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Physical activity and the risk of colorectal cancer in Lynch syndrome

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Abbreviations used

MMR, mismatch repair

MET-h/week, metabolic equivalent of task hours per week

HR, hazard ratio

CI, confidence interval

MLH1, MutL Homolog 1

MSH2, MutS Homolog 2

MSH6, MutS Homolog 6

PMS2, PMS1 Homolog 2

EPCAM, Epithelial Cell Adhesion Molecule

CCFR, Colon Cancer Family Registry

BMI, body mass index

U.S. DHHS, United States Department of Health and Human Services

SD, standard deviation

Article Category Cancer Epidemiology

Novelty and Impact Physical activity is known to reduce colorectal cancer risk in general but its effect is not known for people with Lynch syndrome, who have a strong predisposition to colorectal cancer due to germline mutations in DNA mismatch repair genes. A study of 2,042 mutation carriers suggests an inverse association of physical activity with colorectal cancer risk. If confirmed, increased physical activity could also be recommended to people with Lynch syndrome as a way to modify their risk.

Abstract

Greater physical activity is associated with a decrease in risk of colorectal cancer for the general population; however, little is known about its relationship with colorectal cancer risk for people with Lynch syndrome, carriers of inherited pathogenic mutations in genes affecting DNA mismatch repair (MMR). We studied a cohort of 2,042 MMR gene mutations carriers (n=807, diagnosed with colorectal cancer), from the Colon Cancer Family Registry. Self-reported physical activity in three age-periods (20-29, 30-49, and ≥50 years) was summarized as average metabolic equivalent of task hours per week (MET-h/week) during the age-period of cancer diagnosis or censoring (near-term exposure), and across all age-periods preceding cancer diagnosis or censoring (long-term exposure). Weighted Cox regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for the association between physical activity and colorectal cancer risk. Near-term physical activity was associated with a small reduction in the risk of colorectal cancer (HR ≥35 vs. <3.5 MET-h/week, 0.71; 95% CI, 0.53 – 0.96). The strength and direction of associations were similar for long-term physical activity, although the associations were not nominally significant. Our results suggest that physical activity is inversely associated with the risk of colorectal cancer for people with Lynch syndrome, however, further confirmation is warranted. The potential modifying effect of physical activity on colorectal cancer risk for people with Lynch syndrome could be useful for risk prediction and support counseling advice for lifestyle modification to reduce cancer risk.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer for both men and women with an estimated 135,430 new cases in 2017 in the US [1]. About 2-4% of all colorectal cancers are attributable to Lynch syndrome, in that cases are carriers of inherited pathogenic mutations in genes affecting DNA mismatch repair (MMR) including *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes or deletions in the *EPCAM* gene that influence MMR by epigenetic silencing of *MSH2* [2-4]. People with Lynch syndrome are predisposed to a variety of cancers, in particular colorectal cancer, having on average a risk to age 70 years of 20–50% depending on the sex of the person and the gene mutated [5-10]. There is substantial variation in age-specific cancer risk (penetrance) in mutation carriers, consistent with a modifying effect of genetic, environment, and lifestyle behaviors on cancer risk [6]. Lifestyle factors such as smoking, alcohol consumption, body mass index (BMI), and use of aspirin and supplements have been shown to be associated with altered risk of colorectal and endometrial cancer for people with Lynch syndrome [11-21].

There is strong evidence for an inverse association between physical activity and the risk of colorectal cancer for the general population as found by meta-analyses of a large number of studies [22-26]. The most recent evidence from a large pooled-analysis of 12 cohorts that included 1.44 million adults, was a reduced risk of both colon and rectal cancers associated with highest levels of leisure-time physical activity compared with lowest levels of physical activity (HR, 0.84; 95% CI, 0.77-0.91; and HR, 0.87; 95% CI, 0.80-0.95, for colon and rectal cancer respectively) [24]. An understanding of which modifiable behavioral risk factors modify cancer risk for people with Lynch syndrome would help inform the development of interventions to lower their risk despite the strong genetic predisposition. To date only one study has reported on physical activity and colorectal cancer risk for Lynch syndrome, studying Taiwanese *MLH1* and *MSH2* mutation carriers, and found weak evidence consistent with an inverse association [27].

In the present study, we estimated the association between physical activity and colorectal cancer risk for people with Lynch syndrome using a large dataset from the Colon Cancer Family Registry.

