Exercise Decreases Risk of Future Active Disease in Patients with Inflammatory Bowel Disease in Remission

Patricia D. Jones, MD, MSCR,[*,†] Michael D. Kappelman, MD, MPH,[†,‡] Christopher F. Martin, MSPH,[†,‡] Wenli Chen, MA, MS,[†] Robert S. Sandler, MD, MPH,*[,†] and Millie D. Long, MD, MPH*[,†]*

Background: Although exercise impacts quality of life in patients with inflammatory bowel disease, little is known about its role in disease activity. Among patients with inflammatory bowel disease in remission, we aimed to evaluate the association between exercise and subsequent active disease.

Methods: We performed a prospective study using the Crohn's and Colitis Foundation of America Partners' internet-based cohort of individuals with self-reported inflammatory bowel disease. We identified participants in remission, defined as short Crohn's disease activity index <150 or simple clinical colitis activity index ≤ 2. The primary exposure was exercise status, measured using the validated Godin leisure-time activity index. The primary study outcome, assessed after 6 months, was active disease defined using the above disease activity index thresholds. We used bivariate and multivariate analyses to describe the independent association between exercise and risk of active disease.

Results: We identified 1308 patients with Crohn's disease (CD) and 549 with ulcerative or indeterminate colitis (UC/IC) in remission, of whom 227 (17.4%) with CD and 135 (24.6%) with UC/IC developed active disease after 6 months. Higher exercise level was associated with decreased risk of active disease for CD (adjusted risk ratio: 0.72, 95% confidence interval: 0.55–0.94) and UC/IC (adjusted risk ratio: 0.78, 95% confidence interval: 0.54–1.13).

Conclusions: In patients with CD in remission, those with higher exercise levels were significantly less likely to develop active disease at 6 months. In patients with UC/IC in remission, patients with higher exercise levels were less likely to develop active disease at 6 months; however this was not statistically significant.

(Inflamm Bowel Dis 2015;21:1063–1071)

Key Words: exercise, inflammatory bowel disease, Crohn's disease, ulcerative colitis, godin

Inflammatory bowel disease (IBD), including Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC) are chronic immune-mediated diseases with a clinical course often marked by periods of relapse alternating with periods of quiescence. Environmental factors such as exercise may impact the pathogenesis and course of IBD. Previous studies have shown an association between physical activity and development of IBD. Sonnenberg et al[1] demonstrated an increased prevalence of IBD in patients with sedentary or less physically demanding occupations compared with those with physically demanding jobs. A Swedish case-control study reported that patients who exercised regularly in the previous 5 years were at decreased risk for developing CD, especially if they exercised daily.[2] More recently, Khalili et al[3] found that physical activity was inversely associated with the risk of CD, but not UC.

Less is known about the impact of physical activity on the course of IBD. One population-based study[4] demonstrated that only 25% of patients with IBD exercised with moderate intensity, and that patients with IBD were less likely to report active lifestyles compared with unaffected individuals. Although the effect of exercise on quality of life and stress has been studied in patients with IBD,[5] there are no large prospective studies examining the association between exercise and disease activity. Exercise is associated with variable effects on the gastrointestinal system.[6] Some studies in humans and rodents have suggested that exercise increases proinflammatory cytokines[7,8] Although other studies have shown decreases in these cytokines.[9,10] Athletes are noted to have increased gut microbiota diversity than controls[11]; however, it is unclear how these physiologic changes might impact symptoms of IBD.

Exercise is thought to lead to improved mood, decreased stress, and increased quality of life. There are other physiologic benefits to exercise such as improved bone density[12] and decreased risk of colon cancer,[13] both are of particular importance to patients with IBD. Exercise is important for prevention and treatment of obesity, and obesity is an increasing problem in patients with IBD.[14–16] Obesity may complicate the clinical course of IBD leading to increased rates of hospitalization, perianal

Received for publication November 20, 2014; Accepted December 22, 2014.

From the *Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; †Department of Medicine, Center for Gastrointestinal Biology and Disease, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ‡Division of Gastroenterology and Hepatology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Supported by grants from the National Institutes of Health (T32 DK07634 and P30 DK034987) and by the Crohn's and Colitis Foundation of America.

The authors have no conflicts of interest to disclose.

Reprints: Patricia D. Jones, MD, MSCR, Department of Medicine, Division of Gastroenterology, University of North Carolina at Chapel Hill, 4162 U Bioformatics Building, 130 Mason Farm Road, Chapel Hill, NC 27599-7080 (e-mail: patricia_jones@med.unc.edu).

DOI 10.1097/MIB.0000000000000333

Published online 26 February 2015.

complications,[17] and decreased time to first surgery.[18] Although, the benefits of exercise are likely to outweigh theoretical risks in patients with mild and moderate IBD, little data exist on this topic. We therefore sought to evaluate the association between exercise patterns and subsequent disease activity in a large cohort of patients with IBD.

