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Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts

(Article begins on next page)

RESEARCH

Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts

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Abstract

Objective To examine the association between physical activity and risk of ulcerative colitis and Crohn's disease.

Design Prospective cohort study.

Setting Nurses' Health Study and Nurses' Health Study II.

Participants 194 711 women enrolled in the Nurses' Health Study and Nurses' Health Study II who provided data on physical activity and other risk factors every two to four years since 1984 in the Nurses' Health Study and 1989 in the Nurses' Health Study II and followed up through 2010.

Main outcome measure Incident ulcerative colitis and Crohn's disease.

Results During 3 421 972 person years of follow-up, we documented 284 cases of Crohn's disease and 363 cases of ulcerative colitis. The risk of Crohn's disease was inversely associated with physical activity (P for trend 0.02). Compared with women in the lowest fifth of physical activity, the multivariate adjusted hazard ratio of Crohn's disease among women in the highest fifth of physical activity was 0.64 (95% confidence interval 0.44 to 0.94). Active women with at least 27 metabolic equivalent task (MET) hours per week of physical activity had a 44% reduction (hazard ratio 0.56, 95% confidence interval 0.37 to 0.84) in risk of developing Crohn's disease compared with sedentary women with <3 MET h/wk. Physical activity was not associated with risk of ulcerative colitis (P for trend 0.46). The absolute risk of ulcerative colitis and Crohn's disease among women in the highest fifth of physical activity was 8 and 6 events per 100 000 person years compared with 11 and 16 events per 100 000 person years among women in the lowest fifth of physical activity, respectively. Age, smoking, body mass index, and cohort did not significantly modify the association between physical activity and risk of ulcerative colitis or Crohn's disease (all P for interaction >0.35).

Conclusion In two large prospective cohorts of US women, physical activity was inversely associated with risk of Crohn's disease but not of ulcerative colitis.

Introduction

Ulcerative colitis and Crohn's disease, collectively known as inflammatory bowel disease, are chronic inflammatory disorders of the gastrointestinal tract affecting nearly 1.4 million Americans. Inflammatory bowel disease accounts for over $6 bn in direct healthcare costs annually.[1] In addition, inflammatory bowel disease is associated with important indirect costs, loss of economic productivity, and work disability.[2,3]

Although the exact pathophysiology of Crohn's disease and ulcerative colitis remains largely unknown, findings from ecologic studies,[4] the rising incidence in inflammatory bowel disease over the past several decades,[5] and the relatively modest risk contribution from known genetic risk loci (<15%),[6] highlight the importance of the environment in the development of inflammatory bowel disease. To date, few environmental risk factors have been identified.

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Recent in vivo studies have shown that exercise may induce autophagy, a lysosomal degradation pathway known to protect against diseases such as cancer, neurogenerative disorders, infections, and inflammatory disorders.[7] In parallel, genome wide association studies have identified susceptibility loci to Crohn's disease within autophagy pathways, suggesting a possible mechanistic association between physical activity and risk of inflammatory bowel disease.

We examined the association between physical activity and risk of Crohn's disease and ulcerative colitis in two large ongoing prospective cohort studies of US women, the Nurses' Health Study and Nurses' Health Study II. With more than 20 years of biennially updated and validated data on lifestyle, diet, and medical diagnoses, these cohorts offered us the unique opportunity to examine the association between physical activity assessed at multiple time points over adulthood and subsequent risk of ulcerative colitis and Crohn's disease in the context of other potential risk factors.

Methods

Study population

The Nurses' Health Study is a prospective cohort that began in 1976 when 121 700 US female registered nurses, aged 30 to 55 years, completed a mailed health questionnaire. Follow-up questionnaires are mailed every two years to update health information. In 1989, a parallel cohort, the Nurses' Health Study II, enrolled 116 686 US female registered nurses between the ages of 25 and 42 years. These women have been followed with similar biennial questionnaires. The figure⇓ provides detailed information about the number of participants who were excluded at baseline, were eligible for analyses, and were lost to follow-up.

