Associations between participation in, intensity of, and time spent on leisure time physical activity and risk of inflammatory bowel disease among older adults (PA-IBD): A prospective cohort study

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Abstract

Background

Inflammatory bowel diseases (IBDs) are diseases of the immune system that share some genetic and lifestyle-related predisposing factors. Increasing incidences have been reported in all age groups. Based on experimental studies suggesting a role of physical activity on intestinal inflammation, this study aimed to investigate the association between leisure time physical activity and the risk of IBD in older adults.

Methods

The study is a prospective cohort study using Danish registry data and questionnaire data from the Danish “Diet, Cancer and Health” cohort. The outcome IBD was defined as having at least two diagnoses of Crohn’s disease or ulcerative colitis registered in the National Patient Registry during follow-up between December 1993 and May 1997 until December 2018. Cox proportional hazard models were used to estimate hazard ratios for IBD onset associated with being physically active and with levels of the metabolic equivalent of task (MET) hours/week of physical activity and hours/week spent on six types of physical activity.

Results

In total, 54 645 men and women aged 50-64 years were included, and thereof 529 cases. When comparing physically active with inactive participants measured by MET hours/week there was no statistically significant difference in risk of IBD (0.89 0.13; 6.27), neither when measured as participation in six types of activities. Results did not indicate any dose-response effect when comparing quartile groups of MET hours/week or of five of the six types of activities. For do-it-yourself-work, the third quartile of hours/week was associated with a higher risk of IBD compared to the second quartile (HR=1.44 1.10 ; 1.90. No effect modification was found.

Conclusions

There was no association between physical activity and risk of IBD when comparing physically active with inactive participants. Neither did the results indicate any dose-response effect when comparing quartile groups of MET hours/week. Do-it-yourself work, however, seemed to be associated with a

higher risk of IBD when comparing the third quartile with the second quartile. The study has clinical relevance by its contribution to the explanatory field of the causes of IBD. However, further research is needed to clarify associations between physical activity and risk of IBD.

Background

Physical activity

Over the past two decades, there has been a consensus about the preventative and health promoting effect of physical activity (PA). The World Health Organization (WHO) states(1), PA contributes to various health benefits, such as reducing the risk of several noncommunicable diseases (NCDs) – diseases, which are a result of a combination of genetic, physiological, environmental and behavioural factors(2). Chronic inflammatory bowel diseases (IBD) are an example of important NCDs that have emerged as a worldwide public health challenge, and therefore PA is highly relevant in the discussion of the prevention of these diseases.

Chronic inflammatory bowel diseases

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of the IBDs. They are intestinal disorders resulting from an inappropriate inflammatory response to intestinal microbes(3, 4). Production of pro-inflammatory cytokines by antigen-presenting cells may lead to a secretion of large amounts of tumour necrosis factor alpha (TNF-α). This further stimulates the activation of other pro-inflammatory responses, leading to a more permeable mucosal barrier which can result in microbial antigens from the intestinal lumen gaining access to the mucosal epithelium(5-8).

The diseases represent a public health problem because of their large impact on the patients and their families' quality of life, on the health care system due to costly treatments, and on the society due to absence from work. Furthermore, the diseases have become a worldwide challenge because of their high prevalence and incidence(9-11). In general, research on IBD focus on the occurrence of these diseases in early life (20-40 years of age), but the IBDs are also prevalent as late onset (40+ years of age) diseases(12-14). Reported age-adjusted (45 to 69 years of age) incidences of the IBDs in Denmark are 6-10 for CD(13, 15) and 18-23 for UC(13, 15) per 100 000 person-years. Worldwide incidences up to 23 per 100,000 for CD and 57 per 100,000 for UC have been reported(10).

The detailed aetiology of the IBDs remains unknown, but experimental and observational studies such as meta-analyses and cohort- and case-control studies suggest that CD and UC have both genetic and environmental predisposing factors(16-20). Use of nonsteroidal anti-inflammatory drugs (NSAIDs)(21), use of hormone replacement therapy (HRT)(22), obesity(23, 24) and dietary factors such as red meat(25) and alcohol(26, 27) have been suggested as risk factors for intestinal inflammation and IBD onset, while a preventative role of intake of dietary fibre(16, 28) and fermented dairy products(29, 30) has been suggested. Smoking, however, has been associated with a higher risk of CD, while being protective for UC(31, 32).

The preventative role of PA on the risk of IBD

Studies have also suggested a preventative effect of PA on the risk of IBD. Early studies have investigated the impact of occupational PA and found that occupations characterized by more physical work appeared to be protective compared with those occupations characterized as sedentary(33, 34). A study by Persson et al. investigating the impact of leisure time PA revealed that the relative risk (RR) of CD, was inversely related to weekly regular exercise (RR= 0.6 [0.4; 0.9])(35). Recent studies have found contradictive results. The Nurses' Health Study I and II(36) observed that women aged between 25 to 55 years who engaged in PA of more than 27 metabolic equivalents of task (MET) hours per week, had a 44% lower risk of developing CD compared with women who were inactive(36). Chan et al. found that there was no association between PA and onset of IBD in "the European Prospective Investigation into Cancer and Nutrition" (EPIC) cohort which included people aged between 45 to 80 years old(37). Furthermore, a meta-analysis including, among others, the mentioned studies, presented that higher levels of PA were associated with a reduced risk of CD compared to those with low PA, but no association was found for UC(38).