MATERIALS AND METHODS

Study Cohort

Crohn's and Colitis Foundation of America (CCFA) Partners is an internet-based cohort of adult patients (older than or equal to 18 yr of age) with self-reported IBD (CD, UC, or IC) sponsored by the CCFA. The development of this cohort has been described elsewhere.[19] In brief, patients are recruited through CCFA email rosters, the CCFA website, word of mouth, and social media websites. Those who agree to participate in a complete baseline survey, which collects demographic information and information about disease activity, medication use, physical activity, quality of life, and overall health status. Participants are invited, through email, to complete follow-up surveys on a semiannual basis. A previous validation study of CCFA Partners has shown high levels of accuracy for the presence and type of IBD (97% for both).[20]

From within this cohort, we identified a population of patients who were in remission, defined as having a short Crohn's disease activity index (sCDAI) <150[21] or simple clinical colitis activity index (SCCAI)[22] ≤ 2.[23] We investigated associations between baseline exercise and active disease 6 months later. Active disease was defined as disease activity index above these thresholds.

Inclusion/Exclusion Criteria

All patients in clinical remission during the time of survey completion were included in this analysis. For patients who completed surveys at multiple time points, their first survey indicating clinical remission was used as the baseline for this analysis. We excluded those with pregnancy or recent (within the past month) surgery, fracture, or myocardial infarction, because we expected that these conditions would limit ability to exercise. All individuals with an ostomy were excluded, because these individuals could not complete disease activity indices that rely on reports of bowel movement frequency. Similarly, individuals with a pouch were excluded, because sCDAI and SCCAI may not accurately reflect disease activity in this population.

Assessment of Exercise

The Godin leisure-time activity index was developed to assess exercise behavior[24] and has been validated in different populations.[25,26] Weekly leisure activity score is calculated by the following formula: weekly leisure activity score = (9 × strenuous) + (5 × moderate) + (3 × light).[24] For example, a Godin score of 30 could be achieved by vigorous exercise 3 times per week, moderate exercise 6 times per week, or light exercise 10 times per week performed for at least 15 minutes each time. Baseline exercise status was dichotomized at the median score into categories of higher and lower exercise activity. Baseline exercise status was also stratified into quartiles for secondary analyses.

Outcomes

The primary outcome of interest was the presence of active disease at 6 months, defined as sCDAI >150 for CD or SCCAI >2 for UC/IC on the follow-up survey.

Statistical Analysis

Continuous variables were analyzed using mean values and standard deviations. Categorical variables were expressed using proportions. Comparisons were made using Student's *t* test or the Kruskal–Wallis rank-sum test for continuous variables, and Pearson's chi-square test for categorical variables. We estimated crude and adjusted risk ratios (RR) for active disease at follow-up with respect to baseline physical activity using multivariate log-binomial or Poisson regression modeling. We used stratified analysis and logistic regression modeling with multiple degree-of-freedom likelihood ratio tests to assess for effect modification between physical activity and all variables. Potential confounders, such as age, gender, body mass index (BMI), global health status, and cigarette smoking were identified a priori through a directed acyclic graph based on clinical reasoning. Physical activity tends to decrease with age, which is associated with both incidence and prevalence of IBD.[27] There is no strong gender predilection in IBD[27]; however, gender is associated with physical activity and has been shown to affect subjective measures of disease activity.[28] BMI may impact disease activity[16,17] and is associated with physical activity. Health status is expected to be associated with physical activity because individuals who think they are in excellent health are more likely to exercise than those who think they are in poor health. Also, we hypothesize that one's perception of their health status might be affected by disease activity. There is an inverse relationship between smoking and physical activity,[29] and smoking has variable effects on disease activity in patients with IBD.[30,31] Covariates were also assessed for multicollinearity. We constructed a full model using all potential confounders and eliminated these potential confounders through a backward elimination strategy using a change in estimate approach (threshold of $<10\%$ change). For all analyses, *P*-values were 2-sided, and a *P*-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX).

Ethical Considerations

The study protocol was approved by the Institutional Review Board at University of North Carolina.

RESULTS

Study Cohort

A total of 6626 participants completed both baseline and follow-up surveys and did not have an ostomy. After excluding those not in clinical remission or who had comorbidities affecting ability to exercise, 1857 participants were eligible for inclusion (Fig. 1), 1308 participants had CD, and 549 had UC or IC. The median age was 45 years for CD and 43 years for UC/IC, and the median disease duration was 12 and 9 years for CD and UC/IC, respectively (Tables 1 and 2). The majority of participants were women. Most patients were of normal BMI; however, both groups had overweight and obese participants, defined as BMI from 25 to 29.9 kg/m^2 and greater than 30 kg/m^2, respectively. More patients with CD had been hospitalized and had bowel surgery previously compared with participants with UC/IC. More patients with UC/IC were treated with either oral or rectal 5-aminosalicylate (5-ASA) than patients with CD. More patients with CD were treated with biologics, which included adalimumab, infliximab, certolizumab pegol, or natalizumab. Less than 1% of patients were taking medications as part of a clinical trial.

