphic spine

phantom and thrice weekly using a whole-body phantom. Dual-energy X-ray absorptiometry was used to quantify visceral adipose tissue (cm^2), subcutaneous adipose tissue (cm^2), fat mass (kg), lean mass (kg) and bone mineral density ($g\,m^{-2}$) using Hologic APEX v.13.5 software (Bedford, MA, USA). Dual-energy X-ray absorptiometry-derived visceral adipose tissue has been validated against computed tomography-derived visceral adipose tissue ($r = 0.93$; $P < 0.001$; Micklesfield *et al*, 2012), and has been used across a large body mass spectrum (Bredella *et al*, 2013). Other anthropometric outcomes that were measured in duplicate included height (m), body mass (kg), waist and hip circumferences (cm) and sagittal abdominal diameter (cm). Height and body mass were used to calculate body mass index ($kg\,m^{-2}$).

Statistical analysis. Descriptive statistics presented for baseline variables include counts and proportions for categorical variables and means ± standard deviations for continuous variables. Categorical baseline characteristics were compared among the three groups using Fisher's exact test, and continuous baseline characteristics were compared among the three study groups using the Kruskal–Wallis test. This study was powered to detect changes in the co-primary study outcomes: soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1 (Brown *et al*, 2017). However, the sample size provided adequate statistical power to examine changes in visceral adipose tissue. Based on prior research (Slentz *et al*, 2009), over 6 months we hypothesised a change in visceral adipose tissue of $+14\,cm^2$ in the control group, $+2.9\,cm^2$ in the low-dose group and $-11.6\,cm^2$ in the high-dose group with a pooled standard deviation of $\pm 11\,cm^2$. Against the hypothesis of a dose–response relationship, 39 participants provided ⩾80% power with a type I error rate of 5%. All inferential analyses were conducted on an intention-to-treat basis. Normality of continuous variables was examined using graphical techniques. Change in visceral adipose tissue (and other outcomes) was evaluated from baseline to 6 months in the three groups using repeated-measures mixed-effects regression models. This statistical approach includes all available data and accounts for the correlation between repeated measures. The baseline value of the dependent variable and cancer stage (randomisation stratification factor) were included as covariates in the regression models (Fitzmaurice *et al*, 2012). Group-by-time interaction terms were estimated as fixed-effects in the regression model. Model fit was examined using graphical techniques. Results from the repeated-measures mixed-effects regression models are presented as least-squares mean (LS Mean) ± standard error (s.e.). To evaluate the presence of a dose–response relationship across randomised groups, a test of trend was conducted by examining linear contrasts.

RESULTS

Between January 2015 and August 2015, 39 colon cancer survivors were recruited and randomised with data collection ending in February 2016. Baseline characteristics of study participants are presented in Table 1. One participant did not provide endpoint data (97% follow-up rate).

Exercise prescription program variables have been described in detail (Brown *et al*, 2017). Briefly, over 6 months, adherence to the prescribed volumes of exercise in the low- and high-dose groups were 92.8 ± 2.4% and 89.0 ± 2.6%, respectively ($P = 0.287$). Average exercise volume in the low- and high-dose groups were 141.5 ± 9.9 and 247.2 ± 10.7 $min\,wk^{-1}$, respectively (Δ between groups: 105.7 ± 14.6; $P < 0.001$). Exercise intensity was 70.7 ± 0.8% of the age-predicted maximal heart rate and the proportion of exercise sessions validated with objective heart rate data was 96.8 ± 0.6%, both of which did not differ between the two exercise groups. There were no significant changes in self-reported caloric consumption ($P = 0.743$).

Body composition outcomes using DXA are presented in Table 2. Exercise reduced visceral adipose tissue, the prespecified key body composition outcome, in dose–response fashion ($P_{trend} = 0.008$; Figure 1A). Compared with the control group, the low- and high-dose exercise groups lost $9.5\,cm^2$ (95% CI: −22.4, 3.5) and $13.6\,cm^2$ (95% CI: −27.0, −0.1) in visceral adipose tissue, respectively. Each $60\,min\,wk^{-1}$ increase in exercise predicted a $2.7\,cm^2$ (95% CI: −5.4, −0.1) reduction in visceral adipose tissue. Exercise improved bone mineral density in dose–response fashion ($P_{trend} = 0.015$). Compared with the control group, the low- and high-dose exercise groups gained $0.015\,g\,m^{-2}$ (95% CI: 0.001,