Assessment of physical activity

Starting 1984 in the Nurses' Health Study and 1989 in the Nurses' Health Study II, an assessment of physical activity was obtained when participants were asked about their average time per week during the preceding year spent doing any of the following activities: walking or hiking outdoors; jogging; running; bicycling; swimming laps; tennis; calisthenics, aerobics, aerobic dance, or rowing machine; squash or racquet ball; and performing other vigorous activities (for example, mowing the lawn). Participants also reported their usual outdoor walking pace: unable to walk, easy or casual (<2 mph), normal or average (2-2.9 mph), brisk (3-3.9 mph), or very brisk or striding (≥4 mph). These questions were repeated in 1988, 1992, 1996, 1998, 2000, and 2004 in the Nurses' Health Study and in 1991, 1997, 2001, and 2005 in the Nurses' Health Study II (see supplementary figure). Each activity was assigned a value for metabolic equivalent task (MET) according to established criteria.[8] Each participant's MET score for walking was assigned on the basis of her reported walking pace. We calculated the MET hours per week (MET h/wk) for each activity by multiplying the MET score by the participant's reported number of hours of physical activity per week. Total physical activity was computed as the sum of the MET hours per week from all individual activities. Vigorous activity summed the MET hours per week from all the recreational activities listed, excluding walking. All activities included as vigorous had intensity scores of 6 MET or more. To evaluate long term levels of physical activity during the follow-up, we calculated the cumulative average of MET scores for all available physical activity questionnaires prior to diagnosis of Crohn's disease or ulcerative colitis. We created four variables of updated physical activity,

updated vigorous physical activity, cumulative average physical activity, and cumulative average vigorous activity based on data from total physical activity, vigorous physical activity, and cumulative average of total and vigorous physical activity, respectively. When our detailed assessment was not included on biennial questionnaires we carried physical activity data forward from the prior questionnaire cycle (for example, 1988 data used in 1990-92 follow-up). We otherwise did not carry forward missing data. Women with missing data during a questionnaire cycle in which physical activity was assessed did not contribute person years to the analyses.

In a validation study, 151 randomly selected participants from the Nurses' Health Study II were sent questionnaires on physical activity every three months for a year shortly after they completed the baseline questionnaire.[9] The baseline characteristics of these participants, including age, body mass index, and levels of physical activity were similar to that of the entire cohort. The questionnaires contained a recall of activity in the past week to be completed on receipt and an activity diary to be completed daily for the next seven days. At the end of the year, participants were sent a second physical activity questionnaire about the previous year. The correlation for MET hours per week of moderate or vigorous activity was strong (r=0.62), suggesting that the questionnaire is reasonably valid for ranking participants. For walking, the primary activity among the participants in our analysis, the correlation was 0.70. A previous study also found moderate levels of reproducibility during a two year interval (from 1989 through 1991), with a two year test-retest correlation of 0.59.[9]

Assessment of other covariates

On each biennial questionnaire, women were also asked about pertinent lifestyle factors, including body weight, smoking status, and use of non-steroidal anti-inflammatory drugs, hormone therapy, and oral contraceptives. Participants' self report of body weight, height, and use of non-steroidal anti-inflammatory drugs and oral contraceptives have been previously validated.[10][11] In 1992 in the Nurses' Health Study and in 1991 in the Nurses' Health Study II, women were also asked their latitude of residence at age 30, which we have previously shown to be associated with risk of ulcerative colitis and Crohn's disease.[12] Information about history of appendicectomy was also collected in 1992 in the Nurses' Health Study and in 1995 in the Nurses' Health Study II.

Outcome ascertainment

We have previously detailed our methods for confirming self reported cases of Crohn's disease and ulcerative colitis.[12][13] In brief, since 1976 participants have reported diagnoses of ulcerative colitis or Crohn's disease through an open ended response on biennial surveys. In addition we have specifically queried participants about diagnoses of ulcerative colitis since 1982 and Crohn's disease since 1992. In the Nurses' Health Study II we have specifically queried participants about diagnoses of both ulcerative colitis and Crohn's disease since 1993. When a diagnosis was reported on any biennial questionnaire, two gastroenterologists blinded to exposure information requested and reviewed a supplementary questionnaire and related medical records.