Baseline Characteristics by Exercise

The median Godin score was 28 for CD and 34 for UC/IC. Bivariate analyses were performed using dichotomous categories of exercise (high versus low) (Tables 1 and 2) and quartiles of exercise. CD patients in the lower category of exercise were significantly older than participants in the higher category of exercise. More women were in the less active category compared with the more active category for CD and UC/IC. BMI was higher for the less active category of participants. Among CD participants in the lower exercise category, a higher proportion of them were current smokers, had previous bowel surgery, and were treated with oral steroids compared with those in the higher

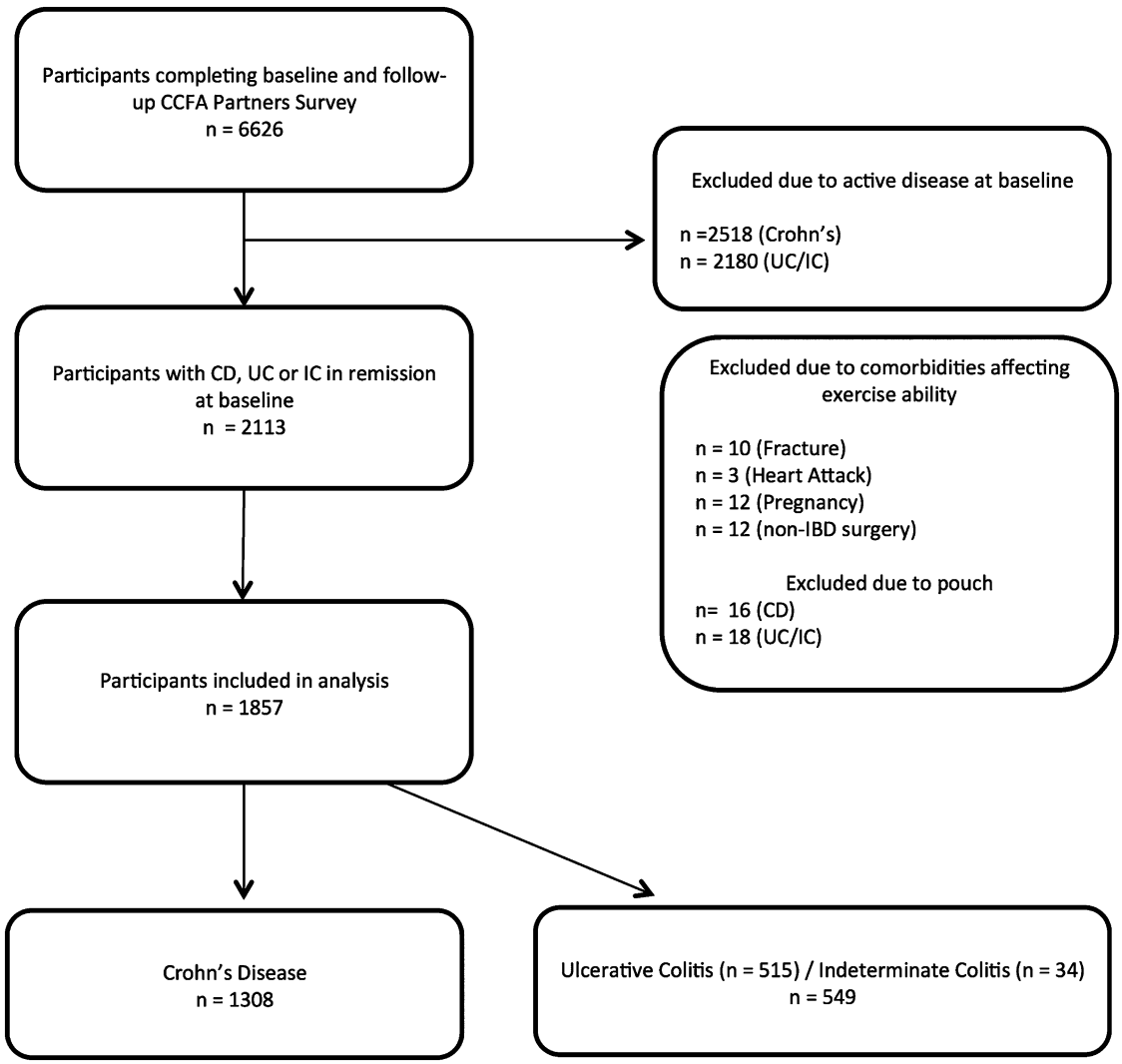

FIGURE 1. Flow diagram of study participants.