Materials and Methods

Study sample

The sample comprised a cohort of men and women with Lynch syndrome who were enrolled in the multi-site Colon Cancer Family Registry (CCFR) between 1998 and 2012. Details about study design and recruitment strategy at each site of the CCFR have been published [28]. Probands were recruited via both population and clinic-based resources in Australia, New Zealand, Canada, and the United States. Recruitment was expanded to include relatives after obtaining informed consent from the proband. Probands and relatives who were at least 18 years old, had a germline pathogenic MMR or *EPCAM* gene mutation, and completed the epidemiological questionnaire at the time of recruitment, were eligible for the current study. Informed consent was obtained from all study participants, and the study protocol was approved by the Institutional Research Ethics Review Board at each recruitment site.

Data collection

Standardized questionnaires were used at the time of recruitment to collect data on demographics, personal and family history of cancer, colorectal cancer screening, and lifestyle and environmental factors including physical activity [29]. The CCFR physical activity questionnaire was derived from a questionnaire that has been previously validated and shown to provide a good measure of physical activity. Questionnaires were administered via in person or telephone interviews or by mail. Colorectal cancer, the primary outcome, other cancer diagnoses, and age at each cancer diagnosis were confirmed from medical records, cancer registry records, or death certificates, wherever possible.

Exposure assessment

Regular physical activity (yes/no), defined as doing the activity once a week for 30 minutes or longer for at least 3 months in a row, was self-reported by decades of life during three age-periods: 20–29 years, 30–49 years, and ≥50 years. Assessment included all types of physical activity performed in or

around the house, at work, or for leisure, such as walking, jogging, running, biking, swimming, racquet sports, vigorous exercise, ball related sports, and any other strenuous activities during each of the three age periods. To allow for all types of physical activity to be reported, respondents could list up to five "other" strenuous activities (defined as "activities that really increase your heart rate, make you hot and cause you to sweat"). Duration and frequency of each type of physical activity performed were reported in number of years, months per year, and hours per week. We multiplied the standard metabolic equivalents of task (MET) values for each activity (obtained from the Compendium of Physical Activities 2011, https://sites.google.com/site/compendiumofphysicalactivities/) by the average number of hours per week engaged in that activity to calculate the MET-hours/week (MET-h/week) of physical activity [30].

Statistical analysis

We conducted weighted Cox proportional hazards regression analyses to estimate the association between physical activity and the risk of colorectal cancer for people with Lynch syndrome as hazard ratios (HR) and 95% confidence intervals (CI). Time at risk started at age 20 and ended at age at first diagnosis of colorectal cancer (outcome), or at age at diagnosis of any other cancer, polypectomy, or age at interview, whichever occurred first. We chose to end observation time (censor) at age of diagnosis of any other cancer or polypectomy because people might have changed their physical activity behavior following their cancer diagnosis and because cancer treatment and surveillance could have altered their colorectal cancer risk. To take the potential correlation in risk between family-members into account, the Huber-White robust variance estimation was used by clustering on family membership [31].

In the CCFR, early-onset colorectal cancer cases and cases with a strong family history were preferentially tested for germline MMR gene mutations. Therefore, our study sample of carriers was not random with respect to their disease or family history status. In our analyses, we took this non-random ascertainment into account by applying probability weights to carriers based on the weighted cohort approach developed by Antoniou et al. [32]. Age-specific incidence of colorectal cancer for

MMR gene mutation carriers was calculated using published estimates of the hazard ratios of colorectal cancer for carriers [33-35] and the age-specific colorectal cancer incidence for the general population [36]. These expected incidence rates were then used to calculate age-specific probability weights for carriers with and without colorectal cancer (Supplementary Table 1) so that in this 'synthetic' cohort, colorectal cancer incidence in each age stratum was consistent with the incidence for carriers if they had been randomly selected from the general population.

Physical activity in MET-h/week was categorized into five categories using the following cut-points: <3.5 (referent group), 3.5 to ≤ 8.75, 8.75 to ≤ 17.5, 17.5 to ≤ 35, and >35 which are respectively equivalent to <1, 1 to ≤ 2.5, 2.5 to ≤ 5, 5 to 10 and >10 hours of brisk walking per week [37]. The category cut-offs were based on guidelines for recommended physical activity issued by the United States Department of Health and Human Services (U.S. DHHS) in 2008 (equivalent to hours of brisk walking/moderate aerobic activity per week; recommended physical activity: 5 hours or more of brisk walking/week [or about 20 MET-h/week]) [38]. Physical activity was analysed as a time-varying covariate in two models. For our first model, we used the average physical activity during the age-period of a person's colorectal cancer diagnosis or censoring, reflective of more recent exposure and called this 'near-term exposure'. For our second model, we used the average physical activity throughout life, calculated as a weighted average of physical activity across all assessed age-periods prior to colorectal cancer diagnosis or censoring and called this 'long-term exposure'. For individuals who received a colorectal cancer diagnosis or were censored in the age-period 20-29 years, 'long-term exposure' was the same as the 'near-term exposure'. HRs were estimated between levels of physical activity compared to the reference group, and per 20 MET-h/week increase in physical activity.

