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Physical Fitness in Adolescence and Subsequent Inflammatory Bowel Disease Risk

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OBJECTIVES: Physical fitness may reduce systemic inflammation levels relevant to the risk of symptomatic Crohn's disease (CD) and ulcerative colitis (UC); we assessed if fitness in adolescence is associated with subsequent inflammatory bowel disease (IBD) risk, independent of markers of risk and prodromal disease activity.
METHODS: Swedish registers provided information on a cohort of 240,984 men (after exclusions) who underwent military conscription assessments in late adolescence (1969–1976). Follow-up started at least 4 years after the conscription assessment until 31 December 2009 (up to age 57 years). Cox's regression assessed the association of physical fitness with CD ($n = 986$) and UC ($n = 1,878$) in separate models, with adjustment including: socioeconomic conditions in childhood; physical fitness, height, body mass index, and erythrocyte sedimentation rate (ESR) in adolescence; and subsequent diagnoses of IBD.
RESULTS: Low fitness was associated with a raised risk of IBD, with unadjusted hazard ratios (and 95% confidence intervals) of 1.62 (1.31–2.00) for CD and 1.36 (1.17–1.59) for UC. The results were attenuated by adjustment, particularly for markers of prodromal disease activity to 1.32 (1.05–1.66) and 1.25 (1.06–1.48), respectively. Raised ESR in adolescence was associated with increased risks for subsequent CD (5.95 (4.47–7.92)) and UC (1.92 (1.46–2.52)).
CONCLUSIONS: The inverse association of physical fitness with IBD risk is consistent with a protective role for exercise. However, evidence of disease activity before diagnosis was already present in adolescence, suggesting that some or all of the association between fitness and IBD may be due to prodromal disease activity reducing exercise capacity and therefore fitness.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBDs) with an incompletely understood etiology,[1–3] but there is an interaction between genetic and environmental factors resulting in an atypical immune response to gut microbiota.[1–3]

Some environmental factors have been reported as risks for IBD. Smoking has been found consistently to represent a raised risk for CD[4–6] and has an inverse association with UC.[5] Other factors that have been associated with IBD include early influences on early life bowel colonization.[5,6] Human studies have indicated that there is an association between physical activity and IBD risk,[6–8] possibly because better physical fitness is associated with a systemic reduction in inflammation,[9,10] and therefore better fitness may reduce the risk of symptomatic IBD onset.[11]

Recently reported results from The Nurses' Health Study[7] showed an inverse association between physical activity with a subsequent diagnosis of CD but not UC. This cohort was limited to women, and physical activity was self-reported on questionnaires in adulthood when the women were aged 30 to 55 years. Our study is complementary as we investigated a general population-based cohort of men using register data in Sweden including a prospectively recorded measure of physical fitness in adolescence. The markers of fitness and potential prodromal disease activity were recorded in late adolescence before typical onset age for IBD, which peaks between ages 20 and 30 years for CD and 30 and 40 years for UC.[12] Subsequent IBD risk was assessed up to age 57 years.

METHODS

Study population. The study population is of males born between 1952 and 1956, assessed for compulsory military conscription in Sweden during 1969–1976. The majority of the men were 18–19 years of age at the conscription assessment, and a small proportion of them were older. The follow-up period for CD and UC began at least 4 years after the conscription assessment date and continued to 31 December 2009 (to a maximum age of 57 years) and men with an IBD diagnosis before follow-up were excluded. All data were obtained from National Swedish Registers.

A total of 284,257 males were identified and exclusions were made for the following reasons: errors in the personal identification number, uncertain vital status or female sex (as conscription was limited almost exclusively to men at this time) or if emigration or death occurred before the conscription

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assessment or follow-up. Also excluded were individuals with missing data for variables used in the analysis. In total, 43,273 (15.2% of the original population) males were excluded, of which 12,022 (4.2%) men did not attend the conscription assessment, and 25,478 (9.4%) men attended but could not proceed to military training owing to medical conditions. Study participants were therefore ostensibly healthy males as would be expected for military training. Participants who had an IBD diagnosis or other disease of the digestive system before the study period as identified by a medical review and examination at the conscription assessment were also excluded. After exclusions, the remaining study population consisted of 240,984 men.

Data sources and measures

Socioeconomic and demographic data. Socioeconomic characteristics of parents during childhood of the cohort members came from the population and housing census in 1960 held by the governmental organization Statistics Sweden (http://www.scb.se/sv_/Vara-tjanster/SCBs-data-for-forskning/SCBs-datalager/).

Occupation of the head of household was characterised as manual workers, agricultural workers, farm owner/managers, office workers, and business owners/managers and other. The Total Population Register provided data on date of birth, sex, region of residence, vital status, and migration.