TABLE 1. Baseline Characteristics of the Crohn's Disease Population in Remission, Overall and Stratified by Activity Level Within CCFA[a] Partners Cohort

	CD (N = 1308); Median (IQR) or Percent			
Characteristic	Overall	Low Activity Level[b] Godin <28	High Activity Level[b] Godin ≥28	*P*
Age, yr	45 (32–58)	48 (34–59)	42 (29–56)	<0.01
Disease duration, yr	12 (5–24)	14 (6–26)	10 (5–21)	<0.01
BMI, kg/m^2	24 (22–28)	25 (20–29)	23 (21–27)	<0.01
sCDAI	79 (58–111)	86 (58–121)	76 (44–107)	<0.01
Gender (% women)	71	75	67	<0.01
Ever smokers, %	34	36	33	0.30
Current smokers, %	5	7	4	0.02
Education (% with ≤high school)	7	8	5	<0.01
Global health status, %				
Excellent/very good	45	35	55	<0.01
Good	44	50	39	
Fair/poor	11	15	6	
Previous bowel surgery, %	47	50	43	<0.01
Current fistula, %	20	21	18	0.17
Ever hospitalized for IBD, %	70	71	68	0.18
5-ASA, oral, %	38	38	38	0.89
5-ASA, rectal, %	2	2	2	0.79
Corticosteroids, %				
Oral	6	7	5	0.05
Rectal	1			
Budesonide, %	4	4	4	0.42
Thiopurines, %	31	31	31	1
Biologics[c], %	37	38	36	0.47

[a]CCFA.
[b]Low activity level is below median Godin index, and high is above median Godin index.
[c]Adalimumab, infliximab, certolizumab pegol, or natalizumab.
5-ASA, 5-aminosalicylic acid; IQR, interquartile range; N, total participants.

exercise category. For all IBD patients, the less active category had the highest proportion of participants with high school education or less, and the more active category had the highest proportion of participants who rated their health status as excellent or very good. There were no significant differences in age at diagnosis, disease duration, last hospitalization, or other IBD medications, when stratified by 2 categories of exercise, dichotomized at the median. These findings were echoed when baseline characteristics were stratified by quartiles of exercise.

Association Between Exercise and the Risk of Active Disease at 6 Months

Exercise status, gender, oral steroids, timing since the last IBD hospitalization, and global health status were all associated with active disease at 6 months for both CD and UC/IC (Table 3). Education level was found to be associated with active disease at 6 months for CD. As reported in other studies,[30,31] individuals with CD who currently smoke had increased risk for active disease at 6 months. For patients with UC/IC, those with active disease had a shorter duration of disease, were younger, and a higher proportion were using rectal 5-aminosalicylates. BMI was not associated with active disease at 6 months.

Crohn's Disease

Among those with CD, 20% of those in low-exercise category experienced relapse or developed active disease at 6 months, compared with 15% of those in the high-exercise category, and this was statistically significant, $P = 0.01$. There was significant interaction between steroids and physical activity found using stratified analysis. For patients using steroids, those in the higher-exercise class (n = 30) had increased risk of active disease (RR = 1.87) compared with those in the lower-exercise class (n = 46). However, for patients who were not on steroids, those in the higher-exercise class (n = 627) had decreased risk of active disease (RR = 0.70) compared with those in the lower-exercise class (n = 603) ($P = 0.01$). When adjusted for other covariates, this interaction remained statistically significant using logistic regression modeling with multiple

TABLE 2. Baseline Characteristics of the UC/IC Population in Remission, Overall and Stratified by Activity Level Within CCFA[a] Partners Cohort

Characteristic	UC/IC (N = 549); Median (IQR) or Percent			
	Overall	Low Activity Level[b] Godin <34	High Activity Level[b] Godin ≥34	*P*
Age, yr	43 (31–56)	43 (31–57)	43 (31–55)	0.55
Disease duration, yr	9 (4–16)	10 (4–16)	8.5 (4–15)	0.36
SCCAI	1 (0–2)	1 (1–2)	1 (0–2)	0.35
BMI, kg/m^2	24 (22–27)	24 (22–28)	23 (21–26)	<0.01
Gender (% women)	69	72	66	0.12
Ever smokers, %	30	29	31	0.66
Current smokers, %	3	3	3	0.79
Education (% with ≤high school)	6	10	2	<0.01
Global health status, %				
Excellent/very good	67	56	77	<0.01
Good	28	36	20	
Fair/poor	5	8	3	
Previous bowel surgery, %	3	2	4	0.22
Ever hospitalized for IBD, %	38	38	38	0.98
5-ASA, oral, %	69	70	69	0.62
5-ASA, rectal, %	13	11	14	0.46
Corticosteroids, %				
Oral	5	7	5	0.35
Rectal	3	2	3	0.59
Budesonide, %	1	1	0	0.04
Thiopurines, %	24	26	23	0.38
Biologics[c], %	17	19	16	0.36

[a]CCFA.
[b]Low activity level is below median Godin index, and high is above median Godin index.
[c]Adalimumab, infliximab, certolizumab pegol, or natalizumab.
5-ASA, 5-aminosalicylic acid; IQR, interquartile range; N, total participants.

degree-of-freedom likelihood ratio tests, $P = 0.05$, and all multivariate analyses included an interaction term.