The biological mechanisms supporting the hypothesis that being physically inactive compared to being active is associated with risk of IBD are based on suggested mechanisms of contracting muscles, adipose tissue, and intestinal inflammation(5). Furthermore, **there is a growing body of evidence pointing at the role of physical activity in the modulation of gut microbiota towards a more diverse composition of the microbiome, which is associated with higher**

immunity(39). The hypothesis is illustrated in figure 1.

Through these mechanisms of contracting muscles, adipose tissue, diversity of the gut microbiome, and intestinal inflammation, PA may have a protective role in the development of IBD.

Aim

Based on the inconclusive previous research, the aim of the present study was as follows: *To investigate the association between PA and risk of IBD onset among older adults using leisure time PA as a proxy for PA*, by:

operationalising leisure time PA as 1) intensity measured in MET hours, and 2) time spent on six different types of activities, to examine if a potential association may be primarily ascribed to specific activities.
analysing intensity and time spent as A) being physically active compared to being inactive, and as B) a dose-response-association.

Furthermore, the study aimed to investigate whether the effect of leisure time PA was modified by the level of occupational PA, age, BMI and smoking habits.

Methods

Design and setting

A prospective cohort study design was used to investigate the described hypothesis. The study was based on data from the Danish “Diet, Cancer and Health” (DCH) cohort and from Danish registries. Participants in the DCH cohort were recruited between December 1993 and May 1997, and included a total of 57 053 participants (27 178 men and 29 875 women) aged between 50 and 64 years of age, with residence in the Copenhagen area or Aarhus area, born in Denmark and with no previous cancer diagnosis in the Danish Cancer Registry. At baseline, the participants completed a lifestyle questionnaire and a food frequency questionnaire (FFQ). Both questionnaires were interviewer-checked and validated regarding PA and diet(42, 43). A detailed description of the DCH cohort has been described elsewhere(44).

Participants, eligibility criteria and follow-up

Inclusion criteria: All men and women included in the DCH cohort with no diagnosis of CD or UC (diagnostic codes described in next section) before entry to the cohort and with information on PA were included in the analyses.

Follow-up: The participants were followed from the date of their first visit at the DCH study clinic until the date of diagnosis of CD or UC, date of death or emigration, or December 31, 2018, whichever came first.

Materials, data sources, and methods

Outcome diagnostic criteria: The outcome late onset IBD was defined by the criteria: 1) having a main diagnosis (A-diagnosis) registered in the Danish National Patient Registry (DNPR)(45) with the International Classification of Diseases (ICD) 8 and 10 codes for CD (563.00–563.09, 563.91 and K50 (including all sub-codes)) and UC (563.19, 563.99, 569.04, and K51 (including all sub-codes)) in years 1977-2018 from a department with a relevant area of specialization (Surgical Gastroenterology, Medical Gastroenterology, Internal medicine) and 2) the diagnosis was followed by at least one additional registration in the DNPR (inpatient or outpatient visit) related to the first diagnosis within 180 days. The date and year of the diagnosis were defined as the date and year of the first diagnosis registered in the DNPR.

Registry data*:* The Danish health registries included the DNPR and the Danish Civil Registration System (DCRS)(46). The DNPR was used to identify patients with IBD during follow-up. ICD-8 and ICD-10 codes from the DNPR was used to identify cases diagnosed before and after entry to the DCH cohort, and to calculate comorbidity in the cohort using the updated Charlson's comorbidity index(47). Comorbidity was categorized as a binary variable (comorbidity=no/yes) to ensure enough power of the group with comorbidity. High completeness of IBD registration in the DNPR has previously been reported(94%), with an estimated positive predictive value of 97% for CD and 90% for UC(48). The DCRS was used to extract follow-up information on death and immigration. Data were linked by the unique identification number assigned to all residents in Denmark at birth or first immigration.

Exposure: The exposure was defined as 1) a binary indicator of exposure: being active/inactive, both for total intensity of PA and separated on the six different types of leisure time PA: walking, housework, gardening, do-it-yourself work, cycling and sports, and as 2) levels of intensity of total PA and time spend on the six types of activities. The intensity was measured as MET hours/week. The

time spent was measured as hours/week.

The MET system is based on the understanding that all activities are assigned an intensity unit based on their rate of energy expenditure. One MET is defined as the energy expenditure at rest (the resting metabolic rate), which for the average adult is approximately 3.5 ml of O_2/kg body weight/min. The intensities of different activities are calculated as the ratio between the associated metabolic rate for the specific activity and the resting metabolic rate(49).

Being active was defined as having an intensity level of ≥3 MET hours/week or as spending >0 hours/week on each type of activity. The cut point for the binary variable of MET hours/week was chosen to correspond to inactivity equivalent of <1 hour of walking at an average pace per week, consistent with prior studies(36). The levels of intensity and time spent were categorised in quartiles. The pre-defined variable for MET hours/week from the DCH dataset was used. The variable is further described below.