The Swedish Military Service Conscription Register. Data on health and development measures in adolescence used for this study came largely from the Swedish Military Conscription Register. During the time relevant to this study, military service was compulsory for all men and exemptions were only granted in cases of documented disability, severe medical condition, or foreign citizenship.[13]

Physical fitness. Eligible men underwent a physical working capacity test using a bicycle ergometer. The men performed a maximal test with high constant load until exhaustion. Starting loads depended on physical statue, history of physical activity, and medical history. The test has been shown to have good reliability.[13] A submaximal test was performed for men unable to perform the standard maximal tests owing to medical conditions. For those unable to participate in the physical fitness assessment at all (due to current infectious disease or other causes), physical fitness was estimated according to physical statue, history of physical activity, and medical history.[13] Values from the physical fitness test were transformed into scores, ranging from 0 (lowest) to 9 (highest performance). We grouped these scores into fifths of their distribution.

Height and body mass index. Height was grouped into fifths of its distribution. Height and weight were used to calculate body mass index (BMI). Implausible values for height, weight, and BMI were excluded: height < 144 cm, weight > 178 kg, and BMI < 15 kg/m^2. We grouped BMI into three categories: underweight (15–18.49), normal weight (18.50–24.99), and overweight/obese (25–60). There were few obese men at the conscription assessment; therefore, they were combined with the overweight category ($\geq$ BMI 25 kg/m^2).

Erythrocyte sedimentation rate. Blood samples were collected at the conscription assessment and analyzed for erythrocyte sedimentation rate (ESR) as a marker of inflammation. ESR was assessed using the Westergren method and is defined as the distance that a column of anticoagulated blood falls for 1 h.[14] ESR was standardized for erythrocyte volume fraction (EVF) by adjustment.[14,15] EVF < 0.20 or > 0.75 and ESR < 1 or > 98 mm/h were treated as non-valid values.[14] ESR was grouped into five categories: 1, 2–6, 7–10, 11–14, and $\geq$15 mm/h.

Gastrointestinal diseases at conscription assessment. Individuals with gastrointestinal diagnoses (except for appendicitis) at the conscription assessment were excluded. The diagnoses were identified by medical examination and record review using codes from the International Classification of Diseases (ICD) revision 8 (ICD-8 codes 530–539, 543, 555–558, and 560–577). Appendicitis before age 20 years was identified through record review (ICD-8 codes 540–542).

Geographical regions. The counties were grouped into three regions, northern, central, and southern.

The National Patient Register. IBD diagnoses were identified through the National Patient Register (http://www.socialstyr-elsen.se/register/halsodataregister/patientregistret). The register is held by The National Board of Health and Welfare, which has been collecting information on in-patient diagnoses since 1964. The register coverage expanded to include all in-patient care in Sweden by 1987, and since 2001, the register also contains information on outpatient visits.[16]

IBD diagnoses. CD and UC diagnoses were coded using ICD, versions 8, 9, or 10. The diagnostics code for CD are: 563.00 for ICD-8, 555.x for ICD-9, and ICD-10 K50.x; and for UC are: 563.10 for ICD-8, 556.x for ICD-9, and ICD-10 K51.x. The study used both primary and secondary diagnoses among both in- and outpatients. A total of 438 of those with IBD had diagnoses of both CD and UC recorded in the Patient Register. The most recent diagnosis was used to define their disease, where more than one IBD phenotype was recorded.[17]

Other gastrointestinal diseases. Individuals with other gastrointestinal diagnoses recorded in the Patient Register before follow-up were also excluded (except appendicitis). The diagnoses were identified by ICD-8 diagnostic codes (530–539, 543, 555–558, and 560–577). Appendectomy due to appendicitis before age 20 years was identified through diagnostic codes (ICD-8 codes 540–542) and surgical procedure codes (4510 and 4511). The measure of appendectomy and appendicitis before age 20 years from the Patient Register was combined into a single variable with the measure from the Conscription Register.

COPD diagnoses. The National Patient Register was used to identify chronic obstructive pulmonary disease (COPD) diagnoses (as marker of smoking behavior in adulthood) coded using ICD, versions 8, 9 or 10. The diagnostic codes for COPD were as follows: 490–492 for ICD-8 and ICD-9; 494 and 496 for ICD-9; and J40–44 and J47 for ICD-10. The study used both primary and secondary diagnoses among both in- and outpatients.