Table 1. Baseline characteristics of the participants

Characteristic	Total ($n = 39$)	Control ($n = 13$)	Low dose ($n = 14$)	High dose ($n = 12$)	*P*
Age, %					
<60 years	25 (64%)	9 (69%)	8 (57%)	8 (67%)	0.840
⩾60 years	14 (36%)	4 (31%)	6 (43%)	4 (33%)	
Sex, %					
Male	15 (38%)	4 (31%)	7 (50%)	4 (33%)	0.601
Female	24 (62%)	9 (69%)	7 (50%)	8 (67%)	
Body mass index, %					
$<25.0\,kg\,m^{-2}$	7 (18%)	3 (23%)	2 (14%)	2 (17%)	0.884
$25.0–29.9\,kg\,m^{-2}$	12 (31%)	5 (38%)	4 (29%)	3 (25%)	
$⩾30.0\,kg\,m^{-2}$	20 (51%)	5 (38%)	8 (57%)	7 (58%)	
Energy intake, $kcal\,day^{-1}$	1735 (1270–1962)	1800 (1233–2110)	1776 (1483–2111)	1632 (1196–1739)	0.725
Cancer stage, %					
I	5 (13%)	1 (8%)	2 (14%)	2 (17%)	0.999
II	14 (36%)	5 (38%)	5 (36%)	4 (33%)	
III	20 (51%)	7 (54%)	7 (50%)	6 (50%)	
Chemotherapy, %	28 (72%)	10 (77%)	10 (71%)	8 (67%)	0.906
Time since treatment, %					
⩽12 months	25 (64%)	8 (62%)	10 (71%)	7 (58%)	0.770
>12 months	14 (36%)	5 (38%)	4 (26%)	5 (42%)	

P-values are from the overall test of group differences. Data are median (interquartile range), or counts with percentages.

Table 2. Body composition outcomes using DXA at baseline and change during 6 months

Outcome	Baseline (mean ± s.d.)	Δ baseline to month 6 (LS mean ± s.e.)	Δ from control (LS mean ± s.e.)
Visceral adipose tissue, cm^2			
Control	112.6 ± 55.2	5.31 ± 4.80	—
Low dose	131.3 ± 45.6	−4.13 ± 4.53	−9.45 ± 6.60
High dose	154.2 ± 60.5	−8.27 ± 4.89	−13.58 ± 6.86[b]
Test for trend		$P=0.008$	
Subcutaneous adipose tissue, cm^2			
Control	388.4 ± 142.6	−3.87 ± 8.64	—
Low dose	381.1 ± 138.6	1.70 ± 8.15	5.57 ± 11.88
High dose	461.9 ± 110.9	−17.86 ± 8.81[a]	−14.00 ± 12.34
Test for trend		$P=0.222$	
Fat mass, kg			
Control	32.8 ± 10.0	−0.01 ± 0.49	—
Low dose	32.6 ± 7.6	−0.13 ± 0.47	−0.12 ± 0.68
High dose	38.1 ± 11.9	−0.71 ± 0.50	−0.70 ± 0.71
Test for trend		$P=0.238$	
Lean mass, kg			
Control	49.9 ± 13.1	0.30 ± 0.35	—
Low dose	52.6 ± 11.1	−0.06 ± 0.33	−0.36 ± 0.48
High dose	53.4 ± 13.8	0.01 ± 0.36	−0.29 ± 0.50
Test for trend		$P=0.450$	
Bone mineral density, $g\,cm^{-2}$			
Control	1.08 ± 0.10	0.006 ± 0.005	—
Low dose	1.03 ± 0.12	0.021 ± 0.005[a]	0.015 ± 0.007[b]
High dose	1.02 ± 0.09	0.020 ± 0.005[a]	0.013 ± 0.007
Test for trend		$P=0.015$	

Abbreviations: DXA = dual-energy X-ray absorptiometry; LS mean = least-squares mean; s.d. = standard deviation; s.e., standard error. Changes in outcomes are estimated using a linear mixed-effects regression model that adjusted for the baseline value of the dependent variable and cancer stage (randomisation stratification factor).
[a]Significantly different from baseline (within-group), $P \leqslant 0.05$.
[b]Significantly different from control, $P \leqslant 0.05$.