***Questionnaire data*:** Information on leisure time PA was based on six questions covering the average number of hours per week spent the past year on the six types of leisure time PA during summer and winter, respectively. The MET hours/week variable was calculated by multiplying the MET value of each specific activity by duration and frequency of the activities. The following MET-values were used according to Ainsworth's *Compendium of Physical Activities*(49, 50): walking 3.0, housework 3.0, gardening 4.0, do-it-yourself work 4.5, cycling 6.0, and sports 6.0.

***Covariates and potential confounders**:* Based on the known and putative IBD risk factors and preventative factors, the analyses were adjusted for occupational PA, smoking, intake of fibre, fermented dairy products, red and processed meat, alcohol, HRT (only for women), NSAID, comorbidity, and also the demographic factors age and gender. These factors were expected to be possible confounders of the association between leisure time PA and risk of IBD.

Information on occupational PA was obtained from a question with five categories (sitting, standing, light manual work, heavy manual work, no occupation). Light and heavy manual work were combined in one category. Total energy intake was measured in mega joule (MJ) per day, alcohol consumption and intake of fibre, fermented dairy products and meat (red and processed meat) were measured in

grams per day – all retrieved from the FFQ. A detailed description of the calculation of the dietary variables in the DCH study is described elsewhere(51). Smoking habits within the past year was defined as current, never or former. The questionnaire also gave information on the use of a pain-relieving drug, which was defined by the variable NSAID and assessed as >1 pill per month during the last year before baseline (yes/no). HRT was divided into the following categories: never, current, and former user.

Statistical analyses

To investigate the risk of and time to IBD event the Cox proportional hazards model with age as the underlying time scale was applied. Death, emigration and loss to follow-up were not considered as competing risks, and thus, were handled as censoring. The assumption of proportional hazards was checked by evaluating parallel curves of the cumulative hazard function on the log-scale. Furthermore, sensitivity analyses modelling time-varying effect of covariates that did not fulfil the proportional hazard assumption, were performed.

Hazard-ratios (HRs) and the corresponding 95% confidence intervals (95% CI) and p-values for IBD onset associated with participation in and levels of leisure time PA were estimated. All analyses were carried out according to the principle of complete-case-analysis(52) to ensure an equal number of participants in all analyses. The analyses were carried out in both a crude model and a model adjusted for baseline values of preventative factors and risk factors for IBD. In the dose-response analyses, inactive individuals were included by assigning indicator variables of being active/inactive, as the IBD risk among inactive individuals may deviate from the risk among active individuals. Since the lowest quartile group of gardening, do-it-yourself-work, cycling, and sports only included inactive people (0 hours/week), the second quartile group was used as a reference for these variables. Furthermore, the analyses were stratified according to strata of age groups (50-59 and 60-64 years), BMI (<25 kg/m^2 and ≥ 25 kg/m$^{2)}$, smoking (‘never smoker’ and ‘current/former smoker’), occupational PA (‘not active at work’, including sitting and not working, and ‘active at work’, including standing and manual work) and work status (not working/working), as these variables were assumed to interact with the effect of leisure time PA.

All analyses were carried out using *Stata version 15* (53). For all tests, a P-value below 0.05 was considered statistically significant.

The study was not submitted to the Southern Denmark Ethics Committee, which is the local ethics committee. The study does not need approval from the Ethics committee or Institutional Review Board by Danish law: “Questionnaire studies and health science registry research projects must be reported to the scientific ethics committee system only if the project includes human biological material”. (the Act on Research Ethics Review of Health Research Projects (Danish: Lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter, Lov nr. 593 af 14. juni 2011, § 14, stk. 2)).(54)

Results

In total, 1 823 individuals were excluded from the study cohort; 59 participants were excluded because they had a CD or UC diagnosis before entry to the DCH cohort; three individuals where excluded because of no link to the DCRS; 1 209 were excluded because of missing values in one or more of the PA variables, and 14 were excluded due to implausible long times spent on leisure time PA (>105 hours/week), which was in accordance with previous studies using the DCH cohort(55, 56). The remaining 538 individuals were excluded because of missing information on other variables. A total of 28 526 women and 26 119 men were included in the analyses. During a mean follow-up of 25 years, 529 IBD cases (106 CD cases and 423 UC) were observed (figure 2).

The median MET hours in each quartile group were as follows: 1st quartile: 27 hours/week; 2nd quartile: 47 hours/week; 3rd quartile: 69 hours/week, and 4th quartile: 112 hours/week (table 1). Table 1 also presents the medians and 25th and 75th percentiles of hours spent on the six types of activity in each quartile group.

Table 1. Median and percentiles of MET hours and hours per week in quartile groups

Dose-response of physical activity	Quartiles of physical activity (hours/week)			
	1st median (p1; p3)	2nd median (p1; p3)	3rd median (p1; p3)	4th median (p1; p3)
MET hours/week	27 (20; 32)	47 (42; 52)	69 (63; 76)	112 (96; 140)
Total activity	7 (6; 9)	12 (11; 14)	18 (16; 20)	29 (25; 36)
Walking	1 (0.5; 1.5)	2.5 (2; 3)	4 (4; 5)	8 (7; 10.5)
Housework	1 (1; 2)	3 (3; 4)	6 (5; 6)	10 (10; 15)
Gardening	0	1 (0.5; 1.5)	2.5 (2; 3)	5 (4; 7.5)
Do-it-yourself-work	0	1 (1; 1)	2 (1.5: 2)	4.5 (3; 7.5)
Cycling	0	1 (0.5; 1)	2 (1.5; 2.5)	5.5 (4; 7.5)
Sports	0	0.5 (0.5; 0.5)	1 (1; 2)	4 (3; 5)

Abbreviations: MET: metabolic equivalent of task, p1; p3: 25th and 75th percentiles.