We found that increased physical activity was associated with a reduced risk of active disease at 6 months, crude RR was 0.68 (95% confidence interval [CI]: 0.53–0.89) (Table 4). Global health status was a candidate confounder based on a priori reasoning and bivariate analysis. However, global health status was highly correlated with quartiles of physical activity ($P < 0.001$ for Spearman's rank correlation), leading to multicollinearity in the models. Thus, global health status was excluded as a potential confounder to avoid overfitting and instability in estimated coefficients. When adjusted for age, education, steroids, gender, BMI, current smoking status, and disease duration, the product term of physical activity and steroids, the RR was 0.72 (95% CI: 0.55–0.94). Results of the fully adjusted model are also in Table 4.

We conducted sensitivity analyses using alternative definitions of active disease. Studies have used a decrease in sCDAI of 70 or greater from the baseline to define remission.[32] When we defined active disease as an increase in sCDAI of 70, we found the crude RR was 0.74 (95% CI: 0.56–0.98) and the adjusted RR was 0.74 (95% CI: 0.56–0.99). We also conducted a sensitivity analysis, which excluded individuals taking steroids because these individuals might have active disease not captured by the sCDAI. The results were nearly identical to those obtained with our original models with a crude RR of 0.68 (95% CI: 0.58–0.89) and adjusted RR of 0.72 (95% CI: 0.55–0.94).

Ulcerative Colitis/Indeterminate Colitis

Among those with UC/IC, 28% of those in the lower-exercise category had active disease at 6 months compared with 21% of those in the high-exercise category, $P = 0.04$. We found that higher exercise was associated with decreased risk of active disease at 6 months, crude RR was 0.76 (95% CI: 0.53–1.09) (Table 4). There were no significant interactions noted. As in building models for CD, global health status was excluded as a potential confounder because of multicollinearity with physical activity. When adjusted for age, education, steroids, gender, BMI, current smoking status, and disease duration, adjusted RR was

TABLE 3. Patient Characteristics by Disease Activity at 6 Months for Crohn's Disease and UC/IC

Characteristic	CD			UC/IC		
	Remission	Active Disease	*P*	Remission	Active Disease	*P*
Physical activity, % <median Godin	48	57	0.01	47	58	0.04
Age, median (IQR), yr	45 (32–58)	43 (31–55)	0.22	44 (32–57)	41 (29–53)	0.03
Duration, median (IQR), yr	12 (5–24)	12 (5–24)	0.59	10 (5–16)	7 (3–14)	<0.01
Gender (% women)	70	77	0.05	67	76	0.06
BMI, median (IQR), kg/m^2	24 (22–27)	25 (22–28)	0.22	24 (22–27)	23 (21–28)	0.74
Ever smokers, %	33	39	0.08	30	29	0.81
Current smokers, %	5	8	0.02	3	1	0.31
Previous bowel surgery, %	46	51	0.18	2	5	0.11
Ever hospitalized, %	69	70	0.68	38	36	0.59
Last IBD hospitalization, %						
<1 yr ago	79	21	<0.01	56	44	0.09
1–2 yrs ago	76	24		72	28	
3–10 yrs ago	83	17		79	21	
>10 yrs ago	89	11		84	16	
Oral 5-ASA, %	38	39	0.64	69	72	0.44
Rectal 5-ASA, %	2	3	0.10	11	18	0.03
Oral prednisone, %	5	9	0.03	4	11	<0.01
Thiopurines, %	31	29	0.55	25	23	0.78
Biologics, %	36	40	0.23	18	15	0.41
Methotrexate, %	3	6	0.06	0.8	0	0.32
Certolizumab pegol, %	4	7	0.02	0.5	0	0.41
Education (% ≤high school)	6	9	<0.01	6	6	0.61
Global health, %			<0.01			<0.01
Excellent/very good	50	20		71	53	
Good	41	61		25	38	
Fair/poor	9	16		4	9	

5-ASA, 5-aminosalicylic acid; IQR, interquartile range.

0.78 (95% CI: 0.54–1.13) (Table 4) We conducted a sensitivity analysis, where active disease was defined as an increase in SCCAI of at least 2 points and the results were similar.

DISCUSSION

There is considerable interest in the impact of exercise on individuals with IBD. Our study is the largest prospective analysis of exercise in patients with IBD to date with 1857 participants included, 1308 with CD, and 549 with UC/IC. We found that increased levels of exercise may decrease the risk active disease at 6 months by 32% in individuals with CD and by 24% in individuals with UC/IC. This decrease in risk persisted when exercise status was adjusted for age, education, steroids, gender, BMI, current smoking status, and disease duration. Studies have demonstrated that patients who exercise more are at decreased risk to develop CD[2,3]; however, there is a paucity of published data about the effects of exercise in patients with established IBD. Much of what is published about the effects of exercise on the gastrointestinal system is incongruent and has to be extrapolated to patients with IBD.