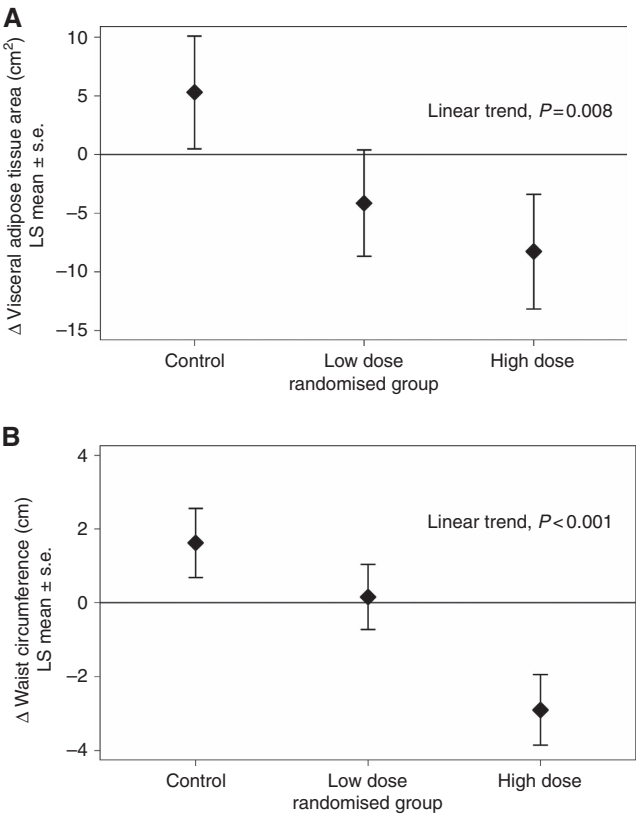

Figure 1. Dose-response effects of exercise on body composition. Between group changes in (**A**) visceral adipose tissue and (**B**) waist circumference from baseline to 6 months. Note: LS mean, least squares mean; s.e., standard error.

0.029) and 0.013 $g\,m^{-2}$ (95% CI: -0.001, 0.028) in bone mineral density, respectively. *Post hoc* sex-stratified body composition outcomes using DXA are presented for hypothesis generating purposes (Supplementary Table S1).

Anthropometric outcomes are presented in Table 3. The finding that exercise reduced visceral adipose tissue was reinforced by the observation that exercise reduced waist circumference (an anthropometric proxy for visceral adipose tissue) in dose–response fashion ($P_{trend} < 0.001$; Figure 1B). Compared with the control group, the low- and high-dose exercise groups lost 1.5 cm (95% CI: −4.0, 1.1) and 4.5 cm (95% CI: −7.1, −1.9) in waist circumference, respectively. Each 60 min wk^{-1} increase in exercise predicted a 0.9 cm (95% CI: −1.4, −0.4) reduction in waist circumference. Changes in visceral adipose tissue were correlated with changes in waist circumference ($r = 0.42$; $P = 0.009$). Improvements in the waist-to-hip ratio did not reach statistical significance ($P_{trend} = 0.054$). No significant change in body mass was observed ($P_{trend} = 0.280$). *Post hoc* sex-stratified anthropometric outcomes are presented for hypothesis generating purposes (Supplementary Table S2).

No serious (grade $\geqslant 3$) adverse events occurred. Non-serious (grade 1 − 2) adverse events have been reported in detail (Brown *et al*, 2017).

DISCUSSION

A 6-month moderate-intensity aerobic exercise program among stage I–III colon cancer survivors resulted in significant linear dose–response reductions in visceral adipose tissue measured by DXA and waist circumference. The findings from this randomised trial provide mechanistic data to support observational evidence that suggests physical activity may lower the risk of recurrence and mortality among colon cancer survivors.