Our primary multivariable models included sex, country of recruitment, ascertainment method, education, BMI at age 20, average daily ethanol intake from alcoholic beverages, and smoking status as potential confounders, identified using a causal diagram (**Figure 1**). Variables not likely to be constant throughout the study period were treated as time-varying covariates. Time-dependent variables were not generated for intake of aspirin or ibuprofen, or intake of multivitamins, calcium, or

folic acid supplements because information on carriers' age at first intake of these medications and supplements was not available. These variables were therefore not included in the primary multivariable models. Fruit, vegetable, and red meat intake, and recent BMI were not included in the primary analysis because they had missing values for participants who received colorectal cancer diagnosis or were censored more than 2 years prior to interview (the questionnaire had specifically asked about these factors 2 years prior to interview). The proportional hazard assumption was not tested because it cannot be interpreted with time-varying exposure. Multiplicative interaction was tested by assessing the change in the log-likelihood ratio after adding a cross-product term between the exposure variable and the potential effect modifiers (i.e. sex, and mutated gene). These were identified *a priori,* assuming that the relationship between physical activity and the risk of colorectal cancer might differ across categories of these variables.

The number of missing values for all the variables are reported in **Table 1**. All univariable and multivariable analyses were complete case analyses (i.e. only included participants with no missing value for the main exposure and covariates included in the model).

The following additional analyses were conducted: analyses separate for colon cancer and rectal cancer (due to limited statistical power, only physical activity on continuous scale i.e., per 20 MET-h/week, was used as exposure in these analyses); analyses restricted to carriers who received a colorectal cancer diagnosis or were censored within 5 years before interview, so as to reduce survival bias; analyses excluding those whose colorectal cancer diagnosis was not confirmed; analyses additionally adjusted for aspirin or ibuprofen, multivitamin, calcium, and folic acid supplements intake, fruit, vegetable, and red meat intake; and analyses that included recent BMI instead of BMI at age 20.

All statistical tests were two-sided. All statistical analyses were performed using STATA 14.0 [39].

Results

We initially identified 2,100 MMR gene mutation carriers. Those who were younger than 20 years at the time of colorectal cancer diagnosis (n=11) or censoring (n=47) were excluded. The final sample included 2,042 carriers from 774 families, of whom 1,155 (57%) were female; 1504 (74%) were recruited through family-cancer clinics; and 744 carried a mutation in *MLH1*, 936 in *MSH2*, 234 in *MSH6*, 106 in *PMS2*, and 22 in *EPCAM* (**Table 1**). Time at risk ended at colorectal cancer diagnosis for 807 carriers (673 located in the colon, 121 in the rectum, and 13 in the colon and rectum). For the remaining 703 study participants, censoring occurred at polypectomy for 346, diagnosis of other cancers for 271, and at age of interview for 618 unaffected carriers. The mean time interval (interquartile range) between interview and either colorectal cancer diagnosis or censored age was 5 (1-14) years for affected carriers and 0 (0 – 7) for unaffected carriers. Median (interquartile range) age at colorectal cancer diagnosis was 42 (35 – 49) years and average colorectal cancer incidence from age 20 years was 1.8% (95% confidence interval (CI), 1.67% – 1.91%) per year. Colorectal cancer diagnosis was confirmed for 752 (93%) of the affected carriers by pathology review or reports, cancer registries, or hospital records. The rest (7%) were based on self-reports or reports from spouse or relatives.

Lifestyle risk factors of the included MMR gene mutation carriers are summarized in **Table 1**. Carriers diagnosed with colorectal cancer were more likely to be men (54.4% vs. 36.6%), to have more than 28 grams average daily ethanol intake from alcoholic beverages (13.8% vs. 7.2%), to be current smokers (33.3% vs. 22.8%), and to have been overweight or obese at age 20 (24% vs. 20%). They were less likely to take ≥4 servings per day fruits and vegetables (8.6% vs. 21.7%) or to have taken aspirin (12.6% vs. 16.4%), or multivitamin (17.8% vs. 27.0%), calcium (6.8% vs. 10.8%), and folic acid (4.8% vs. 9.6%) supplements.