We excluded participants who subsequently denied the diagnosis on the supplementary questionnaire or permission to review their records. Data were extracted on diagnostic tests, histopathology, anatomic location of disease, and disease behavior. Using standardized criteria,[14-17] the diagnosis of

ulcerative colitis was based on a typical clinical presentation at four weeks or less and an endoscopic or surgical pathological specimen consistent with ulcerative colitis (for example, evidence of chronicity). The diagnosis of Crohn's disease was based on a typical clinical history for four weeks or less and endoscopy or radiologic evaluation demonstrating small bowel findings, or surgical findings consistent with Crohn's disease combined with pathology suggesting transmural inflammation or granuloma. Disagreements were resolved through consensus. Among those women for whom we received adequate medical records, the case confirmation rate for inflammatory bowel disease was 78%.[13] Women for whom we did not confirm Crohn's disease or ulcerative colitis were included in the analyses as non-cases. After excluding all cases of Crohn's disease and ulcerative colitis at the baseline questionnaire and among women with missing information on physical activity, we included 284 incident cases of Crohn's disease and 363 incident cases of ulcerative colitis. These incidence rates are largely consistent with those reported in other US populations.[18-20]

Statistical analysis

Person time for participants was calculated from the date of return of their baseline questionnaires to the date of the diagnosis of ulcerative colitis or Crohn's disease, date of last returned questionnaire, or 1 June 2010 for the Nurses' Health Study and 1 June 2009 for the Nurses' Health Study II, whichever came first. At baseline we excluded participants with missing data on physical activity and a history of inflammatory bowel disease or cancer (with the exception of non-melanoma skin cancer). We used Cox proportional hazards modeling with an Anderson-Gill data structure for time varying covariates to adjust for other known or suspected risk factors prior to each two year interval to calculate adjusted hazard ratios and 95% confidence interval. Because weight may be influenced by preclinical disease, we adjusted for body mass index using the baseline value, consistent with prior analyses.[21] We modeled physical activity in fifths or categorically (<3, 3-<9, 9-<18, 18-<27, and ≥27 MET h/wk) consistent with prior studies.[22] Categories were chosen to correspond to the equivalent of <1, 1-<3, 3-<6, 6-<9, and ≥9 hours of walking at an average pace per week.

In separate analyses of each study we observed no heterogeneity in the association of physical activity with Crohn's disease or ulcerative colitis (P for heterogeneity >0.69 for both). Thus we pooled individual level data from each study and adjusted for cohort in all analyses. We evaluated the effect of measurement error in assessing physical activity data on risk of ulcerative colitis or Crohn's disease using a previously described risk set regression calibration method.[23] This analysis was carried out using cumulatively average updated data on physical activity with a general linear measurement error model. We also examined the association between physical activity and risk of ulcerative colitis or Crohn's disease according to stratums of age, smoking, and body mass index and evaluated these for potential interaction using cross classified categories of these risk factors and physical activity. We tested the significance of interactions by using the log likelihood ratio test comparing the model with cross classified categories with a model that included these factors as independent variables. We used SAS version 9.1.3 for these analyses. All P values were two sided and we considered values <0.05 to be statistically significant.

Results

Through 2010 we documented 284 incident cases of Crohn's disease and 363 incident cases of ulcerative colitis among 194 711 women who contributed 3 421 973 person years of follow-up. Compared with women in the lowest fifth of physical activity, women in the highest fifth were less likely to be obese (body mass index ≥30) or current smokers (table 1⇓). There were no significant differences according to age, history of appendicectomy, and use of non-steroidal anti-inflammatory drugs, oral contraceptives, or postmenopausal hormone therapy according to fifths of physical activity.

Compared with women in the lowest fifth of overall physical activity, the age adjusted risk of Crohn's disease decreased with increasing level of physical activity (table 2⇓). The risk was not significantly altered after adjusting for known and potential risk factors for Crohn's disease, including body mass index, smoking, appendicectomy, and use of oral contraceptives, non-steroidal anti-inflammatory drugs, and postmenopausal hormone therapy (P for trend 0.02). Compared with women in the lowest fifth of physical activity, the multivariate adjusted hazard ratio of Crohn's disease was 0.74 (95% confidence interval 0.52 to 1.05) for the second fifth of physical activity, 0.88 (0.63 to 1.24) for the third fifth, 0.65 (0.45 to 0.95) for the fourth fifth, and 0.64 (0.44 to 0.94) for the highest fifth.

According to prespecified categories of activity, the risk of Crohn's disease decreased with increasing levels of physical activity (P for trend 0.007). Compared with women in the lowest category of physical activity (<3 MET h/wk), the multivariate adjusted hazard ratio of Crohn's disease was 0.65 (95% confidence interval 0.44 to 0.95) among those in the 3-<9 MET h/wk category, 0.73 (0.51 to 1.06) in the 9-<18 MET h/wk category, 0.48 (0.30 to 0.75) in the 18-<27 MET h/wk category, and 0.56 (0.37 to 0.84) in the ≥27 MET h/wk category. We estimated that each 10 MET h/wk (equivalent to approximately 2.5 hours of brisk walking per week) increase in physical activity was associated with a 6% reduction in risk of Crohn's disease (hazard ratio 0.94, 95% confidence interval 0.87 to 1.00). After correcting for measurement error, we observed a larger, albeit non-statistically significant effect estimate (hazard ratio 0.83, 95% confidence interval 0.63 to 1.11).