Baseline characteristics of the cohort grouped in quartiles of MET hours of PA per week are presented in table 2. Due to asymmetric distributions, continuous variables were presented as medians with interquartile ranges. The groups differ on several parameters. A higher proportion of the youngest age group (50-54 years) was represented in each MET quartile group, but the proportion was higher in the lowest quartile group compared to the highest quartile group. A higher proportion of women, were represented in all MET quartile groups except the lowest quartile group. A markedly higher proportion of people not working and a lower proportion of people with sedentary work were represented in the highest MET quartile group compared to the distribution in the lowest MET group.

Table 2. Baseline characteristics of participants in quartile groups of MET hours/week

N study population=54 645	Quartile groups of MET hours/week			
	1st (N = 13 827)	2nd (N = 13 554)	3rd (N = 13 720)	4th (N = 13 544)
MET hours/week[a]	27 (20; 32)	47 (42; 52)	69 (63; 76)	112 (96; 140)
Age	56 (53; 60)	56 (53; 60)	56 (53; 60)	57 (53; 61)
Age groups				
50-54 years	6 084 (44)	6 057 (45)	5 907 (43)	5 116 (38)
55-59 years	4 330 (31)	4 214 (31)	4 221 (31)	4 156 (31)
60-64 years	3 413 (25)	3 283 (24)	3 592 (26)	4 272 (31)
Gender				
Women	6 476 (47)	7 125 (53)	7 548 (55)	7 377 (54)
Men	7 351 (53)	6 429 (47)	6 172 (45)	6 167 (46)
Physical activity at work				
Sedentary	5 894 (43)	5 598 (41)	4 910 (36)	3 254 (24)
Standing	2 382 (17)	2 425 (18)	2 348 (17)	2 254 (17)
Manual	3 089 (22)	3 142 (23)	3 413 (25)	3 895 (29)
Not working	2 462 (18)	2 389 (18)	3 049 (22)	4 141 (31)
Dietary factors				
Energy (MJ/d),	9.2 (7.5; 11.0)	9.4 (7.7; 11.0)	9.6 (8.0; 11.0)	10.0 (8.3; 12.0)
Dietary fibre intake (g/d)	19 (15; 23)	20 (16; 25)	21 (17; 26)	22 (17; 27)
Meat intake (g/d)	109 (78; 148)	105 (76; 143)	105 (75; 143)	107 (77; 150)
Fermented dairy products	38 (12; 176)	53 (16; 198)	60 (18; 204)	68 (19; 205)
Alcohol intake (g/d)	13 (6; 31)	13 (6; 31)	13 (6; 31)	13 (5; 31)
Smoking				
Never	4 588 (33)	4 881 (36)	5 068 (37)	4 732 (35)
Former	3 840 (28)	4 011 (30)	4 075 (30)	3 864 (28)
Current	5 399 (39)	4 662 (34)	4 577 (33)	4 948 (37)
BMI (kg/m^2)				
< 25.0	5 407 (39)	6 015 (44)	6 201 (45)	6 025 (44)
≥ 25	8 420 (61)	7 539 (56)	7 519 (55)	7 519 (56)
Comorbidity				
No (CCI = 0)	13 300 (96)	13 151 (97)	13 306 (97)	13 078 (97)
Yes (CCI = ≥ 1)	527 (4)	403 (3)	414 (3)	466 (3)
NSAID				
No	9 337 (68)	9 075 (67)	9 248 (67)	9 155 (68)
Yes (> 1 pill/month)	4 490 (32)	4 479 (33)	4 472 (33)	4 389 (32)
HRT (women, N = 28 406)				
Never	3 547 (55)	3 914 (54)	4 065 (54)	4 013 (54)
Current	1 954 (30)	2 113 (30)	2 287 (30)	2 193 (30)
Former	975 (15)	1 098 (15)	1 196 (16)	1 171 (16)

[a] Median and 25th and 75th percentiles (p1; p3) are presented for continuous variables. Number, N, and percent (%) are presented for categorical variables. All values after exclusion of missings.

Abbreviations: MET: *metabolic equivalent of task*; g/d: *gram per day*; BMI: *body mass index*; CCI: *Charlson's comorbidity index*; HRT: *hormone replacement therapy*; NSAID: *nonsteroidal anti-inflammatory drugs*; *Active/inactive*

An intensity of ≥3 MET hours/week as an indicator of being active was not associated with any significantly lower risk of IBD (0.89 [0.13; 6.27]) after adjustment for potential confounders. Engaging in any of the six types of leisure time activities neither was associated with a lower risk (table 3).