Compared with the lowest level of near-term physical activity (<3.5 MET-h/week), there was a suggestion that physical activity ≥35 MET-h/week was associated with a 29% lower risk of colorectal cancer (HR, 0.71; 95 CI, 0.53 – 0.96). There was also evidence for a marginal dose-dependent relationship——an increase in levels of near-term physical activity was associated with a decrease in

colorectal cancer risk (HR for physical activity per 20 MET-h/week, 0.95; 95 CI, 0.91 – 0.99). For colon and rectal cancers separately, the HR estimates were similar, were not nominally significant, and did not differ materially from one another (**Table 2**). From the analysis limited to those who were diagnosed with colorectal cancer or censored within 5 years before interview, the HR estimates were comparable to those above (Supplementary **Table 2)**. For long-term physical activity and the risk of colorectal cancer, the estimates were suggestive of an inverse association with magnitudes of effect similar to those for near-term physical activity but estimates were not nominally significant (**Table 3**).

In our study, we found no evidence for an interaction between physical activity and sex (P=0.9), or the MMR gene mutated (P=0.9). There was no evidence for a non-linear association on the logarithmic scale between physical activity and the risk of colorectal cancer. Estimates from analysis limited to those with confirmed colorectal cancer and analysis further adjusted for other potential confounders yielded similar results to our primary analysis (details not shown).

Discussion

From this study of a large cohort of people with Lynch syndrome, we found a suggestive trend towards lower risk of colorectal cancer associated with higher level of physical activity during the age-period of colorectal cancer diagnosis or censoring. People with the highest level of physical activity (>35 MET-h/week, equivalent to >10 hours of brisk walking per week) were at lowest risk of colorectal cancer. The associations with physical activity over all age-periods prior to colorectal cancer diagnosis or censoring were similar though not of themselves nominally significant.

The U.S. DHHS physical activity guidelines recommend at least 150 minutes/week (2.5 hours/week) of moderate-intensity aerobic activity and 300 minutes/week (5 hours) for more extensive health benefits. To make our results more interpretable and generalizable per the DHHS guidelines, we created 5 levels of physical activity from low to high, categorized as <1 hour (referent), 1-2.5 hours, 2.5-5 hours (recommended), 5-10 hours and >10 hours of physical activity/week. Interestingly, we

found that physical activity levels were higher than the recommended level for 32% of the participants in this cohort. Higher overall levels of physical activity were also reported by Giovannucci et al, in their study of the association of quintiles of physical activity and colorectal adenomas and cancer among males, using a validated questionnaire similar to the one used in our study [40]. The upper 2 quintiles of median physical activity reported in their study was 22.6 and 46.8 MET-h/week, levels higher than the recommended guidelines, for 40% of the participants. The higher levels of physical activity could be due to an overestimation of MET hours/week of physical activity because the questionnaire accounted for both leisure and non-leisure time physical activity, or this could be a more health aware cohort because of their mutation status, and higher levels of physical activity may have been reported because it is considered socially desirable to exercise. Given that our results do not show a statistically significant beneficial effect of the DHS recommended 2.5-5 hours of physical activity on the risk of colorectal cancer for people with Lynch syndrome, and a statistically significant association is found only at the highest level of near-term physical activity or an increase of 20MET-h/week, it is possible that people with Lynch syndrome may need to be even more physically active than the DHS recommendation for beneficial effect on colorectal cancer risk reduction. However, these are results from a single study and further validation is warranted before making recommendations.

To the best of our knowledge, our study is the largest to date to systematically investigate the association between physical activity and colorectal cancer risk for people with Lynch syndrome. One previous study [27] of a Taiwanese cohort of 301 *MLH1* and *MSH2* mutation carriers, reported the association between vigorous leisure time physical activity (obtained by self-report over the year prior to interview) and colorectal cancer risk. They found a decreased risk of colorectal cancer for those performing vigorous leisure time physical activity compared to those that did not, for *MLH1* mutation carriers (HR, 0.55; 95% CI 0.35–0.86) [27]. This study was limited by a small sample size and assessed vigorous physical activity as a dichotomous (yes/no) variable over a short time period. Nevertheless, both studies have shown that colorectal cancer risk is inversely associated with physical activity even

though there are differences in exposure definition, study design, analysis methods, as well as country of study.

For the general population, there is accumulated evidence showing an inverse association between physical activity and colorectal cancer risk [23-26, 41]. Therefore, physical activity is considered as a modifiable lifestyle behavior for which there is "convincing" evidence of its efficacy in decreasing colorectal cancer risk [41]. The direction and strength of observed association comparing highest to lowest levels of physical activity in our study were similar to those reported for the general population. For the general population, the most recent evidence is from a large pooled analysis of 12 cohorts that included 1.44 million adults [24]. The authors found a reduced risk for colon (HR, 0.84; 95% CI, 0.77-0.91) and rectal cancer (HR, 0.87; 95% CI, 0.80-0.95) associated with highest levels of leisure-time physical activity compared with lowest levels, even after adjusting for BMI [24]. The World Cancer Research Fund meta-analysis comparing the highest to lowest total physical activity levels gave a relative risk of 0.80 for colorectal cancer (95% CI, 0.72 – 0.88) [22]. A beneficial effect of physical activity has been postulated to occur through various mechanisms, including an increase in antitumor immune defense, a decrease in insulin and insulin-like growth factors which stimulate cell proliferation and inhibit cell death, and possibly a reduction in gastrointestinal transit time leading to reduction in exposure of the gut lining to carcinogens [42]. The same biological mechanisms could be postulated to also play a role in modifying cancer risk for people with Lynch syndrome.