Statistical analysis. Cox regression was used to evaluate the association between physical fitness in adolescence and the risk of subsequent CD and UC in adulthood. The follow-up for both CD and UC began at least 4 years after the conscription assessment date until first recorded CD or UC diagnosis, death, emigration, or study end on 31 December 2009 (to a maximum of age 57 years), whichever occurred first. Separate models were used for CD and UC. The

proportional hazards assumption was tested graphically and no evidence of violation was found.

The unadjusted associations were calculated and then the models were adjusted for socioeconomic and demographic factors, as well as a marker of IBD risk, in childhood and adolescence (comprising appendicitis before age 20 years, parental socioeconomic index (SEI), region of residence, and year of birth), and for markers of potential prodromal disease activity in adolescence (ESR, EVF, height, and BMI). All measures were modeled as categorical variables.

Sensitivity analyses. We conducted an analysis excluding individuals most likely to have the most severe (undiagnosed) disease activity in adolescence, defined as low EVF ($\leq$39) or elevated ESR ($\geq$15). We performed a second set of analyses with follow-up beginning from 15 years after the conscription assessment date, and excluded those with a diagnosis of IBD during this 15-year period, to ensure diagnostic accuracy, which increased at the end of the 1970s and to assess whether physical fitness in adolescence is associated with a first IBD diagnosis so many years later. We additionally investigated the possibility of selection and surveillance bias in the study population through analysis limited to men with a primary diagnosis of IBD and excluding people with estimated rather than measured physical fitness tests scores.

Owing to the lack of information on smoking, we evaluated if longer duration and heavier smoking is associated with poorer physical fitness in adolescence by examining associations with subsequent diagnoses of COPD.

All analyses were conducted using SPSS software version 22. *P*-values <0.05 and 95% confidence intervals (CIs) not including 1.00 were considered statistically significant.

Ethical permission. Uppsala Regional Ethics Committee (Dnr 2014/324) approved for this project.

RESULTS

Participant characteristics. The study participants comprised 240,984 men, followed from at least 4 years after the conscription assessment in adolescence to a maximum of age 57 years. Median follow-up time beginning from 4 years after the assessment was 32.73 (range 0.01–36.29) years for both CD and UC. During the follow-up period, 986 diagnoses of CD and 1,878 of UC were identified as presented in Table 1.

Men with CD were less likely to be physically fit, tended to have lower BMI and higher inflammation levels in adolescence, compared with men without IBD. Similar associations were seen for UC, although of lower magnitude. Men with UC were less likely to have had appendicitis before age 20 years.

Physical fitness in adolescence and subsequent CD risk in adulthood at least 4 years after the conscription assessment. The unadjusted results show that lower physical fitness is associated with an increased risk of CD (Table 2). Men in the lowest fitness category have the highest hazard ratio (HR) (and 95% CIs) of 1.62 (1.31–2.00), compared with those in the highest fitness category.

Adjustment for appendicitis before age 20 years, socioeconomic and demographic factors in childhood and

Table 1 Baseline characteristics of study participants by IBD diagnosis

	No IBD, *N* = 238,120	CD, *N* = 986	UC, *N* = 1,878
	N (%)	*N* (%)	*N* (%)
Physical fitness			
Lowest fifth	38,539 (16.2)	210 (21.3)	349 (18.6)
2nd fifth	49,589 (20.8)	218 (22.1)	436 (23.2)
3rd fifth	43,107 (18.1)	193 (19.6)	355 (18.9)
4th fifth	63,190 (26.5)	219 (22.2)	450 (24.0)
Highest fifth	43,695 (18.3)	146 (14.8)	288 (15.3)
BMI			
Underweight	27,610 (11.6)	152 (15.4)	240 (12.8)
Normal weight	192,800 (81.0)	771 (78.2)	1,530 (81.5)
Overweight/obese	17,710 (7.4)	63 (6.4)	108 (5.8)
ESR in adolescence			
ESR 1 mm/h	56,553 (23.7)	185 (18.8)	432 (23.0)
ESR 2–6 mm/h	157,234 (66.0)	579 (58.7)	1,178 (62.7)
ESR 7–10 mm/h	15,580 (6.5)	100 (10.1)	150 (8.0)
ESR 11–14 mm/h	4,709 (2.0)	48 (4.9)	56 (3.0)
ESR $\geq$ 15 mm/h	4,044 (1.7)	74 (7.5)	62 (3.3)
Height			
Lowest fifth	49,876 (20.9)	238 (24.1)	451 (24.0)
2nd fifth	38,159 (16.0)	176 (17.8)	318 (16.9)
3rd fifth	58,319 (24.5)	225 (22.8)	451 (24.0)
4th fifth	48,326 (20.3)	179 (18.2)	356 (19.0)
Highest fifth	43,440 (18.2)	168 (17.0)	302 (16.1)
Parental SEI in 1960			
Manual worker	97,030 (40.7)	440 (44.6)	797 (42.4)
Agricultural workers	9,083 (3.8)	54 (5.5)	66 (3.5)
Farm owner/managers	23,492 (9.9)	67 (6.8)	177 (9.4)
Office workers	65,848 (27.7)	245 (24.8)	492 (26.2)
Business owners/ managers	25,401 (10.7)	104 (10.5)	187 (10.0)
Others (unknown)	17,266 (7.3)	76 (7.7)	159 (8.5)
Appendicitis < 20 years			
No	236,192 (99.2)	981 (99.5)	1,875 (99.8)
Yes	1,928 (0.8)	5 (0.5)	3 (0.2)