In analyses in which we considered only the baseline report of physical activity (1986 in the Nurses' Health Study and 1989 in the Nurses' Health Study II), we observed a similar trend with lower risk of Crohn's disease (P for trend 0.03). To evaluate the effect of long term physical activity, we examined the cumulative average of physical activity data in relation to risk of Crohn's disease and observed similar associations (P for trend 0.01, table 2). Compared with women in the lowest fifth of cumulative physical activity, the multivariate adjusted hazard ratio of Crohn's disease among women in the highest fifth of cumulative physical activity was 0.68 (95% confidence interval 0.46 to 1.01).

As walking accounted for the majority of physical activity among the participants, we considered the specific effect of vigorous physical activity, consisting of jogging, running, biking, swimming, tennis, aerobics, and other vigorous exercises, on risk of Crohn's disease (table 2). Compared with women in the lowest fifth of vigorous physical activity, women in the highest fifth had a multivariate adjusted hazard ratio of 0.66 (95% confidence interval 0.43 to 1.02, P for trend 0.09). Similarly, compared with women in the lowest fifth of cumulative average of vigorous physical activity, women in the highest fifth had a multivariate adjusted hazard ratio of 0.63 (0.42 to 0.95, P for trend 0.02).

We explored the possibility that prediagnosis symptoms of Crohn's disease may have limited physical activity and therefore may account for our observed inverse association. Thus we performed lag analyses using physical activity data collected at least four years prior to each two year follow-up interval and observed similar associations. Compared with women in the lowest fifth of cumulative average of physical activity, women in the highest fifth had a multivariate adjusted hazard ratio of 0.71 (0.46 to 1.09, P for trend 0.03). Similarly, compared with women in the lowest fifth of cumulative average of vigorous physical activity, women in the highest fifth had a multivariate adjusted hazard ratio of 0.68 (0.43 to 1.06, P for trend 0.02).

In contrast to Crohn's disease, we did not observe an association between physical activity and risk of ulcerative colitis (table 3⇓). Compared with women in the lowest fifth of overall physical activity, the multivariate adjusted hazard ratio of ulcerative colitis among women in highest fifth of physical activity was 0.91 (95% confidence interval 0.65 to 1.26). We also did not observe any association between physical activity and ulcerative colitis according to prespecified categories (<3, 3 -<9, 9-< 18, 18-< 27, ≥27 MET h/wk) (P for trend 0.42). Similarly, there was no association between cumulative average of physical activity and risk of ulcerative colitis. Compared with women in the lowest fifth of physical activity, women in the highest fifth had a multivariate adjusted hazard ratio of 0.93 (95% confidence interval 0.66 to 1.30). We also did not observe an association between updated (P for trend 0.49) and cumulative average (P for trend 0.40) assessments of vigorous physical activity and risk of ulcerative colitis (table 3).

Finally, as body mass index, age, and smoking may modify the effect of physical activity on risk of Crohn's disease and ulcerative colitis, we examined associations according to stratums defined by these variables. The association of physical activity with either Crohn's disease or ulcerative colitis was not modified by age (≤40, >40), body mass index (<25, ≥25), and smoking (never, ever) (all P for interaction >0.35).

Discussion

In two large prospective cohorts of US women, physical activity was associated with a lower risk of Crohn's disease but not of ulcerative colitis. These results were consistent even after accounting for known and possible risk factors for Crohn's disease, including smoking and body mass index. We observed that women who engaged in physical activity of more than 27 metabolic equivalent task (MET) hours per week, or the equivalent of more than nine hours per week of walking at an average pace, had a 44% lower risk of developing Crohn's disease compared with women who were inactive (<3 MET h/wk). This risk relative reduction translated into a change in incidence rate of 11 cases per 100 000 person years among women in the highest category of physical acitivty to 7 cases per 100 000 person years among those in the lower category of physical activity.