This study has several strengths, including the use of data from the Colon Cancer Family Registry that were based on detailed assessment of physical activity and other covariates in a standardized manner. The questionnaire used to capture physical activity was a suitable fit for the purpose for our study because a large proportion of our participants were from 4 US centers; with a good match on a similar predominantly Caucasian population but with other ethnic groups and other – but similar – countries (Canada and Australia) included; and with similar population patterns of physical activity. We categorized the physical activity variable to align with the 2008 U.S. Department of Health and Human Services physical activity guidelines (equivalent to hours of brisk walking/moderate aerobic

activity per week), to make the results interpretable and generalizable [38]. We used a weighted cohort approach to overcome bias related to ascertainment of participants, which can occur in a retrospective study when participants are selected based on phenotype [32]. Published estimates for hazard ratios of colorectal cancer of carriers of MLH1, MSH2, MSH6, and PMS2 were used in our calculation of weights. However, because *EPCAM* has been discovered as a Lynch syndrome susceptibility gene relatively recently in 2009 [43, 44], robust estimates for HRs associated with EPCAM were lacking and therefore not taken into account in these calculations. It is unlikely that this would influence our overall results since EPCAM carriers were only 1.1% of the study participants. To avoid immortal time bias, we started the observation time for our study at age 20 years, instead of at birth, and although physical activity behaviour patterns may be established earlier in life, physical activity was assessed only at age 20 and beyond for this study. By commencing observation time at age 20, we excluded the time-period during which there is very low incidence of colorectal cancer even in MMR gene mutation carriers. The rationale for analysing physical activity during the age-period of the cancer diagnosis or censoring was (a) reporting of recent exposure (near-term physical activity) may be more accurate and more relevant than reporting of long-term exposure (over multiple decades for our study) because the latter is more likely to be influenced by poor recall; and (b) for comparability, as most studies assess physical activity in the year preceding the interview/questionnaire. On the other hand, in our study we cannot rule out reverse causation, which might in part explain the stronger effects observed for near-term exposure. To further mitigate the effects of poor recall and survival bias, we performed subgroup analysis of those who reported physical activity within 5 years of cancer diagnosis or interview. For the statistical analysis, physical activity and other time-varying covariates were analysed as time-dependent to allow for changes in exposure over time.

An important limitation of our study was the possibility of residual confounding, not only because of the observational nature of the data, but also because of having treated exposure as time-varying, which might have introduced time-varying confounding, for example by BMI. Although we analysed a large cohort of people with Lynch syndrome, a larger sample is needed for separate analysis of the association of physical activity with colon and rectal cancer and for testing interactions. Because

physical activity was self-reported and carriers with colorectal cancer were aware of their disease status at the time of interview, their report on physical activity might have been different from those without disease, introducing recall bias which may lead to inflated or understated risk estimates. Replication of our findings by a prospective cohort is warranted.

In summary, our analyses have shown that self-reported physical activity was inversely associated with colorectal cancer risk for people with Lynch syndrome. If our findings are confirmed by other large studies especially prospective studies, physical activity could be useful for risk prediction and for recommendation to people with Lynch syndrome, as a way of possible colorectal cancer risk reduction.

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Disclaimer

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Table 1- Characteristics of people with Lynch syndrome included in the study[#]