BMI, body mass index; CD, Crohn's disease; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; N, number; SEI, socioeconomic index; UC, ulcerative colitis.

adolescence, as well as markers of potential prodromal disease activity, led to attenuation of the estimates. The attenuation was due largely to adjustment for markers of potential prodromal disease activity in adolescence. Individuals with the poorest physical fitness in adolescence remained at a statistically significantly higher risk of being diagnosed with CD in adulthood with an HR of 1.32 (1.05–1.66), in comparison with men with highest fitness. Low BMI and systemic inflammation (measured by ESR) in adolescence were associated with a graded increase in CD risk. Elevated ESR ($\geq$15) in adolescence produces an HR of 5.95 (4.47–7.92) for its association with CD. There was modest association between low parental SEI in childhood and raised CD risk in adulthood.

Sensitivity analysis: physical fitness in adolescence and subsequent CD risk in adulthood at least 4 years after the conscription assessment, excluding those with elevated ESR or low EVF. A total of 910 CD diagnoses were identified after excluding those who had high ESR ($\geq$15) or low EVF ($\leq$39) in adolescence. The results were consistent

Table 2 Physical fitness in adolescence and subsequent Crohn's disease risk in adulthood at least 4 years after the conscription assessment

Characteristics	Events/N	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Physical fitness			
Lowest fifth	210/39,099	1.62 (1.31–2.00)	1.32 (1.05–1.66)
2nd fifth	218/50,244	1.30 (1.05–1.60)	1.15 (0.92–1.42)
3rd fifth	193/43,658	1.33 (1.07–1.64)	1.19 (0.96–1.49)
4th fifth	219/63,860	1.03 (0.84–1.27)	0.98 (0.80–1.21)
Highest fifth	146/44,129	Reference	Reference
BMI			
Underweight	170/28,003	1.36 (1.14–1.62)	1.21 (1.01–1.46)
Normal weight	830/195,106	Reference	Reference
Overweight/obese	65/17,881	0.90 (0.69–1.16)	0.86 (0.66–1.11)
ESR in adolescence			
ESR 1 mm/h	185/57,170	Reference	Reference
ESR 2–6 mm/h	579/158,998	1.21 (1.01–1.44)	1.22 (1.03–1.46)
ESR 7–10 mm/h	100/15,828	2.13 (1.65–2.76)	2.16 (1.67–2.79)
ESR 11–14 mm/h	48/4,813	3.36 (2.42–4.67)	3.37 (2.43–4.69)
ESR $\geq$ 15 mm/h	74/4,181	6.03 (4.54–8.02)	5.95 (4.47–7.92)
Height			
Lowest fifth	257/50,564	1.22 (1.00–1.49)	1.11 (0.91–1.37)
2nd fifth	195/38,657	1.18 (0.96–1.46)	1.11 (0.90–1.37)
3rd fifth	241/58,996	0.99 (0.81–1.21)	0.96 (0.79–1.17)
4th fifth	192/48,862	0.95 (0.77–1.18)	0.94 (0.76–1.16)
Highest fifth	180/43,911	Reference	Reference
Parental SEI in 1960			
Manual worker	440/98,268	1.19 (1.02–1.40)	1.17 (1.00–1.37)
Agricultural workers	54/9,203	1.55 (1.16–2.08)	1.54 (1.14–2.07)
Farm owner/managers	67/23,738	0.74 (0.56–0.97)	0.76 (0.58–0.99)
Office workers	245/66,587	Reference	Reference
Business owners/managers	104/25,693	1.09 (0.87–1.37)	1.10 (0.87–1.38)
Others (unknown)	76/17,501	1.19 (0.92–1.54)	1.16 (0.90–1.51)
Appendicitis < 20 years			
No	981/239,054	Reference	Reference
Yes	5/1,936	0.65 (0.27–1.56)	0.61 (0.25–1.48)

BMI, body mass index; CI, confidence interval; ESR, erythrocyte sedimentation rate; EVF, erythrocyte volume fraction; HR, hazard ratio; N, number; SEI, socioeconomic index.
Adjusted* for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20 years, region of residence, and year of birth.