Table 3. Risk of inflammatory bowel disease according to being physically active

Indicator variables of physical activity	Crude		Adjusted[a]	
	HR[b]	95% CI	HR[b]	95% CI
MET hours/week				
Active (>3 MET hours/week)	0.77	(0.11; 5.49)	0.89	(0.13; 6.27)
Active (>0 hours/week) in each activity				
Walking	1.02	(0.73; 1.44)	1.07	(0.76; 1.52)
Housework	1.03	(0.72; 1.47)	1.04	(0.72; 1.50)
Gardening	0.87	(0.72; 1.05)	0.97	(0.79; 1.19)
Do-it-yourself work	0.87	(0.73; 1.03)	0.92	(0.75; 1.14)
Cycling	0.87	(0.73; 1.04)	0.93	(0.77; 1.12)
Sports	0.92	(0.78; 1.09)	1.02	(0.85; 1.22)

[a]Adjusted for age, gender, occupational physical activity, smoking, energy intake, intake of meat, fibre, fermented dairy products and alcohol, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, comorbidity. The six types of activity were mutually adjusted. [b]Inactive is the reference for all estimates. Abbreviations: MET: metabolic equivalent of task; HR: hazard ratio; CI: confidence interval

Dose-response

Table 4. Risk of inflammatory bowel disease according to quartiles of physical activity

Quartile groups of physical activity	Crude		Adjusted[a]	
	HR[b]	95% CI	HR[b]	95% CI
MET hours/week				
2nd quartile	0.94	(0.75; 1.19)	0.97	(0.76; 1.22)
3rd quartile	0.81	(0.63; 1.03)	0.82	(0.64; 1.05)
4th quartile	0.86	(0.68: 1.09)	0.83	(0.65; 1.07)
Walking (hours/week)				
2nd quartile	0.89	(0.71; 1.11)	0.86	(0.68; 1.09)
3rd quartile	0.87	(0.68; 1.13)	0.83	(0.63; 1.08)
4th quartile	0.96	(0.76; 1.21)	0.86	(0.67; 1.11)
Housework (hours/week)				
2nd quartile	1.10	(0.88; 1.37)	1.12	(0.88; 1.43)
3rd quartile	0.95	(0.74; 1.22)	0.97	(0.74; 1.29)
4th quartile	1.14	(0.91; 1.44)	1.12	(0.84; 1.47)
Gardening (hours/week)				
1st quartile	1.10	(0.88; 1.36)	0.98	(0.78; 1.24)
3rd quartile	0.82	(0.64; 1.06)	0.81	(0.62; 1.04)
4th quartile	1.01	(0.80; 1.28)	0.95	(0.74; 1.23)
Do-it-yourself (hours/week)				
1st quartile	1.27	(1.01; 1.59)	1.17	(0.92; 1.49)
3rd quartile	1.43	(1.09; 1.86)	1.44	(1.10; 1.90)
4th quartile	0.99	(0.76; 1.29)	0.97	(0.73; 1.29)
Cycling (hours/week)				
1st quartile	1.04	(0.83; 1.31)	0.97	(0.77; 1.23)
3rd quartile	0.91	(0.70; 1.16)	0.91	(0.70; 1.17)
4th quartile	0.82	(0.63; 1.07)	0.83	(0.64; 1.09)
Sports (hours/week)				
1st quartile	1.03	(0.72; 1.50)	0.94	(0.66; 1.36)
3rd quartile	0.94	(0.64; 1.37)	0.92	(0.63; 1.35)
4th quartile	0.96	(0.64; 1.43)	0.99	(0.66; 1.48)

[a]Adjusted for age, gender, occupational physical activity, smoking, energy intake, intake of meat, fibre, fermented dairy products and alcohol, nonsteroidal anti-inflammatory drugs, hormone

replacement therapy, comorbidity. The six types of activity were mutually adjusted. [b]1st quartile is the reference for MET hours, walking and housework. 2nd quartile is reference for gardening, do-it-yourself, cycling and sports. Abbreviations: MET: metabolic equivalent of task; HR: hazard ratio; CI: confidence interval

Compared with participants in the lowest quartile of MET hours/week, there were no statistically significantly higher or lower risk of IBD with increasing MET hours/week. Furthermore, no statistically significantly associations were found for quartiles of walking, housework, gardening, cycling and sports. For do-it-yourself-work, the unadjusted HRs indicated that the lowest and the third quartiles was associated with a higher risk of IBD compared to the second quartile of hours/week (HR=1.27 [1.01 ; 1.59] and HR=1.43 [1.09 ; 1.86]). Furthermore, in the adjusted analyses the association remained significant for the third quartile (HR=1.44 [1.10 ; 1.90].

Stratification

The results of the stratified analyses indicated that the dose-response estimates were not modified by age (50-59 and 60-64), occupational PA (sedentary/not working and standing/manual work), BMI (<25.0 and ≥25.0), smoking (never and former/current) or work status (not working and working) (all P for *z*-tests>0.05).

Discussion

This cohort study of Danish middle-aged men and women did not find any support for the hypothesis that being physically active compared to inactive measured by MET hours/week and as participation in six types of activities lowered the risk of IBD. Generally, estimates had wide confidence intervals.

Comparison with other studies

The findings of this study may to some extent be compared with those of the EPIC cohort, which did not observe an association between PA and risk of CD and UC(37). Compared with the present study, the EPIC study (which included participants from the DCH cohort) only included 75 CD cases and 177 UC cases and was also unable to account for long-term changes in PA.