The linear dose–response reductions in visceral adipose tissue and waist circumference with increasing exercise volume are similar to prior dose–response exercise interventions in other populations (Kay and Fiatarone Singh, 2006). For example, among overweight and obese men and women with dyslipidaemia, increasing exercise volume produced larger reductions in visceral adipose tissue and waist circumference (Slentz *et al*, 2009). Excess visceral adipose tissue is associated with a higher risk of disease recurrence and mortality among colon cancer survivors (Xiao *et al*, 2016). Prior epidemiologic studies have often quantified visceral adipose tissue using quartiles or quintiles (Xiao *et al*, 2016), which challenges direct comparison of our results to these prior studies. In the general population, each 10 cm^2 increase in visceral adipose tissue is associated with an 8–10% increase in the risk of death (Kuk *et al*, 2006; Katzmarzyk *et al*, 2012). In our study, the low- and high-dose exercise groups lost 9.5 and 13.6 cm^2 in visceral adipose tissue, respectively, over 6 months compared with the control group. In a cohort of 536 colon cancer survivors, each 5 cm increase in waist circumference was associated with an 8–10% increase in the risk of colon cancer-specific and all-cause mortality (Haydon *et al*, 2006). In our study, the low- and high-dose exercise groups lost 1.5 and 4.5 cm in waist circumference, respectively, over 6 months compared with the control group. Collectively, these data suggest that the observed exercise-induced changes in body composition may hold clinical importance for colon cancer survivors.

In our study, we observed a modest, though not statistically significant, increase in visceral adipose tissue and waist circumference

Table 3. Anthropometric outcomes at baseline and change during 6 months

Outcome	Baseline (mean ± s.d.)	Δ baseline to month 6 (LS mean ± s.e.)	Δ from control (LS mean ± s.e.)
Body mass, kg			
Control	83.7 ± 22.1	0.43 ± 0.61	—
Low dose	86.2 ± 13.1	−0.51 ± 0.57	−0.95 ± 0.84
High dose	92.2 ± 24.3	−0.32 ± 0.62	−0.76 ± 0.87
Test for trend		$P=0.280$	
BMI, kg m^{-2}			
Control	29.2 ± 6.0	0.14 ± 0.22	—
Low dose	29.5 ± 4.3	−0.17 ± 0.21	−0.31 ± 0.30
High dose	32.5 ± 6.9	−0.11 ± 0.23	−0.25 ± 0.32
Test for trend		$P=0.354$	
Waist circumference, cm			
Control	98.0 ± 17.1	1.62 ± 0.94	—
Low dose	98.7 ± 11.9	0.16 ± 0.89	−1.46 ± 1.29
High dose	106.9 ± 14.6	−2.90 ± 0.96[a]	−4.52 ± 1.34[b]
Test for trend		$P<0.001$	
Hip circumference, cm			
Control	103.4 ± 13.5	1.85 ± 1.42	—
Low dose	104.5 ± 10.3	0.18 ± 1.34	−1.67 ± 1.95
High dose	110.6 ± 15.0	0.02 ± 1.45	−1.84 ± 2.03
Test for trend		$P=0.518$	
Waist to hip ratio			
Control	0.94 ± 0.09	−0.005 ± 0.011	—
Low dose	0.94 ± 0.07	0.001 ± 0.011	0.005 ± 0.016
High dose	0.97 ± 0.09	−0.029 ± 0.012[a]	−0.023 ± 0.016
Test for trend		$P=0.054$	
Sagittal abdominal diameter, cm			
Control	22.6 ± 4.0	0.45 ± 0.32	—
Low Dose	22.4 ± 3.6	0.01 ± 0.30	−0.43 ± 0.44
High Dose	23.9 ± 4.0	0.01 ± 0.32	−0.45 ± 0.46
Test for trend		$P=0.200$	

Abbreviations: BMI = body mass index; LS mean = least-squares mean; s.d. = standard deviation; s.e. = standard error. Changes in outcomes are estimated using a linear mixed-effects regression model that adjusted for the baseline value of the dependent variable and cancer stage (randomisation stratification factor).
[a]Significantly different from baseline (within-group), $P \leqslant 0.05$.
[b]Significantly different from control, $P \leqslant 0.05$.

over 6 months among usual-care control group participants. This observation has been reported in the control groups of prior exercise trials (Slentz *et al*, 2009), and underscores the deleterious effect of continued sedentary behaviour. Excess energy intake is preferentially stored as visceral adipose tissue during extended periods of inactivity (Belavý *et al*, 2014). It is important to note that we did not observe significant changes in body mass. Exercise preferentially utilises visceral adipose tissue as an energetic substrate, often without altering total body mass (Lee *et al*, 2005; Johnson *et al*, 2009). Health-care providers who prescribe exercise to colon cancer survivors should inform patients that exercise may not significantly reduce body mass, and that body mass alone should not be used as an indicator of exercise efficacy, as important physiologic changes are likely to occur in the absence of weight loss.