Table 3 Physical fitness in adolescence and subsequent Crohn's disease risk at least 15 years after the conscription assessment

Characteristics	Events/N	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Physical fitness			
Lowest fifth	150/38,078	1.53 (1.20–1.96)	1.31 (1.00–1.70)
2nd fifth	151/48,961	1.19 (0.93–1.52)	1.09 (0.84–1.40)
3rd fifth	140/42,527	1.27 (0.99–1.64)	1.19 (0.92–1.53)
4th fifth	169/62,245	1.05 (0.83–1.34)	1.03 (0.81–1.32)
Highest fifth	110/42,849	Reference	Reference

BMI, body mass index; CI, confidence interval; ESR, erythrocyte sedimentation rate; EVF, erythrocyte volume fraction; HR, hazard ratio; N, number; SEI, socioeconomic index.
Adjusted* for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20 years, region of residence, and year of birth.

with main analysis. Lowest physical fitness was associated with a higher CD risk compared with high fitness, producing an adjusted HR of 1.38 (1.09–1.75).

Sensitivity analysis: physical fitness in adolescence and subsequent CD risk at least 15 years after the conscription assessment. Later study entry with a time lag of at least 15 years after the conscription date identified 724 CD diagnoses. The results were consistent with main analysis.

Compared with highest physical fitness, the unadjusted and adjusted HR are 1.53 (1.20–1.96) and 1.31 (1.00–1.70), respectively, for those with lowest compared with highest fitness (Table 3).

Sensitivity analysis: CD as primary diagnosis at least 4 years after the conscription assessment. This analysis considered only primary diagnoses and identified 773 CD diagnoses after excluding those who had an estimated

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physical fitness test score at conscription. The results were consistent with main analysis. Compared with highest physical fitness, the unadjusted and adjusted HR are 1.62 (1.29–2.04) and 1.29 (1.01–1.66), respectively, for those with lowest compared with highest fitness.

Physical fitness in adolescence and subsequent UC risk in adulthood at least 4 years after the conscription assessment. The results indicate a dose-dependent association where lower physical fitness is associated with an increased risk of UC (Table 4). Individuals with the poorest fitness had an increased risk of UC, compared with those with highest physical fitness producing an adjusted HR of 1.25 (1.06–1.48). Raised systemic inflammation (ESR) in adolescence produced an adjusted HR of 1.92 (1.46–2.52) and shorter stature in adolescence was associated with an increased risk of UC in adulthood. Being overweight/obese in adolescence was associated with a lower risk of UC. There is an association of modest magnitude between low parental SEI in childhood and raised UC risk in adulthood. Also, appendicitis before age 20 years is statistically significantly inversely associated with UC risk.

Sensitivity analysis: physical fitness in adolescence and subsequent UC disease risk in adulthood at least 4 years after the conscription assessment, excluding those with elevated ESR or low EVF. A total of 1,814 UC diagnoses were identified after excluding those who had low EVF ($\leq$39) or high ESR ($\geq$15) at the conscription assessment. The results were similar to main analysis. Lower physical fitness was associated with UC risk in comparison with high fitness, with an adjusted HR of 1.24 (1.05–1.47).

Sensitivity analysis: physical fitness in adolescence and subsequent UC at least 15 years after the conscription assessment. With a time lag of at least 15 years after the conscription assessment date, 1,571 UC diagnoses were identified. The magnitudes of associations were similar to main analysis (Table 5). Lower physical fitness was associated with a raised risk of UC before and after adjustment, with HRs of 1.37 (1.15–1.63) and 1.25 (1.04–1.51), respectively, for the lowest fitness group compared with the highest.

Sensitivity analysis: ulcerative colitis as primary diagnosis at least 4 years after the conscription assessment. In this analysis, only primary diagnoses were considered. A total of 1,551 primary UC diagnoses were identified after excluding everyone who had an estimated physical fitness test score at conscription. The results were similar to the main analysis. Lower physical fitness was associated with a raised risk of UC with HR before and after adjustment of 1.43 (1.21–1.69) and 1.32 (1.10–1.58), respectively, in the lowest compared with highest fitness groups.

Physical fitness in adolescence and subsequent COPD. A total of 1,881 participants had a COPD diagnosis and there was an association between physical fitness in adolescence and COPD risk in adulthood. Among the individuals with lowest physical fitness, 1.2% had COPD, whereas 0.9%, 0.8%, 0.7%, and 0.4%, had COPD in the progressively higher fitness groups. Compared with highest fitness group, the risk for COPD associated with the lowest fitness group has hazard ratios (and 95% CIs) of 2.95 (2.49–3.50) before adjustment 2.76 (2.30–3.31) after adjustment.

