Association between Cardiorespiratory Fitness and Colorectal Cancer in the UK Biobank

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Abstract

Background: Increased cardiorespiratory fitness is related to decreased risk of major chronic illnesses, including cardiovascular disease, type 2 diabetes, and cancer, but its association with colorectal cancer specifically has received very little attention.

Methods: We examined the relation of cardiorespiratory fitness to colorectal cancer in 59,191 UK Biobank participants aged 39-70 years without prevalent cancer at baseline, followed from 2009 to 2014. Submaximal bicycle ergometry was conducted at study entry, and cardiorespiratory fitness was defined as physical work capacity at 75% of the maximum heart rate, standardised to body mass ($PWC_{75\%}$). Multivariable Cox proportional hazards regression was performed to obtain hazard ratios (HR) and corresponding 95% confidence intervals (CI).

Results: During a mean follow-up of 4.6 years, 232 participants developed colorectal cancer (151 colon cancers; 79 rectal cancers). When comparing the 75^{th} to the 25^{th} percentiles of $PWC_{75\%}$, the multivariable-adjusted HR of colorectal cancer was 0.78 (95% CI: 0.62-0.97). That relation was largely driven by an inverse association with colon cancer (HR 0.74, 95% CI: 0.56-0.97) and less so with rectal cancer (HR 0.88, 95% CI: 0.62-1.26; p value for difference by colorectal cancer endpoint=0.056). The inverse relation of cardiorespiratory fitness with colorectal cancer was more evident in men (HR 0.72, 95% CI: 0.55-0.94) than women (HR 0.99, 95% CI: 0.71-1.38), although the gender difference was not statistically significant (p value for interaction=0.192).

Conclusions: Increased cardiorespiratory fitness is associated with decreased risk of colorectal cancer. Potential heterogeneity by colorectal cancer anatomic subsite and gender requires further study.

Keywords:
Cardiorespiratory Fitness, Colorectal Cancer, Incidence, UK Biobank, Gender-specific

Introduction

A substantial body of evidence shows that self-reported physical activity protects against risk of colorectal cancer [1, 2]. In contrast, very few studies considered cardiorespiratory fitness as a potential cause of decreased colorectal cancer risk [3-8], although its objective measurement yields more valid estimates than self-reported assessments of physical activity [9-11]. The sparse data available suggest that increased cardiorespiratory fitness is associated with decreased risk of colorectal cancer [5-7]. Therefore, attaining a high level of fitness through increased activity behaviour may represent a useful strategy for colorectal cancer prevention. Cardiorespiratory fitness is genetically determined by 25% to 65% as estimated by twin studies but it represents a highly modifiable trait, even by sporadic physical activity [12].

Strengthening the evidence base for a possible protective role of cardiorespiratory fitness in colorectal cancer development would increase the prognostic value of assessing fitness in clinical practice as a biomarker capable of helping select high risk patients for colorectal cancer screening. Colorectal screening represents a highly effective preventive measure because adenomas and other precursor lesions can be detected and removed before progressing to overt cancer [13, 14].

We therefore conducted a detailed, prospective analysis of cardiorespiratory fitness in relation to colorectal cancer in a large cohort of women and men. Our study differs from previous investigations in considering colorectal cancer anatomic subsites and providing novel data on the association in women.

Methods

Study Population and Data Collection

Data were drawn from the UK Biobank, a large population-based prospective cohort study with long-term follow-up conducted in the United Kingdom (UK) [15]. Briefly, between 2006 and 2010, over 500,000 men and women aged 39 to 70 years from different socioeconomic backgrounds attended a baseline examination in one of 22 assessment centres. Extensive information on lifestyle and health-

related information was obtained via touchscreen questionnaires, personal interviews, physical measurements, and sampling of biomaterial. Physical measures (e.g., height, weight, waist and hip circumferences) were performed by trained personnel conforming to a standardised protocol. All participants provided written informed consent [15]. The UK Biobank was approved by the North West Multi-centre Research Ethics Committee (MREC).

A subsample of 79,213 participants was selected for bicycle ergometer fitness testing. Participants were divided into 5 risk categories: (1) 'minimal risk, cycle at 50% level', (2) 'small risk, cycle at 35%', (3) 'medium risk, cycle at constant level', (4) 'high risk, take measurement at rest-only', (5) 'electrocardiography (ECG) to be avoided, either unsafe or pointless'. Only those with minimal and small risk were included in the incremental exercise test [16]. Of these, 63,535 participants generated usable measurements. After excluding 4,344 participants with prevalent malignant cancer other than non-melanoma skin cancer, the population for analysis comprised 59,191 participants (Figure 1).

Assessment of Cardiorespiratory Fitness

The submaximal bicycle ergometer test was conducted with a stationary eBike using Firmware v1.7. Depending on the individual risk category derived from interview questions and measurements, participants were assigned to individual exercise protocols. A 4-lead ECG device (CAM-USB 6.5 using software Cardiosoft v6.51) was used to record ECGs during the pretest phase (15 seconds), the constant phase (2 minutes with a work load of 30 W for women/ 40 W for men), the incremental phase (4 minutes with a work load increasing to 35% of maximum work load for small risk; 50% for minimal risk) and during recovery (1 minute). Maximum workload was estimated based on age, gender, height, weight, and resting heart rate [16].