Exercise is believed to have variable effects on the gastrointestinal system and may lead to gastrointestinal symptoms such as increased urge to defecate[33,34] through unclear mechanisms. Previously postulated mechanisms for gastrointestinal symptoms include decreased gastrointestinal blood flow, increased gastrointestinal motility, increased mechanical bouncing, and altered neuroendocrine modulation.[6] Decrease in splanchnic blood flow during exercise can lead to ischemia-induced inflammation and increased intestinal permeability, which could impact the disease course in patients with IBD. Some studies suggest that exercise may worsen disease activity by increasing levels of interleukin (IL)-6,[7,35] IL-17, IL-10, tumor necrosis factor-alpha,[8] neutrophils, lymphocytes, and monocytes.[7] Extreme exercise may increase the number of CD4 and CD8 lymphocytes, natural killer cells and the level of free radicals,

TABLE 4. Risks Ratios for the Development of Active Disease for Participants with Godin Lesiure Time Activity Index Above Median Compared with Those Below Median and Adjusted RRs for Covariates

	CD[a,b]			UC/IC[c]		
Covariate	RR	95% CI	*P*	RR	95% CI	*P*
Physical activity-crude[d]	0.68	0.53–0.89	<0.01	0.76	0.53–1.09	0.13
Physical activity-adjusted	**0.72**	**0.55–0.94**	**0.02**	**0.78**	**0.54–1.13**	**0.18**
Age, yr	0.99	0.98–1	0.08	1	0.98–1	0.64
BMI, <18.5 kg/m^2	1			1		
BMI, 18.5–24.99 kg/m^2	1.15	0.50–2.63	0.49	0.98	0.47–2.06	0.96
BMI, 25–29.99 kg/m^2	1.41	0.61–3.28	0.61	1.05	0.48–2.27	0.91
BMI, ≥30 kg/m^2	1.19	0.50–2.84	0.53	1.28	0.58–2.83	0.54
Current smoker	1.65	1.11–2.47	0.01	0.67	0.16–2.07	0.48
Disease duration, yr	1	0.99–1	0.69	0.98	0.95–1	0.02
Male gender	0.80	0.59–1.07	0.13	0.79	0.55–1.14	0.21
Steroids	1.21	0.63–2.29	0.57	2.33	1.57–3.46	<0.01
Greater than high school education	0.70	0.47–1.06	0.09	1.20	0.58–2.48	0.62
Physical activity × steroids	2.20	0.98–4.97	0.06	—	—	—

The bolded values represent the risk ratios and associated confidence intervals obtained from the fully adjusted models.
[a]Risks ratios were adjusted for age, education, steroids, gender, BMI, current smoking status, and disease duration and calculated using the log-binomial method.
[b]All models for CD include the product term of physical activity and steroids as significant interaction was noted.
[c]Risks ratios were adjusted for age, education, steroids, gender, BMI, current smoking status, and disease duration and calculated using the Poisson method.
[d]Unadjusted RR.

reactive oxygen species, and reactive nitrogen species, which could contribute to intestinal inflammation.[36] In contrast, other studies have demonstrated decreased levels of IL-6 and tumor necrosis factor-alpha in exercised mice.[10] Regular exercise attenuated the microscopic and macroscopic effects of dextran sodium sulfate–induced colitis in exercised mice compared with sedentary mice,[37] but it is unclear how physiologic changes noted in exercised rodents correlate with disease activity in humans with IBD.

Light and moderate exercise is believed to be safe in patients with IBD,[33,34] and several studies support this belief. An evaluation of moderate-intensity exercise in 6 males with ileal CD demonstrated a decrease in total transit time similar to that seen in 6 age-matched healthy controls, but there was no increase in intestinal permeability, lipid peroxidation, or gastrointestinal symptoms.[38] In a prospective evaluation of patients with inactive or mildly active CD,[5] participants walked 3 times per week in a structured group or individually, and 42% of participants reported a decrease in disease-related symptoms and 58% of participants reported improved body image and life satisfaction. This study did not include a control group, and the beneficial effects could be due to group interaction; however, a later study randomized participants to an independent walking program versus no exercise[39] and found that the control group had a statistically significant worsening of disease activity, whereas the exercise group reported a significant reduction in symptoms.

Despite the uncertainty in understanding how exercise impacts IBD, there are known physiologic benefits to exercise, which may be important for patients with IBD. Unfortunately, patients with CD and UC are more likely to be inactive compared with those without IBD[4,40] and were found to have decreased aerobic and anaerobic exercise capacity when compared with healthy patients.[41] Patients who have had surgical resection may have diminished exercise capacity commensurate with the amount of intestine resected.[42,43] These factors might prevent patients with IBD from reaping the known benefits of exercise. Exercise may improve skeletal health and has been shown to improve bone mineral density in patients with IBD.[12] Many patients with CD have some degree of bone loss[44] and are at increased risk to develop fracture.[45] Physical activity has been shown to decrease the risk of colon cancer,[13] and this association might have implications in the IBD population already at increased risk for colon cancer. Exercise may also be beneficial for extraintestinal manifestations of IBD and related conditions such as ankylosing spondylitis. Even if exercise does not exert its effect directly on disease activity, it may improve perception of pain, decrease fatigue, and improve body composition, sleep, and quality of life.[35,39] Experts have recommended a prescription of exercise for patients with IBD that consists of walking 20 to 30 minutes at 60% of maximal heart rate 3 days per week along with resistance training for 2 to 3 times per week for its impact on bone mineral density[35]; however, this has not been tested prospectively. Our study suggests that this level of activity is not only safe but may potentially decrease the risk of active disease at 6 months. It is unknown if exercise is protective against flare or if persons who are healthier have a decreased risk of flare and increased ability to participate in exercise.