DISCUSSION

The study assessed the association of physical fitness in adolescence with subsequent CD and UC risk in adulthood. Low physical fitness in adolescence was associated with a raised risk of both CD and UC. Adjustment for parental SEI and appendicitis before age 20 years, as well as markers of potential prodromal disease activity (systemic inflammation indicated by ESR, height, and BMI), led to attenuation of the estimates. The attenuation was due largely to adjustment for markers of potential prodromal disease activity in adolescence.

The etiology of IBD is believed to involve both genetic and environmental factors.[1–3] The pathology is thought to result from an inappropriate inflammatory response to gut microbiota, rather than the normal homeostasis that exists between host and colonizing organisms.[1–3] Physical fitness may reduce inflammation levels,[9,10] and animal studies suggest that exercise can protect the bowel by reducing inflammatory cytokine and apoptotic protein expression.[9] Exercise has also been found to decrease local proinflammatory responses in mice recovering from chemically induced acute inflammation in a mouse model of UC,[10] and therefore if inflammation is downregulated, the risk of symptomatic IBD may be reduced. Poor physical fitness is unlikely to be the cause of IBD, but as there is evidence of long-term subclinical disease activity consistent with an IBD diagnosis,[18] high levels of physical fitness may theoretically reduce inflammation risk sufficiently to prevent or delay the transition to frank symptomatic disease. Exercise has been confirmed to reduce circulating levels of cytokines in older people.[19] Apart from reducing inflammatory cytokine levels, exercise can induce autophagy.[11] Genetic variants coding for proteins involved in autophagy have been associated with IBD and CD in particular (e.g. ATG16L1).[20] Interestingly, a genetic variant strongly associated with CD (NOD2) has been associated with autophagy function.[20] All these findings may help to explain associations of physical activity and physical fitness with IBD.

A recent study of nurses reported an association of physical activity with CD but not UC.[7] Our results show an association with both CD and UC, although the association with UC is of lower magnitude than for CD. Other studies have also found an association of fitness with CD and UC risk,[6,8] but some have not.[4,5] Our study is complementary to the results from the Nurses' cohort[7] as we examined men, whereas the earlier research was among women. Our study also has some complementary methodological aspects. We used a physical fitness test in adolescence, whereas many of the earlier studies used self-reported measures of fitness or exercise,[4–8] which can result in significant misclassification.[21] Another potential advantage is that fitness was measured in adolescence rather than at various ages in later adult life: this may reduce the possibility that subclinical IBD activity influenced fitness, as both CD and UC may have a long natural history,[18] with typical onset between ages 20 and 40 years,[12] but with inflammation possibly present some time before frank

Table 4 Physical fitness in adolescence and subsequent ulcerative colitis risk in adulthood at least 4 years after the conscription assessment

Characteristics	Events/*N*	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Physical fitness			
Lowest fifth	349/39,100	1.36 (1.17–1.59)	1.25 (1.06–1.48)
2nd fifth	436/50,246	1.31 (1.13–1.53)	1.24 (1.06–1.44)
3rd fifth	355/43,655	1.24 (1.06–1.44)	1.18 (1.01–1.38)
4th fifth	450/63,860	1.07 (0.93–1.24)	1.05 (0.90–1.21)
Highest fifth	288/44,130	Reference	Reference
BMI			
Underweight	240/28,004	1.08 (0.94–1.24)	1.00 (0.87–1.16)
Normal weight	1,530/195,106	Reference	Reference
Overweight/obese	108/17,881	0.77 (0.64–0.94)	0.78 (0.64–0.95)
ESR in adolescence			
ESR 1 mm/h	432/57,172	Reference	Reference
ESR 2–6 mm/h	1178/158,995	0.97 (0.86–1.09)	0.97 (0.86–1.09)
ESR 7–10 mm/h	150/15,832	1.25 (1.03–1.52)	1.24 (1.02–1.51)
ESR 11–14 mm/h	56/4,813	1.53 (1.15–2.03)	1.53 (1.15–2.03)
ESR $\geq$ 15 mm/h	62/4,179	1.95 (1.49–2.57)	1.92 (1.46–2.52)
Height			
Lowest fifth	451/50,567	1.29 (1.11–1.49)	1.20 (1.04–1.40)
2nd fifth	318/38,653	1.18 (1.01–1.39)	1.13 (0.96–1.33)
3rd fifth	451/58,998	1.10 (0.95–1.28)	1.07 (0.92–1.24)
4th fifth	356/48,861	1.05 (0.90–1.23)	1.04 (0.89–1.21)
Highest fifth	302/43,912	Reference	Reference
Parental SEI in 1960			
Manual worker	797/98,271	1.08 (0.96–1.20)	1.05 (0.94–1.18)
Agricultural workers	66/9,203	0.94 (0.73–1.22)	0.92 (0.71–1.20)
Farm owner/managers	177/23,736	0.97 (0.82–1.15)	0.95 (0.80–1.13)
Office workers	492/66,587	Reference	Reference
Business owners/managers	187/25,691	0.98 (0.83–1.16)	0.96 (0.81–1.14)
Others (unknown)	159/17,503	1.24 (1.04–1.48)	1.22 (1.02–1.46)
Appendicitis < 20 years			
No	1,875/239,054	Reference	Reference
Yes	3/1,937	0.20 (0.07–0.63)	0.20 (0.06–0.62)