Comparison with other studies

Our findings are consistent with findings from two prior case-control studies.[24][25] The first of these studies,[24] using occupation as a proxy for physical activity, described an inverse correlation between occupations involving exercise and risk of ulcerative colitis and Crohn's disease. The other study[25] used a single mailed questionnaire to obtain data on physical activity from cases and controls and observed an inverse association between regular physical activity and risk of ulcerative colitis or Crohn's disease. Because these case-control studies had

limited ascertainment of physical activity as well as other lifestyle factors, our cohort analysis, with detailed and updated information on activity and other known or putative risk factors for Crohn's disease, significantly extends these findings. Our results, however, contrast with those of the European Prospective Investigation into Cancer and Nutrition cohort, which failed to observe a relation between physical activity and risk of ulcerative colitis and Crohn's disease.[26] However, this study included only 67 cases of Crohn's disease and was unable to account for changes in physical activity and body mass index over long term follow-up.

Although our understanding of the pathogenesis of ulcerative colitis and Crohn's disease remains incomplete, the discovery of distinct genetic susceptibility loci for both diseases points to potential diverging biological pathways.[27][28] Most notably, genome-wide association studies have identified several distinct candidate genes for Crohn's disease (for example, *ATG16L1, IRGM*) primarily involved in the regulation of autophagy. Recent observations that physical activity might induce autophagy may therefore explain the unique association between physical activity and risk of Crohn's disease.[7] In addition, previous physiologic and in vitro studies suggest a role for physical activity in reducing chronic inflammation and regulating innate immunity.[29]

Strengths and limitations of this study

Our study has several notable strengths. Firstly, our prospective study design avoids the potential recall and selection biases of retrospective, case-control studies that collect data on lifestyle after diagnosis of Crohn's disease or ulcerative colitis. Secondly, we confirmed all cases of Crohn's disease and ulcerative colitis through a review of medical records, a significant advantage over studies that rely on self report or discharge codes, which may not accurately reflect true diagnoses. Thirdly, the availability of detailed and validated information on body mass index, prior oral contraceptive use, and smoking allowed us to control for several potential risk factors that may have influenced our observed associations. Fourthly, in our analysis we collected information on physical activity every two to four years and used time varying exposures in our Cox models. Thus we were able to account for changes in participants' physical activity level over time, minimizing the possibility of exposure misclassification. Lastly, our validation study[9] demonstrated that our participants self reported physical activity is relatively valid and reproducible.

We acknowledge several limitations. Firstly, our cohort may not be representative of the overall US population. However, as we have previously reported,[12] our age specific incidence of Crohn's disease and ulcerative colitis are largely similar to rates from other US populations. In addition, previous studies have shown that the prevalence of risk factors, such as smoking and body mass index, in our cohort are consistent with those of the broader population of US women.[30][31] Secondly, despite our high follow-up rate over 20 years and participants' health literacy as nurses, it is possible that some cases of ulcerative colitis and Crohn's disease were not reported. However, such misclassification of the outcome would tend to attenuate our risk estimates towards the null. Thirdly, we acknowledge that our observed association may have been influenced by measurement bias or inaccuracies arising from self reported measures of physical activity. However, we observed consistent associations between physical activity and risk of Crohn's disease and ulcerative colitis across different subgroups of body mass index and smoking. In addition, adjusting for measurement errors did not significantly alter our observed risk estimates.

Fourthly, we acknowledge that the mean age at diagnosis of inflammatory bowel disease in our cohorts is older than the age at diagnosis of inflammatory bowel disease in the general population. However, as we have previously shown,[12 13 32] the distribution of known risk factors (for example, smoking and use of oral contraceptives), anatomic location, and disease behavior among women with inflammatory bowel disease in our cohorts is similar to other population based cohorts. These findings suggest that our results will likely have relevance to the greater population of patients with inflammatory bowel disease. None the less, further studies are needed to examine the association of physical activity with the incidence of Crohn's disease with onset at younger ages. Fifthly, our study is observational and we cannot exclude the possibility of residual confounding. However, adjustment for the most important risk factors previously identified for ulcerative colitis and Crohn's disease did not appreciably alter our results. Lastly, we acknowledge that there could be significant between person heterogeneity in the calculation of energy expenditure from physical activity based on factors such as levels of fitness, body size, as well as various environmental factors such as latitude, external temperature, and humidity. These factors may affect the accuracy of MET hours per week values as a reflection of energy expenditure. However, since such biases are non-differential, it would bias our results towards the null and therefore could potentially further strengthen our observed associations.