A combined study of the Nurses' Health studies I and II used detailed and updated information on physical activity and known risk factors for CD and UC and included 284 CD cases and 363 UC cases.

They reported a HR of 0.56 (0.37; 0.84) for the risk of developing CD when comparing active women with at least 27 MET hours/week of PA with sedentary women with <3 MET hours/week. No association was found for UC. Age, smoking, and BMI also did not significantly modify the association between PA and risk of UC or CD. Furthermore, the findings from the Nurse's Health studies are consistent with findings from two prior case-control studies(35, 57). Persson et al. used a mailed questionnaire to obtain information on PA from cases and controls and reported an inverse association between weekly regular PA and risk of CD but not UC(35). Klein et al. found that IBD patients had lower levels of PA during their pre-illness period than clinic controls(57).

A meta-analysis by Wang et al. (38) argues that the variations in definitions of PA across studies make it difficult to compare them. The Nurse's health study also used MET hours/week and therefore was more comparable with the present study compared to the EPIC study, where they used a PA index combining occupational and recreational PA. However, the median of MET hours/week in the highest quartile group in this study was 112 hours/week compared to only 45 hours/week in the Nurse's Health study. Thus, the study population in the present study generally reported very high numbers of hours spent on leisure time PA, complicating the comparability. The Nurse's Health study found an effect at 27 MET hours/week when compared to the lowest category of PA (<3 MET hours/week). If the effect of PA has a threshold value the effect is probably not shown in this study, as this study uses a higher PA level as reference group (27 MET hours/week) and not the < 3 MET hours/week as in the Nurse's Health study.

Strengths and limitations

The present study has several strengths. A major strength is its prospective design, which reduced selection bias. As the participants were followed using registries, the loss to follow-up was minimal. Information on PA and covariates were measured several years before the onset of disease, and hence, were unrelated to IBD status later during follow-up. Another major strength is the linkage to the DNPR, which is considered of high validity and completeness, and the restrictive diagnostic criteria by including only A-diagnoses and cases with at least two diagnoses during follow-up. This approach ensured that a high proportion of the identified cases really had IBD, hence increasing the

specificity but lowering the sensitivity, as some ‘real’ IBD cases might not have been identified. Moreover, the diagnostic criteria were in accordance with the criteria used in a Danish nationwide cohort study of IBD using data from the DNPR(13).

The study had three notable limitations. *Firstly*, the available data did not allow examining the association between timing in life of PA and risk of IBD. It could be argued that a potential protective effect of PA is due to the accumulated PA exposure during life. Whether the PA level reported at baseline is representative of the PA level during whole life can be questioned.

Second, there were only 106 CD and 423 UC cases. These numbers are higher than in the EPIC study, but still limit the opportunity to look at the diseases separately. The low number of cases can be explained by the restriction to the age group 50–64 years, which is not the ages of typical IBD onset (20-30 years)(13). On the other hand, 50-64 years old is an age group with increasing incidence (12-14).

Thirdly, although the DCH questionnaire is demonstrated to be a reliable and valid tool(43), the limitations according to self-reported information should be considered. PA is in general difficult to measure accurately in observational studies as there is a risk of measurement error and misclassification. The participants had generally reported very high levels of PA per week equivalent of up to 15 hours/week, hence it is possible that physical activity may have been overreported. This must have been independent of the outcome and may have resulted in bias towards the null hypothesis in the analysis of the dichotomised exposure variables. In the analyses with the exposure in quartiles groups, the misclassification resulted in a risk of both over- and underestimation of the association. Overall, the results of the present study should be interpreted with caution.

Although the present study cannot explicitly conclude that individuals likely reduce their risk of IBD through participation in PA, there are plausible biological mechanisms for how PA may be involved in the aetiology of IBD. These mechanisms originate from the so far evidence from experimental animal and human studies suggesting that PA may exert its anti-inflammatory effect via a reduction in visceral fat mass and/or by induction of an anti-inflammatory intestinal environment(5, 6). Therefore, there is a rationale for future cohort studies investigating the association. Further research is needed

to clarify the association which is not fully understood by the present study.

Conclusion

In conclusion, this study did not find any association between intensity of and time spent on physical activity and risk of IBD when comparing physically active with inactive participants. Neither did the results indicate any dose-response effect when comparing quartile groups of MET hours/week and hours/week spent on specific activities. Do-it-yourself work, however, seemed to be associated with a higher risk of IBD when comparing the third quartile with the second quartile of hours/week. The five other activities (walking, housework, cycling, gardening and sport) did not show any significant associations. The study has important public health implications in a society dominated by a sedentary lifestyle, and clinical relevance by its contribution to the explanatory field of the causes of IBD.

Abbreviations

PA = physical activity

IBD = inflammatory bowel disease

CD = Crohn’s disease

UC = ulcerative colitis

DCH = Diet, Cancer and Health

EPIC = European Prospective Investigation into Cancer and Nutrition

MET = metabolic equivalent of task

NSAID = nonsteroidal anti-inflammatory drugs

HRT = hormone replacement therapy

HR = hazard ratio

95% CI = 95% confidence interval

p1 and p3 = 25^{th} and 75^{th} percentiles

Declarations

Ethics approval and consent to participate

The study is approved by the Danish Data Protection Agency (2012-58-0018). The study is an open register-based cohort study. The study does not need approval from the Ethics committee or

Institutional Review Board by Danish law: “Questionnaire studies and health science registry research projects must be reported to the scientific ethics committee system only if the project includes human biological material”. (the Act on Research Ethics Review of Health Research Projects (Danish: Lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter, Lov nr. 593 af 14. juni 2011, § 14, stk. 2)).(54)

Consent for publication

Consent was obtained from the participants in the “Diet, Cancer and Health” study.