BMI, body mass index; CI, confidence interval; ESR, erythrocyte sedimentation rate; EVF, erythrocyte volume fraction; HR, hazard ratio; N, number; SEI, socioeconomic index.
Adjusted* for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20, region of residence, and year of birth.

Table 5 Physical fitness in adolescence and subsequent ulcerative colitis risk at least 15 years after the conscription assessment

Characteristics	Events/*N*	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Physical fitness			
Lowest fifth	289/38,078	1.37 (1.15–1.63)	1.25 (1.04–1.51)
2nd fifth	370/48,961	1.35 (1.15–1.59)	1.27 (1.07–1.50)
3rd fifth	299/42,527	1.26 (1.06–1.50)	1.20 (1.01–1.43)
4th fifth	376/62,245	1.09 (0.93–1.28)	1.07 (0.91–1.26)
Highest fifth	237/42,849	Reference	Reference

BMI, body mass index; CI, confidence interval; ESR, erythrocyte sedimentation rate; EVF, erythrocyte volume fraction; HR, hazard ratio; N, number; SEI, socioeconomic index.
Adjusted* for BMI, ESR, EVF, height, parental SEI, appendicitis before age 20, region of residence, and year of birth.

symptomatic onset and diagnosis.[18] Another potential advantage of this study is the use of markers of disease activity and development that may signal the presence of prodromal disease activity in adolescence when physical fitness was measured.

Despite exclusion of men with IBD or other gastrointestinal diagnoses in adolescence, there was evidence of prodromal disease activity in those who would receive a subsequent IBD diagnosis, often several years later. ESR was raised in adolescents who would subsequently develop IBD, particularly for CD. ESR levels were less pronounced in those who would subsequently receive a UC diagnosis and we speculate that ESR might be a less sensitive marker of subclinical UC disease activity, alternatively, UC disease activity may have a later age at onset.[12] BMI was on average lower in those who would develop CD and there was evidence of shorter stature associated with subsequent UC. Lower body mass is typically associated with IBD even in remission,[22,23] due to

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malabsorption, especially in CD,[23] and thus undiagnosed disease activity is likely to explain associations with being underweight in our study. We adjusted for BMI as one of the markers of subclinical disease; however, the reduction in magnitude of association between fitness and IBD after adjustment for BMI may have been due to collinearity with fitness as well as because it is a measure of prodromal disease activity. The influence of adjustment for the markers of subclinical disease activity in adolescence for the association of fitness with IBD suggests that early disease activity may reduce exercise capacity and thus physical fitness. This suggests that in studies where fitness is measured at a later age, there is an even greater scope for subclinical disease activity to impair fitness, rather than fitness protecting against CD and UC. To further test this possibility, we excluded men with blood markers indicating greatest likelihood of disease activity in adolescence and found that a raised risk of IBD associated with lower level physical fitness remained, adding some evidence of a potential beneficial influence of physical fitness. However, the markers available to us may not be sufficiently sensitive to identify disease activity in all of those with IBD in its early stages. For example, fecal calprotectin might be a more useful maker, which is effective for detecting intestinal inflammation.[24] Thus, even though our results suggest subclinical disease activity, we may still be underestimating its magnitude.

Physical fitness was measured at one point, so we cannot be sure of its persistence, although literature indicates that physical fitness patterns in adolescence are relevant in adulthood.[25,26] Even though the main analysis excluded IBD diagnoses in the first 4 years of follow-up, this was extended to 15 years in a sensitivity analysis to further examine if the association of physical fitness in adolescence has a longer-term association with the risk of an IBD diagnosis, and further reduce the possibility that higher levels of disease activity that would result in more rapid investigation and diagnosis do not account for the findings. The magnitude of the estimates is consistent with a persistent effect, with the strongest evidence for the association with UC.