Conclusion

In two large prospective cohorts of US women, increased physical activity was associated with a lower risk of Crohn's disease but not of ulcerative colitis. Whether these associations with disease incidence may imply a benefit of physical activity on disease activity in patients with existing Crohn's disease is unclear and merits further study. In addition, further studies on the effect of physical activity on risk and progression of Crohn's disease in the context of known genetic risk factors in autophagy and innate immunity pathways will help elucidate the mechanism underlying this association. Ultimately, this may lead to lifestyle interventions among subgroups with known genetic risk factors for Crohn's disease to modify the risk of disease or among patients with established disease to limit its progression.

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What is already known on this topic

Few studies have explored the association between physical activity and risk of Crohn's disease and ulcerative colitis

Many previous studies have limited information on physical activity and lifestyle factors that can influence or modify this association

What this study adds

Our data show that increased physical activity is associated with a lower risk of Crohn's disease but not of ulcerative colitis

Taken together with previous observations that physical activity may induce autophagy and modulate innate immunity, our findings suggest that such pathways may play a stronger role in the cause of Crohn's disease compared with ulcerative colitis

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Tables

Table 1| Baseline characteristics of participants in Nurses' Health Study and Nurses' Health Study II according to fifths of physical activity*. Values are numbers (percentages) unless stated otherwise

Characteristics	Physical activity (MET h/wk)				
	Lowest fifth (n=38 117)	2nd fifth (n=39 119)	3rd fifth (n=39 346)	4th fifth (n=39 182)	Highest fifth (n=38 947)
Mean (SD) age (years)	42.4 (10.6)	42.3 (10.8)	42.2 (10.9)	42.2 (11.0)	41.8 (11.3)
Geographical latitude at age 30:					
Southern	5811 (15.2)	5335 (13.6)	5606 (14.3)	5466 (14.0)	5358 (13.8)
Middle	14 913 (39.1)	15 831 (40.5)	15 823 (40.2)	15 587 (39.8)	14 773 (37.9)
Northern	10 318 (27.1)	11 217 (28.7)	11 313 (28.8)	11 600 (29.6)	11 456 (29.4)
Foreign/unknown	7075 (18.6)	6736 (17.2)	6604 (16.8)	6529 (16.7)	7360 (18.9)
Baseline body mass index:					
<20	4198 (11.0)	4282 (11.0)	4443 (11.3)	4808 (12.3)	5926 (15.2)
20-24.9	17 123 (44.9)	19 107 (48.8)	20 644 (52.5)	21 794 (55.6)	22 302 (57.3)
25-29.9	9567 (25.1)	9827 (25.1)	9513 (24.2)	8896 (22.7)	7685 (19.7)
≥30	7229 (19.0)	5903 (15.1)	4746 (12.0)	3684 (9.4)	3034 (7.8)
Smoking:					
Never	20 821 (54.6)	22 219 (56.8)	22 602 (57.4)	22 432 (57.2)	21 809 (56.0)
Former	9368 (24.6)	9762 (25.0)	10 640 (27.1)	11 195 (28.6)	11 527 (29.6)
Current	7928 (20.8)	7138 (18.3)	6104 (15.5)	5555 (14.2)	5615 (14.4)
Regular use of ≥2 tablets/wk NSAIDs	4994 (13.1)	5028 (12.9)	4904 (12.5)	4977 (12.7)	4968 (12.8)
Ever use of oral contraceptives	25 976 (68.2)	26 610 (68.0)	26 932 (68.5)	26 852 (68.5)	26 535 (68.1)
Postmenopause	11 513 (30.2)	11 787 (30.1)	11 905 (30.3)	11 888 (30.3)	11 882 (30.5)
Postmenopausal hormone use†:					
Never	6126 (53.2)	6129 (52.0)	5918 (49.7)	5781 (48.6)	5885 (49.5)
Former	2494 (21.7)	2534 (21.5)	2571 (21.6)	2624 (22.1)	2461 (20.7)
Current	2893 (25.1)	3124 (26.5)	3416 (28.7)	3483 (29.3)	3536 (29.8)
History of appendicectomy	6716 (17.6)	6906 (17.7)	6999 (17.8)	6879 (17.6)	6627 (17.0)

MET h/wk=metabolic equivalent task hours per week.