	No colorectal cancer N = 1,235 (60%)	Colorectal cancer N = 807 (40%)	Total N = 2,042
Age (year), [a]			
Mean (SD)	41.8 (12.9)	42.6 (10.3)	42.1 (12.0)
Median [interquartile range]	41 [32 - 50]	42 [35 - 49]	42 [33 - 50]
Sex, n (%)			
Female	787 (63.7)	368 (45.6)	1155 (56.6)
Male	448 (36.3)	439 (54.4)	887 (43.4)
Mismatch repair gene mutated, n (%)			
MLH1	394 (31.9)	350 (43.4)	744 (36.4)
MSH2	607 (49.1)	329 (40.8)	936 (45.8)
MSH6	163 (13.2)	71 (8.8)	234 (11.5)
PMS2	58 (4.7)	48 (5.9)	106 (5.2)
EPCAM	13 (1.1)	9 (1.1)	22 (1.1)
Study sites, n (%)			
Canada	172 (13.9)	132 (16.4)	304 (14.9)
Australia	716 (58.0)	381 (47.2)	1097 (53.7)
USA	347 (28.1)	294 (36.4)	641 (31.4)
Ascertainment method, n (%)			
Clinic	975 (78.9)	529 (65.6)	1504 (73.7)
Population	260 (21.1)	278 (34.4)	538 (26.3)
Education level, n (%)			
Some high school or less	244 (19.8)	192 (23.8)	436 (21.4)
Completed high school/ some tertiary study	409 (33.1)	267 (33.1)	676 (33.1)
Vocational/technical school	226 (18.3)	127 (15.7)	353 (17.3)
University degree	340 (27.5)	206 (25.5)	546 (26.7)
Missing	16 (1.3)	15 (1.9)	31 (1.5)
Average daily ethanol intake from any alcoholic beverage (grams/day), [b] n (%)			
0	324 (26.2)	201 (24.9)	525 (25.7)
>0 – ≤14	585 (47.4)	314 (38.9)	899 (44.0)
>14 – ≤28	113 (9.1)	85 (10.5)	198 (9.7)
>28	89 (7.2)	111 (13.8)	200 (9.8)
Missing	124 (10.0)	96 (11.9)	220 (10.8)
Cigarette smoking, [c] n (%)			
Never smoker	670 (54.3)	364 (45.1)	1034 (50.6)
Former smoker	276 (22.3)	171 (21.2)	447 (21.9)
Current smoker	282 (22.8)	269 (33.3)	551 (27.0)
Missing	7 (0.6)	3 (0.4)	10 (0.5)
Body mass index at age 20, [d] n (%)			
Normal	822 (66.6)	510 (63.2)	1332 (65.2)
Overweight	196 (15.9)	151 (18.7)	347 (17.0)
Obese	49 (4.0)	43 (5.3)	92 (4.5)
Underweight	114 (9.2)	63 (7.8)	177 (8.7)
Missing	54 (4.4)	40 (5.0)	94 (4.6)
Body mass index 2 years before diagnosed/ censored age, [d,*] n (%)			
Underweight	23 (1.9)	10 (1.2)	33 (1.6)
Normal	351 (28.4)	101 (12.5)	452 (22.1)
Overweight	244 (19.8)	123 (15.2)	367 (18.0)
Obese	118 (9.6)	71 (8.8)	189 (9.3)
Missing	499 (40.4)	502 (62.2)	1001 (49.0)
Fruit and vegetable intake (servings/day), [e,*] n (%)			
<2	201 (16.3)	125 (15.5)	326 (16.0)
2.01 – 3	143 (11.6)	54 (6.7)	197 (9.6)
3.01 – 4	139 (11.3)	54 (6.7)	193 (9.5)
≥4.01	268 (21.7)	69 (8.6)	337 (16.5)
Missing	484 (39.2)	505 (62.6)	989 (48.4)

Table 1- Characteristics of people with Lynch syndrome included in the study[#] – *continued*

	No colorectal cancer	Colorectal cancer	Total
	N = 1,235 (60%)	N = 807 (40%)	N = 2,042
Red meat intake (servings/day), [f, *] n (%)			
<0.30	225 (18.2)	99 (12.3)	324 (15.9)
0.31 – 0.60	262 (21.2)	95 (11.8)	357 (17.5)
0.61 – 0.90	106 (8.6)	48 (5.9)	154 (7.5)
≥0.91 or more	159 (12.9)	68 (8.4)	227 (11.1)
Missing	483 (39.1)	497 (61.6)	980 (48.0)
Aspirin and/or ibuprofen intake, [g] n (%)			
<1 month	955 (77.3)	655 (81.2)	1610 (78.8)
≥1 month	202 (16.4)	102 (12.6)	304 (14.9)
Missing	78 (6.3)	50 (6.2)	128 (6.3)
Multivitamin supplement intake, [g] n (%)			
<1 month	830 (67.2)	615 (76.2)	1445 (70.8)
≥1 month	334 (27.0)	144 (17.8)	478 (23.4)
Missing	71 (5.7)	48 (5.9)	119 (5.8)
Calcium supplement intake, [g] n (%)			
<1 month	1047 (84.8)	727 (90.1)	1774 (86.9)
≥1 month	133 (10.8)	55 (6.8)	188 (9.2)
Missing	55 (4.5)	25 (3.1)	80 (3.9)
Folic acid supplement intake, [g] n (%)			
<1 month	1074 (87.0)	741 (91.8)	1815 (88.9)
≥1 month	119 (9.6)	39 (4.8)	158 (7.7)
Missing	42 (3.4)	27 (3.3)	69 (3.4)
Average physical activity during the age-period of colorectal cancer diagnosis or censoring (MET-h/week), [h,i] n (%)			
<3.5	240 (19.4)	164 (20.3)	404 (19.8)
≥3.5 – <8.75	137 (11.1)	83 (10.3)	220 (10.8)
≥8.75 – <17.5	194 (15.7)	108 (13.4)	302 (14.8)
≥17.5 – <35	253 (20.5)	154 (19.1)	407 (19.9)
≥35	379 (30.7)	260 (32.2)	639 (31.3)
Missing	32 (2.6)	38 (4.7)	70 (3.4)
Average physical activity during lifetime (MET-h/week), [h, j] n (%)			
<3.5	133 (10.8)	94 (11.6)	227 (11.1)
≥3.5 – <8.75	133 (10.8)	86 (10.7)	219 (10.7)
≥8.75 – <17.5	194 (15.7)	110 (13.6)	304 (14.9)
≥17.5 – <35	270 (21.9)	159 (19.7)	429 (21.0)
≥35	428 (34.7)	293 (36.3)	721 (35.3)
Missing	77 (6.2)	65 (8.1)	142 (7.0)