Strengths of this study include that physical fitness and markers of potential prodromal disease activity were objectively and prospectively measured, as were potential confounding factors such as socioeconomic index of the family of origin and appendicitis before age 20 years was also included as this can influence the risk of UC.[27] The inverse association of appendicitis before age 20 years with UC[27–29] was as expected. Our cohort is large and representative of the general population of men with a long follow-up duration from late adolescence. Our study also has some potential limitations. We lack data on smoking, which has been shown to increase the risk of CD and worsen its course and considered to be protective for UC and improve its course after the onset.[5,6] We adjusted for a measure of inflammation in adolescence, which has been linked with smoking, although not always consistently.[14,30] The Nurses' health study[7] reported that smoking did not modify the associations of fitness with CD and UC, but we could not examine the role of smoking directly as it was not recorded for our cohort. The majority of the study population would have been smokers in late adolescence, at the time of our study. We assessed if heavier or persistent smoking is associated with poorer physical fitness in adolescence by examining associations with subsequent diagnoses of COPD in later adulthood. Although COPD diagnoses will only identify a small subset of smokers, it does provide information on the pattern of association with our measure of physical fitness. As expected, poorer physical fitness was associated with COPD, indicating these men are more likely to be heavier and persistent smokers, even though adjustment attenuated the association of fitness with COPD somewhat. Therefore, smoking is likely to account for at least some of the association between fitness and CD risk. However, as smoking is inversely associated with UC risk, this cannot explain its association with fitness and suggests that smoking is not the sole reason for an association with IBD.

The study is restricted to males, but the results are consistent with those for females from the Nurses' Health Study.[7] We also have information on the timing of IBD diagnoses, but this does not indicate symptomatic onset. There might be diagnostic delay, which is common in adult populations.[31] In one of the sensitivity analyses, there was at least a 15-year delay between the measures in adolescence and first record of an IBD diagnosis in the Patient Register. The results provided evidence of subclinical disease activity and lower levels of physical fitness in adolescence among those who would have a diagnosis of IBD over 15 years later. The use of diagnoses identified through a register can potentially result in error due to diagnostic inaccuracy. For this reason, we conducted sensitivity analyses limiting IBD diagnoses to where they were the primary reason for attending an outpatient clinic or hospital admission. An assessment of the Inpatient register found that for more common diagnoses that were the primary reason for hospital admission, over 85% of diagnoses are recorded accurately.[16] Our results indicate no evidence of problems due to diagnostic accuracy. The incidence rates for IBD in this study suggest that we are not under- or overidentifying the number with IBD substantially. During the main follow-up period, the incidence rates were 13.0 per 100,000 person-years (95% CI: 12.2–13.8) and 24.8 per 100,000 person-years (23.7–25.9) for CD and UC, respectively. Annual rates in Europe during the same study period were consistent with our findings and reported to be between 0.3 and 12.7 per 100,000 for CD, and between 0.6 and 24.3 per 100,000 for UC.[32]

Although there may have been some variation in diagnostic accuracy during our study period, the majority of diagnoses would have made using colonoscopy, with histological and radiological criteria.[33,34] Colonoscopy has been available universally in Sweden since the late 1970s,[35] and based on data from the Uppsala region in Sweden, colonoscopy is today used as diagnostic procedure in nearly all patients (99%) with CD[36] and 75% of those with UC.[37] In recent years, magnetic resonance imaging, computed tomography scan, and capsule endoscopy have also been increasingly used as diagnostic procedures, to complement colonoscopy.[36] Our sensitivity analysis starting follow-up at least 15 years after the conscription assessment would therefore include only IBD diagnosis made when colonoscopy was the main diagnostic method for IBD. Diagnosis of IBD using colonoscopy has been reported to be 89% accurate,[38] thus we are confident that the vast majority of IBD diagnoses in our study are accurate.

In conclusion, the inverse association of physical fitness with IBD risk is consistent with a protective role for exercise.

However, evidence of disease activity before diagnosis was already present in adolescence, thus some or even all of the association between fitness and IBD may be due to prodromal disease activity reducing exercise capacity and therefore fitness.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Exercise and physical fitness has been suggested to protect against inflammatory bowel disease (IBD) risk.

WHAT IS NEW HERE

✓ There is an inverse association between physical fitness in adolescent and subsequent IBD risk particularly for Crohn's disease (CD).

✓ Some of the association may be explained by subclinical disease activity prior to diagnosis limiting exercise capacity and therefore physical fitness.

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