There are several strengths to this study. Individuals within the CCFA Partners cohort come from a geographically diverse area, with every US state and territory represented. Diagnoses within CCFA Partners have been validated within a subset, with 97% accuracy for the diagnosis of IBD.[20] Validated scales for exposures such as exercise and disease activity, previously used in self-report, were used in this study. The large number of participants allows for adequate power to investigate the effects of exposures, whereas taking into account confounding factors and interactions. There was a significant interaction between oral corticosteroids and physical activity in patients with CD. Participants on steroids who were in the higher-exercise category had increased risk of active disease at 6 months; however, these patients make up a small percentage of patients (4.3%) in the higher-exercise category. It is possible that despite a sCDAI ≤150, these patients were not truly in remission and differ from the remainder of the study population.

This study does have limitations. One limitation of this study is that the patients who participate in CCFA Partners likely represent a highly motivated subset of patients who might not reflect the majority of patients with IBD, impacting external generalizability. Physical activity is self-reported using the Godin leisure-time activity index, and patients could exaggerate or underestimate physical activity. With this study design, it was not possible to assess exercise activity objectively, and this is a limitation. Also, the same score on the Godin leisure-time activity index could be obtained by many different exercise regimens, introducing variability into the exposure. Although the CCFA Partners core baseline adult survey asks about surgeries within the month before survey completion, surgeries performed within the past year could impact exercise ability. We were unable to exclude such individuals, and this is a limitation of the study. Although global health status and physical activity do not measure the same thing in the general population, they were highly correlated; and therefore, we were unable to control for the effect of global health on disease activity. Another limitation of this study is that sCDAI[46] and SCCAI are subjective markers of disease activity. Despite these limitations, this is the largest study to date that examines the effect of exercise on disease of patients with IBD to date. Previously, the largest study of physical activity and IBD course included only 32 subjects[39] compared with our study, which includes nearly 1900 persons.

In conclusion, we found that higher levels of exercise at baseline were inversely associated with the presence of active disease after 6 months in patients with CD. This study highlights the need for assessment of exercise status as a potential environmental factor in disease activity. If these results were replicated, exercise could be prescribed to prolong, and possibly promote, remission in patients with IBD.

ACKNOWLEDGMENTS

Author contributions: *Study concept and design*, P. D. Jones, M. D. Long; *analysis and interpretation of results*, P. D. Jones, C. F. Martin, M. D. Long; *manuscript drafting*, P. D. Jones; *study design*, M. D. Kappelman, C. F. Martin, W. Chen; *data collection*, M. D. Kappelman, C. F. Martin, W. Chen, R. S. Sandler, M. D. Long; *interpretation of results*, M. D. Kappelman, W. Chen, R. S. Sandler; *final approval of manuscript*, M. D. Kappelman, C. F. Martin, W. Chen, R. S. Sandler, M. D. Long.

REFERENCES

1. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. *Gut*. 1990;31:1037–1040.
2. Persson PG, Leijonmarck CE, Bernell O, et al. Risk indicators for inflammatory bowel disease. *Int J Epidemiol.* 1993;22:268–272.
3. Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts. *BMJ*. 2013;347:f6633.
4. Mack DE, Wilson PM, Gilmore JC, et al. Leisure-time physical activity in Canadians living with Crohn disease and ulcerative colitis: population-based estimates. *Gastroenterol Nurs.* 2011;34:288–294.
5. Loudon CP, Corroll V, Butcher J, et al. The effects of physical exercise on patients with Crohn's disease. *Am J Gastroenterol.* 1999;94:697–703.
6. Peters HP, De Vries WR, Vanberge-Henegouwen GP, et al. Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. *Gut*. 2001;48:435–439.
7. Ploeger H, Obeid J, Nguyen T, et al. Exercise and inflammation in pediatric Crohn's disease. *Int J Sports Med.* 2012;33:671–679.
8. Hoffman-Goetz L, Spagnuolo PA, Guan J. Repeated exercise in mice alters expression of IL-10 and TNF-alpha in intestinal lymphocytes. *Brain Behav Immun.* 2008;22:195–199.
9. Saxena A, Fletcher E, Larsen B, et al. Effect of exercise on chemically-induced colitis in adiponectin deficient mice. *J Inflamm (Lond).* 2012;9:30.
10. Packer N, Hoffman-Goetz L. Exercise training reduces inflammatory mediators in the intestinal tract of healthy older adult mice. *Can J Aging.* 2012;31:161–171.
11. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*. 2014;63:1913–1920.
12. Robinson RJ, Krzywicki T, Almond L, et al. Effect of a low-impact exercise program on bone mineral density in Crohn's disease: a randomized controlled trial. *Gastroenterology*. 1998;115:36–41.
13. Friedenreich C, Norat T, Steindorf K, et al. Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev.* 2006;15:2398–2407.
14. Steed H, Walsh S, Reynolds N. A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts.* 2009;2:370–372.
15. Geerling BJ, Badart-Smook A, Stockbrugger RW, et al. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. *Am J Clin Nutr.* 1998;67:919–926.
16. Long MD, Crandall WV, Leibowitz IH, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17:2162–2168.
17. Blain A, Cattan S, Beaugerie L, et al. Crohn's disease clinical course and severity in obese patients. *Clin Nutr.* 2002;21:51–57.
18. Hass DJ, Brensinger CM, Lewis JD, et al. The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol.* 2006;4:482–488.
19. Long MD, Kappelman MD, Martin CF, et al. Development of an internet-based cohort of patients with inflammatory bowel diseases (CCFA Partners): methodology and initial results. *Inflamm Bowel Dis.* 2012;18:2099–2106.
20. Randell RL, Long MD, Cook SF, et al. Validation of an internet-based cohort of inflammatory bowel disease (CCFA partners). *Inflamm Bowel Dis.* 2014;20:541–544.
21. Thia K, Faubion WA Jr, Loftus EV Jr, et al. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. *Inflamm Bowel Dis.* 2011;17:105–111.
22. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. *Gut*. 1998;43:29–32.

23. Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol.* 2009;7:1081–1088.
24. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci.* 1985;10:141–146.
25. Godin G, Jobin J, Bouillon J. Assessment of leisure time exercise behavior by self-report: a concurrent validity study. *Can J Public Health.* 1986; 77:359–362.
26. Gionet NJ, Godin G. Self-reported exercise behavior of employees: a validity study. *J Occup Med.* 1989;31:969–973.
27. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis.* 2007;13:254–261.
28. Lesuis N, Befrits R, Nyberg F, et al. Gender and the treatment of immune-mediated chronic inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease and psoriasis: an observational study. *BMC Med.* 2012;10:82.
29. Nadell MJ, Mermelstein RJ, Hedeker D, et al. Work and non-work physical activity predict real-time smoking level and urges in young adults. *Nicotine Tob Res.* [published online ahead of print November 1, 2014]. DOI: 10.1093/ntr/ntu244.
30. Mahid SS, Minor KS, Soto RE, et al. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc.* 2006;81:1462–1471.
31. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. *Am J Gastroenterol.* 2012;107:1399–1406.
32. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359: 1541–1549.
33. Ng V, Millard W, Lebrun C, et al. Exercise and Crohn's disease: speculations on potential benefits. *Can J Gastroenterol.* 2006;20:657–660.
34. Bi L, Triadafilopoulos G. Exercise and gastrointestinal function and disease: an evidence-based review of risks and benefits. *Clin Gastroenterol Hepatol.* 2003;1:345–355.
35. Perez CA. Prescription of physical exercise in Crohn's disease. *J Crohns Colitis.* 2009;3:225–231.
36. Packer N, Hoffman-Goetz L, Ward G. Does physical activity affect quality of life, disease symptoms and immune measures in patients with inflammatory bowel disease? A systematic review. *J Sports Med Phys Fitness.* 2010;50:1–18.
37. Kasimay O, Guzel E, Gemici A, et al. Colitis-induced oxidative damage of the colon and skeletal muscle is ameliorated by regular exercise in rats: the anxiolytic role of exercise. *Exp Physiol.* 2006;91:897–906.
38. D'Inca R, Varnier M, Mestriner C, et al. Effect of moderate exercise on Crohn's disease patients in remission. *Ital J Gastroenterol Hepatol.* 1999; 31:205–210.
39. Ng V, Millard W, Lebrun C, et al. Low-intensity exercise improves quality of life in patients with Crohn's disease. *Clin J Sport Med.* 2007;17:384–388.
40. Werkstetter KJ, Ullrich J, Schatz SB, et al. Lean body mass, physical activity and quality of life in paediatric patients with inflammatory bowel disease and in healthy controls. *J Crohns Colitis.* 2012;6:665–673.
41. Ploeger HE, Takken T, Wilk B, et al. Exercise capacity in pediatric patients with inflammatory bowel disease. *J Pediatr.* 2011;158:814–819.
42. Brevinge H, Berglund B, Bosaeus I, et al. Exercise capacity in patients undergoing proctocolectomy and small bowel resection for Crohn's disease. *Br J Surg.* 1995;82:1040–1045.
43. Narula N, Fedorak RN. Exercise and inflammatory bowel disease. *Can J Gastroenterol.* 2008;22:497–504.
44. Lee N, Radford-Smith G, Taaffe DR. Bone loss in Crohn's disease: exercise as a potential countermeasure. *Inflamm Bowel Dis.* 2005;11:1108–1118.
45. Mauro M, Armstrong D. Evaluation of densitometric bone-muscle relationships in Crohn's disease. *Bone*. 2007;40:1610–1614.
46. Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology*. 2002;122:512–530.