Availability of data and material

The data that support the findings of this study are available from Open Patient data Explorative Network (OPEN) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Danish Health Data Authority. Permissions obtained to access data before the initiation of this project were obtained from The Danish Data Protection Agency, and furthermore from the data owners: The Danish Cancer Society and the Danish Health Data Authority.

Competing interests

The author declares to have no competing interests.

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Authors' contributions

The first author (NFR) designed the study, made the statistical analyses and interpretation of the data, and wrote the first draft of the manuscript. NFR, BHB, KHR and VA contributed to the manuscript and accepted the final version. BHB especially contributed with epidemiologic knowledge, KHR

contributed with specialised knowledge within registry research and the individual Danish registries. VA together with NFR developed the project idea and VA contributed with specialised clinical knowledge within IBDs and know of the DCH cohort.

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Figures

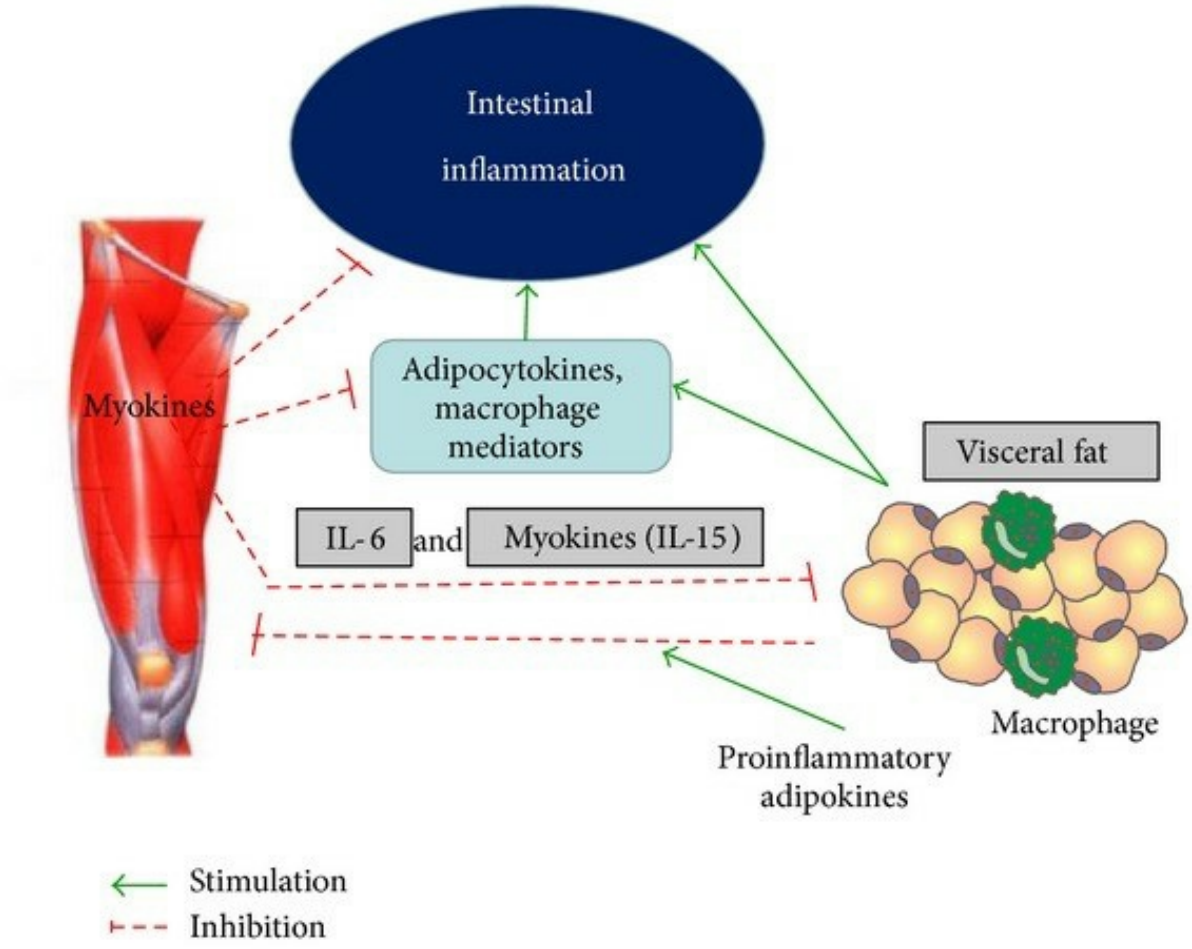

Figure 1

Crosstalk between skeletal muscle, adipose tissue, and intestinal inflammation" by Jan Bilski et al., licensed under CC by 3.0 The hypothesis in this study is based on the suggested mechanism of crosstalk between skeletal muscle, adipose tissue and inflammation in the gut by Jan Bilski and colleagues(5). Pathologically modified visceral adipose tissue has been demonstrated to secrete pro-inflammatory cytokines including TNF-a. Exercise may exert its anti-inflammatory response via a reduction in visceral fat mass and by inhibition of the secretion of pro-inflammatory cytokines, by releasing anti-inflammatory cytokines and myokines such as interleukin 6 (IL-6) from contracting muscles(5). It has further been suggested that the effect of physical activity could depend on its intensity, duration, and type of exercise, with regular exercise being beneficial, while acute, strenuous exercise