[#]at the time of colorectal cancer diagnosis or age of another cancer, or polypectomy, or interview for colorectal cancer-unaffected participants (whichever came first) [a] Age at diagnosis of colorectal cancer for affected participants; age at diagnosis of another cancer or polypectomy or interview for colorectal cancer-unaffected participants (whichever came first); [b] Average daily ethanol intake was calculated as weighted average of daily ethanol intake from any alcoholic beverage when carriers were in their 20s, 30s and 40s and 50s and above; [c] former smokers defined as carriers who had smoked at least 1 cigarette per day for at least 3 months and had quit more than 2 years before age at colorectal cancer or censored age; current smokers defined as carriers who had smoked at least 1 cigarette per day for at least 3 months and continued within 2 years of age at colorectal cancer or censored age; [d] underweight <18.5 kg/m^2, normal (18.5 – <25.0) kg/m^2, overweight (25.0 – <30 kg/m^2), obese (≥30 kg/m^2); [e] a serving of fruit defined as 1 medium fresh fruit, or ½ cup of chopped, cooked, or canned fruit, or¼ cup of dried fruit, or 6 ounce of fruit juice; a serving of vegetable defined as 1 cup raw leafy vegetables, or ½ cup of other vegetables, or cooked or chopped raw, 6 ounces of vegetable juice; [f] a serving of red meat defined as 2-3 ounces of red meat, or a piece of meat about the size of a deck of cards; [g] at least twice a week; [h] Standard metabolic equivalent of task (MET) assigned to each activity multiplied by the number of hours per week engaged in that activity was used to calculated MET-h/week; MET hours per week translated into time equivalent spent walking per week 3.5 = 1 hour; 8.75 = 2.5 hours; 17.5 = 5 hours; 35 = 10 hours of brisk walking; [i] physical activity during the age period of a patient's colorectal cancer diagnosis 20s, 30s and 40s, or 50s and above; [j] average MET-h/week calculated as a weighted average of physical activity when carriers were in their 20s, 30s and 40s and 50s and above. [*]carriers who were diagnosed with colorectal cancer or censored more than 2 years before interview had missing for this variable

Table 2. Hazard ratios for associations between **average physical activity during the age-period of colorectal cancer diagnosis or censoring** (i.e., near-term) and the risk of colorectal cancer for people with Lynch syndrome

				Univariable model		Multivariable model [a]	
		Cases	Person-years	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Colorectal cancer	Average physical activity (MET-h/week)						
	<3.5	164	7293.1	1 [Reference]		1 [Reference]	
	≥3.5 – <8.75	83	3895	0.95 (0.67 – 1.35)	0.78	0.96 (0.63 – 1.46)	0.85
	≥8.75 – <17.5	108	5891.2	0.85 (0.62 – 1.16)	0.31	0.91 (0.63 – 1.30)	0.60
	≥17.5 – <35	154	8704.2	0.82 (0.62 – 1.10)	0.19	0.83 (0.59 – 1.15)	0.26
	≥35	260	17782.1	0.77 (0.59 – 1.01)	0.06	0.71 (0.53 – 0.96)	0.03
	Per 20 MET-h/week	769	43565.6	0.97 (0.93 – 1.01)	0.14	0.95 (0.91 – 0.99)	0.02
Colon cancer [b]	Average physical activity, per 20 MET-h/week	639	43435.6	0.98 (0.94 – 1.02)	0.42	0.96 (0.92 – 1.01)	0.09
Rectal cancer [c]	Average physical activity, per 20 MET-h/week	118	42917.3	0.91 (0.82 – 1.01)	0.08	0.91 (0.83 – 1.01)	0.10

MET, metabolic equivalent of task; CI, colorectal cancer; HR, hazard ratio.