*Values are standardized to age distribution of study population. All variables are derived from baseline questionnaires (1986 in Nurses Health Study and 1989 in Nurses Health Study II) with exception of geographic location (1992 and 1993, respectively), oral contraceptive use (1984 and baseline, respectively), and appendicectomy (baseline and 1995, respectively).

†Percentages among postmenopausal women.

Table 2| **Physical activity and risk of Crohn's disease in Nurses' Health Study and Nurses' Health Study II (1984-2010)**

Variables	Physical activity fifth					P for trend
	Lowest	2nd	3rd	4th	Highest	
Updated physical activity*:						
Median (SD) MET h/wk	1.0 (1.0)	5.1 (1.8)	11.2 (2.9)	21.5 (5.0)	45.2 (33.2)	
No of cases	72	54	63	48	47	
Person years	667 291	684 398	689 222	692 548	688 514	
Age adjusted (95% CI)	1.00	0.71 (0.50 to 1.02)	0.83 (0.59 to 1.17)	0.61 (0.42 to 0.88)	0.60 (0.42 to 0.87)	0.005
Multivariable adjusted (95% CI)†	1.00	0.74 (0.52 to 1.05)	0.88 (0.63 to 1.24)	0.65 (0.45 to 0.95)	0.64 (0.44 to 0.94)	0.02
Cumulative average physical activity (MET h/wk):						
Median (SD) MET h/wk	2.6 (1.5)	7.2 (2.1)	13.0 (3.1)	21.6 (5.0)	41.4 (29.9)	
No of cases	59	66	63	50	46	
Person years	601 262	694 609	720 478	724 306	681 317	
Age adjusted (95% CI)	1.00	0.95 (0.67 to 1.35)	0.88 (0.62 to 1.25)	0.67 (0.46 to 0.98)	0.65 (0.44 to 0.95)	0.005
Multivariable adjusted (95% CI)†	1.00	0.98 (0.69 to 1.40)	0.92 (0.64 to 1.32)	0.71 (0.47 to 1.03)	0.68 (0.46 to 1.01)	0.01
Updated vigorous physical activity‡ (MET h/wk):						
Median (SD) MET h/wk	0 (0.02)	0.5 (1.0)	4.5 (2.4)	8.8 (5.1)	28.5 (29.8)	
No of cases	54	78	52	58	42	
Person years	560 547	942 886	532 859	702 710	682 970	
Age adjusted (95% CI)	1.00	0.92 (0.61 to 1.40)	1.01 (0.68 to 1.50)	0.90 (0.61 to 1.33)	0.64 (0.42 to 0.98)	0.05
Multivariable adjusted (95% CI)†	1.00	0.92 (0.61 to 1.40)	1.04 (0.70 to 1.53)	0.92 (0.62 to 1.37)	0.66 (0.43 to 1.02)	0.09
Cumulative average vigorous physical activity (MET h/wk):						
Median (SD) MET h/wk	0 (1.0)	0.5 (2.7)	3.7 (5.2)	7.4 (8.9)	21.0 (30.8)	
No of cases	53	69	67	49	46	
Person years	517 491	829 798	668 005	725 927	680 753	
Age adjusted (95% CI)	1.00	0.84 (0.58 to 1.22)	0.95 (0.66 to 1.36)	0.66 (0.44 to 0.98)	0.63 (0.42 to 0.94)	0.01
Multivariable adjusted (95% CI)†	1.00	0.84 (0.57 to 1.21)	0.96 (0.66 to 1.38)	0.67 (0.45 to 0.99)	0.65 (0.42 to 0.97)	0.02

MET h/wk=metabolic equivalent task hours per week.

*Mean of physical activity over follow-up.

†Models adjusted for age (months), smoking (never, former, current), body mass index at baseline (<20, 20-24.9, 25-29.9, ≥30), oral contraceptive use (never, former, current), hormone therapy (never, former, current, premenopause), appendicectomy (no, yes), geographic latitude of residence at age 30 (southern, middle, northern, missing/unknown), cohort (National Nurses' study, National Nurses' Study II), and non-steroid anti-inflammatory drug use (<2 tablets/week, ≥2 tablets/week).

‡Defined as jogging, running, biking, swimming, tennis, aerobics, and other vigorous exercises.