could lead to a release of inflammatory cytokines(5, 40). But still, these mechanisms are not fully understood, and exercise such as running has also been found to induce increases in IL-6(24, 41). Note: Reproduced from “The Role of Physical Exercise in Inflammatory Bowel Disease”, Bilski, J. et al., 2014, BioMed Research International Volume 2014, Article ID 429031. http://dx.doi.org/10.1155/2014/429031. Copyright 2014 Jan Bilski et al. licensed under CC by 3.0.

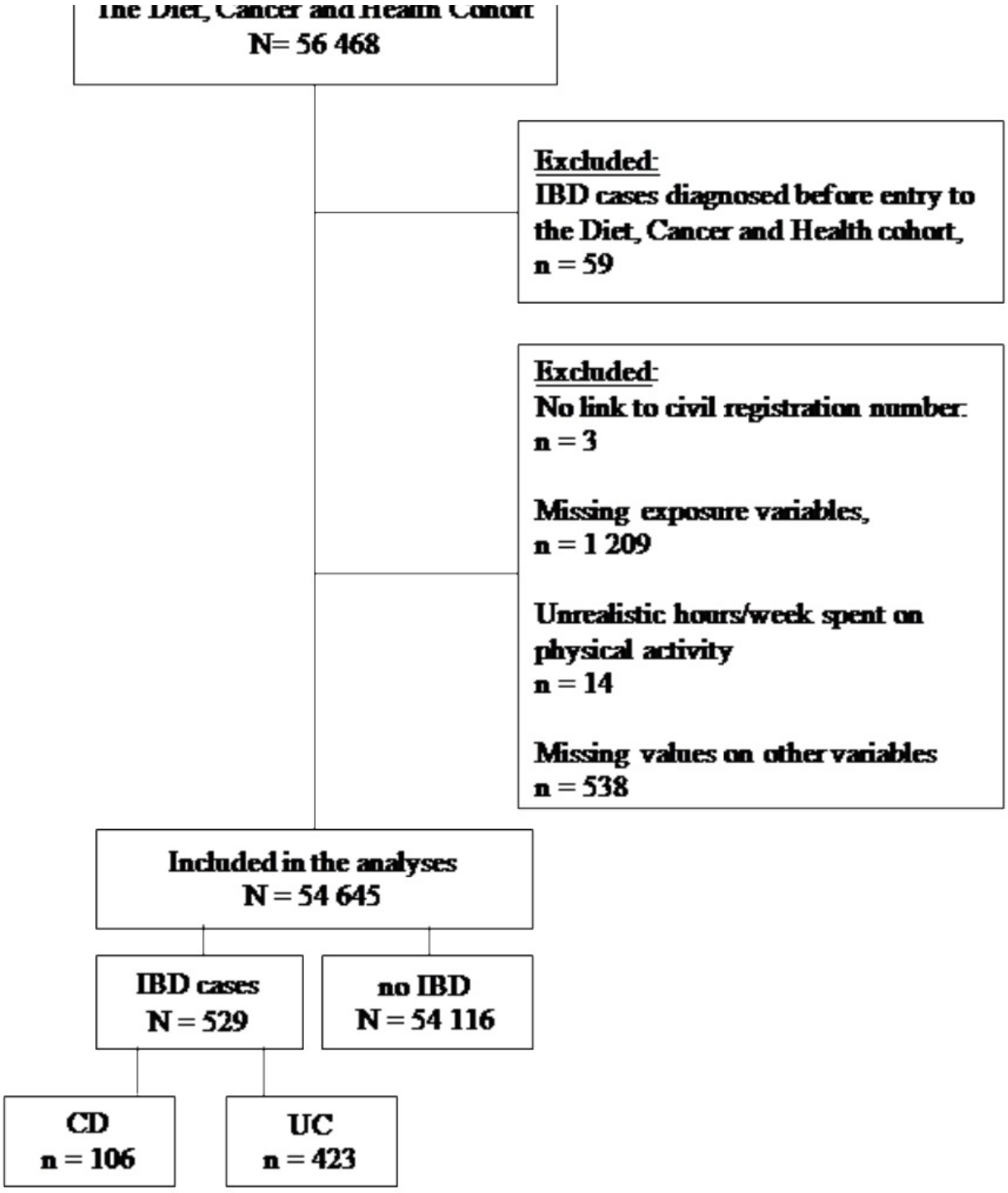

Figure 2

Flowchart of the study population. Some patients (N=23) had received a diagnosis of both CD and UC during their disease course. These patients were classified according to the last diagnosis as the last diagnosis registered was regarded as the most valid, knowing that some patients change diagnosis during their disease follow-up.

Supplementary Files

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Supplemental table S1.pdf