[a] All multivariable models were adjusted for country (categorical), education (categorical), ascertainment (binary), sex (binary), BMI at age 20 (categorical), smoking status (categorical, time-varying), and average daily ethanol intake from alcoholic beverages (categorical, time-varying)

[b] Number of colon cancers: 673; participants with synchronous colon and rectal cancer (n=13) were not included as cases in the analysis

[c] Number of rectal cancers: 121; participants with synchronous colon and rectal cancer (n=13) were not included as cases in the analysis

Table 3. Hazard ratios for associations between **average physical activity during lifetime** (i.e., long-term) and the risk of colorectal cancer for people with Lynch syndrome

				Univariable model		Multivariable model [a]	
		Cases*	Person-years	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Colorectal cancer	Average physical activity (MET-h/week)						
	<3.5	94	5360.1	1 [Reference]		1 [Reference]	
	≥3.5 – <8.75	86	4240	0.88 (0.60 – 1.31)	0.54	0.83 (0.53 – 1.32)	0.44
	≥8.75 – <17.5	110	6040.2	0.77 (0.53 – 1.11)	0.16	0.81 (0.54 – 1.22)	0.31
	≥17.5 – <35	159	8947.2	0.84 (0.61 – 1.17)	0.30	0.84 (0.58 – 1.23)	0.37
	≥35	293	18211.1	0.80 (0.59 – 1.09)	0.16	0.72 (0.50 – 1.03)	0.07
	Per 20 MET-h/week	742	42798.6	1.00 (0.96 – 1.04)	0.93	0.98 (0.94 – 1.02)	0.32
Colon cancer [b]	Average physical activity, per 20 MET-h/week	614	42670.6	1.01 (0.97 – 1.05)	0.60	0.99 (0.95 – 1.03)	0.60
Rectal cancer [c]	Average physical activity, per 20 MET-h/week	117	42176.3	0.93 (0.84 – 1.03)	0.14	0.94 (0.86 – 1.03)	0.21

MET, metabolic equivalent of task; CI, colorectal cancer; HR, hazard ratio.

* For 72 individuals (27 cases) only data on physical activity during the age-period of cancer diagnosis or censoring (near-term exposure) was available. For these, 'long-term exposure' was coded as missing and they were excluded from analyses with average physical activity throughout life as the exposure. This explains the difference in number of cases and total person-years in this table compared with **Table 2**.

[a] All multivariable models were adjusted for country (categorical), education (categorical), ascertainment (binary), sex (binary), BMI at age 20 (categorical), smoking status (categorical, time-varying), and average daily ethanol intake from alcoholic beverages (categorical, time-varying)

[b] Number of colon cancers: 673; participants with synchronous colon and rectal cancer (n=13) were not included as cases in the analysis

[c] Number of rectal cancers: 121; participants with synchronous colon and rectal cancer (n=13) were not included as cases in the analysis

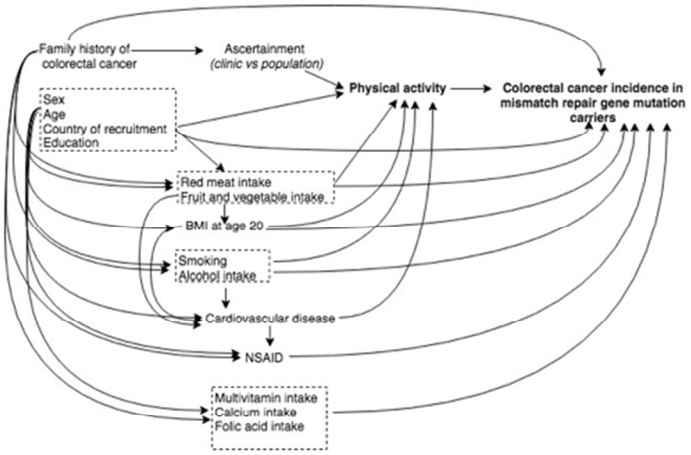

Figure 1 - Assumed causal diagram for the association between physical activity and colorectal cancer in mismatch repair gene mutation carriers. Abbreviations NSAID non-steroidal anti-inflammatory drug

338x190mm (54 x 54 DPI)