The biologic or biobehavioural pathways through which exercise may favourably alter disease outcomes among colon cancer survivors are unknown. Excess visceral adipose tissue and waist circumference are associated with an increased risk of disease recurrence and mortality among colon cancer survivors (Xiao *et al*, 2016). Visceral adipose tissue is an active endocrine organ that secretes various bioactive compounds such as adipokines, cytokines, hormone-like factors and other metabolites (Ahima and Flier, 2000), that have been hypothesised to influence disease recurrence and progression (Park *et al*, 2011, 2014). Excess visceral adipose tissue and other states associated with adiposity such as hyperinsulinaemia activate the PI3K–Akt–mTOR pathway (McCurdy and Klemm, 2013). Activation of the PI3K–Akt–mTOR pathway is associated with the growth and progression of colon cancer metastases (Gulhati *et al*, 2011), and silencing of this pathway inhibits the growth of metastases by inducing cell-cycle arrest and apoptosis (Zhang *et al*, 2009).

Several polymorphisms within adiposity-related genes predict disease recurrence among colon cancer survivors (Sebio *et al*, 2015). For example, PPAR-γ rs1801282 regulates transcription factors for several genes that influence colon cancer growth (Sarraf *et al*, 1998). Furthermore, PPAR-γ rs1801282 predicts the progression from impaired glucose tolerance to type 2 diabetes (Kilpelainen *et al*, 2008; Brito *et al*, 2009). Physical activity reduces the risk of progression from impaired glucose tolerance to type 2 diabetes that is attributed to this polymorphism (Kilpelainen *et al*, 2008; Brito *et al*, 2009). Type 2 diabetes is associated with an inferior prognosis in colon cancer (Meyerhardt *et al*, 2003). Future research will be needed to discern if the disease-specific benefits of physical activity for colon cancer survivors are achieved through similar pathways as that of type 2 diabetes prevention.

There are several limitations to this trial. The primary limitation to this trial is the small sample size, which limited our statistical power to examine other body composition outcomes. The small sample size allowed for numeric differences in baseline body composition and anthropometric measures. Our analyses plan prespecified that the baseline value of the dependent variable would be included in the model to account for baseline differences; however, we cannot rule out that the observed differences may be partly due to regression to the mean. The small sample size also reduces the generalisability of our findings. As we have previously described (Brown *et al*, 2016), trial participants were younger than the population from which they were recruited. This has important implications for the generalisability of our findings to the broader population of colon cancer survivors. The duration of the exercise intervention was 6 months, and it is not known if the dose–response effects of exercise on visceral adipose tissue would be maximised or sustained over a longer time horizon. Trial participants were not recruited based on having excess visceral adipose tissue at baseline. It is not known if the exercise-induced reductions in visceral adipose tissue would be similar or larger in magnitude among a sample who all had excess visceral adipose tissue at baseline.

There are several strengths to this trial. The use of two intervention groups, each prescribed a distinct dose of exercise, allowed us to examine how visceral adipose tissue changed along the exercise dose curve. The exercise program was flexible, emphasising a home-based program, blended with ongoing behavioural and clinical support from an exercise physiologist. The provision of home-based treadmills succeeded in providing a reasonable incentive for participation, as recruitment was completed ahead of schedule and succeeded in promoting favourable adherence to the exercise prescription over 6 months. Completion of the prescribed exercise dose was objectively quantified using heart-rate monitors with long-term ($\geqslant$3 month) memory. Data collection was completed by staff blinded to study group who followed standardised protocols. Participants in this trial had later stage of disease than the population from which they were recruited (Brown *et al*, 2016), which represents colon cancer survivors at highest risk for disease recurrence. Participants had a variety of comorbid conditions that are common among colon cancer survivors including hypertension, hyperlipidaemia, diabetes and cardiovascular disease. Endpoint data collection was satisfactory (97% complete).

In conclusion, the findings from this randomised trial demonstrate the dose–response effects of moderate intensity aerobic exercise to favourably reduce visceral adipose tissue among selected patients recently treated for stage I–III colon cancer. The findings from this randomised trial may be useful to health-care

providers to improve the specificity of exercise prescriptions for colon cancer survivors. The findings from this randomised trial are also useful for investigators to begin to understand the mechanistic pathways that are hypothesised to mediate the relationship between exercise and disease outcomes in this population. Visceral adipose tissue may be a mechanism through which exercise reduces the risk of disease recurrence among colon cancer survivors.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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