Table 3| Physical activity and risk of ulcerative colitis in Nurses' Health Study and Nurses' Health Study II (1984-2010)

| Variables	Physical activity fifth					P for trend
	Lowest	2nd	3rd	4th	Highest	
Updated physical activity* (MET h/wk):						
Median (SD) MET h/wk	1.0 (1.0)	5.1 (1.8)	11.2 (2.9)	21.5 (5.0)	45.2 (33.2)	
No of cases	74	67	85	63	74	
Person years	667 291	684 398	689 222	692 548	688 514	
Age adjusted (95% CI)	1.00	0.88 (0.63 to 1.23)	1.10 (0.80 to 1.51)	0.82 (0.58 to 1.15)	0.96 (0.70 to 1.33)	0.70
Multivariable adjusted (95% CI)†	1.00	0.87 (0.62 to 1.21)	1.06 (0.78 to 1.46)	0.78 (0.56 to 1.10)	0.91 (0.65 to 1.26)	0.46
Cumulative average physical activity (MET h/wk):						
Median (SD) MET h/wk	2.6 (1.5)	7.2 (2.1)	13.0 (3.1)	21.6 (5.0)	41.4 (29.9)	
No of cases	67	72	80	71	73	
Person years	601 262	694 609	720 478	724 306	681 317	
Age adjusted (95% CI)	1.00	0.94 (0.68 to 1.32)	1.02 (0.73 to 1.41)	0.89 (0.64 to 1.25)	0.99 (0.71 to 1.38)	0.83
Multivariable adjusted (95% CI)†	1.00	0.92 (0.66 to 1.29)	0.98 (0.71 to 1.36)	0.85 (0.61 to 1.20)	0.93 (0.66 to 1.30)	0.56
Updated vigorous physical activity‡ (MET h/wk):						
Median (SD) MET h/wk	0 (0.02)	0.5 (1.0)	4.5 (2.4)	8.8 (5.1)	28.5 (29.8)	
No of cases	68	90	59	79	67	
Person years	560 547	942 886	532 859	702 710	682 970	
Age adjusted (95% CI)	1.00	0.99 (0.69 to 1.42)	0.90 (0.63 to 1.29)	1.01 (0.74 to 1.44)	0.90 (0.64 to 1.28)	0.64
Multivariable adjusted (95% CI)†	1.00	0.99 (0.69 to 1.42)	0.90 (0.63 to 1.29)	1.01 (0.72 to 1.41)	0.87 (0.61 to 1.23)	0.49
Cumulative average vigorous physical activity (MET h/wk):						
Median (SD) MET h/wk	0 (1.0)	0.5 (2.7)	3.7 (5.2)	7.4 (8.9)	21.0 (30.8)	
No of cases	68	71	86	66	72	
Person years	517 491	829 798	668 005	725 927	680 753	
Age adjusted (95% CI)	1.00	0.75 (0.53 to 1.05)	1.04 (0.76 to 1.44)	0.76 (0.54 to 1.07)	0.88 (0.63 to 1.22)	0.57
Multivariable adjusted (95% CI)†	1.00	0.74 (0.52 to 1.04)	1.02 (0.74 to 1.41)	0.73 (0.52 to 1.03)	0.84 (0.60 to 1.18)	0.40

MET h/wk=metabolic equivalent task hours per week.

*Mean of physical activity over follow-up.

†Models adjusted for age (months), smoking (never, former, current), body mass index at baseline (<20, 20-24.9, 25-29.9, ≥30), oral contraceptive use (never, former, current), hormone therapy (never, former, current, premenopause), appendicectomy (no, yes), geographic latitude of residence at age 30 (southern, middle, northern, missing/unknown), cohort (National Nurses' study, National Nurses' Study II), and non-steroid anti-inflammatory drug use (<2 tablets/week, ≥2 tablets/week).

‡Defined as jogging, running, biking, swimming, tennis, aerobics, and other vigorous exercises.

Figure
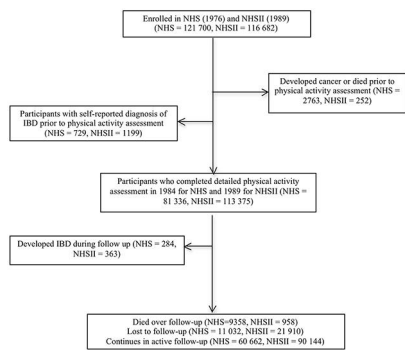
Flow of eligible participants in study. NHS=Nurses' Health Study; NHSII=Nurses' Health Study II; IBD=inflammatory bowel disease