VO_{2max} can be estimated from submaximal exercise tests and validation studies show good validity against VO_{2max} obtained in maximal exercise tests (correlation coefficients ranging from 0.69 to 0.98) as well as good test-retest reliability (correlation coefficient 0.92) [17, 18]. However, ergometry in

the UK Biobank was only conducted to at most 50% of a predefined maximum work load, and the linear relationship between heart rate and work load is not assured to persist up to maximum heart rate, especially in older people [16, 19, 20]. Therefore, to obtain an estimate comparable between participants, we estimated physical work capacity at 75% of maximum heart rate ($PWC_{75\%}$). This measure incorporates the age dependent decline of maximum heart rate and is independent of resting heart rate, the measurement of which is prone to error [19, 21]. It shows good face validity and is highly correlated with the working capacity index at 65% of the heart rate reserve per kilogram of body weight, another measure of cardiorespiratory fitness (intraclass correlation coefficient=0.96) [19, 21]. $PWC_{75\%}$ has previously been used to monitor cardiorespiratory fitness levels as an objective criterion measure of cardiorespiratory fitness [22-26].

In linear regression models, we considered measured heart rate (bpm) during the incremental phase as independent variable and the corresponding work load (W) as the dependent variable for each participant. Although we needed to assume a linear relationship between heart rate and work load, $PWC_{75\%}$ could be obtained by interpolation or, if necessary, less extreme extrapolation using the individual regression equation $PWC_{75\%} = intercept + heart\,rate_{75\%} \cdot slope$. As the maximum heart rate declines with age, we used the empirical formula $208 - 0.7 \cdot age$ to calculate the age-predicted maximum heart rate [27]. $PWC_{75\%}$ was further divided by body mass to obtain PWC per kg body weight (W/kg) [21, 19]. To remove implausible cardiorespiratory fitness values and to avoid loss of information, exposure data were winsorized at the 1st and 99th percentiles of women and men, respectively [28]. The exposure distribution stratified by gender is illustrated in Figure 2.

Cohort Follow-up and Colorectal Cancer Ascertainment

The UK Biobank conducts follow-up of participants' vital status by linkage to routine data from the UK National Health Service [15]. Type of cancer was coded using the International Classification of Diseases (ICD), 9th and 10th Revision (ICD-9 or ICD-10) [29, 30] and information on tumour morphology and histology was derived using the ICD-O-3. Date of complete follow-up was 30

November 2014 for linkage in England and Wales. Survival was followed up by linkage to national death registries. Colorectal cancer was defined as ICD codes C18, C19, and C20. Colon cancer was defined as C18, rectal cancer as C19 and C20, proximal colon cancer as C18.0-C18.5, and distal colon cancer as C18.6-C18.7. Other colon cancer subsites (C18.8 and C18.9) were included only in the analyses of colon cancers and colorectal cancers, as the numbers of cases were too small for subsite analyses. Primary malignant colorectal cancers that were diagnosed at different sites at the same time were not included in subsite analyses.

Covariables

Regression models were adjusted for potential confounders assumed to affect cardiorespiratory fitness or colorectal cancer endpoints. We assumed that direct causes of the exposure or outcome, excluding possible instrumental variables, would identify a sufficient set of covariates [31]. Figure S1 in the Online Resource presents a directed acyclic graph for the identification of causal paths and potential confounding variables [32, 33]. Basic models were adjusted for age (continuous), gender (women/men), and study centre (Sheffield/Liverpool/Hounslow/Croydon/Birmingham). Fully adjusted models additionally included education (University or College degree/A-levels, AS-levels, NVQ, HND, HNC or equivalent or other professional qualification/O-levels, CSEs or equivalent/ none of the above), income (<31,000 £/31,000 £–51,999 £/>51,999 £), sedentary behaviour (hours/day of television watching), waist-to-hip ratio (waist circumference (cm) divided by hip circumference (cm)), height (cm), alcohol consumption (never/former/current), smoking behaviour (never/former/current), frequency of processed meat intake (<2 per week/2-3 per week/>3 per week), past colorectal cancer screening (yes/no), family history of bowel cancer (yes/no), and nonsteroidal anti-inflammatory drug (NSAID) use (yes/no). In models containing only women, we additionally adjusted for use of hormone replacement therapy (yes/no). In additional analyses, we further adjusted for prevalent non-gestational diabetes (yes/no) and physical activity (MET-minutes per week). The latter was recorded with the self-administered version of the IPAQ (International Physical Activity Questionnaire) short form.

Statistical Analysis

Age-adjusted baseline characteristics of the study population, stratified by gender-specific quartile of cardiorespiratory fitness, were calculated by direct standardization according to the age distribution of the cohort. Cox proportional hazards regression models with age as the underlying time metric were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the association between cardiorespiratory fitness and colorectal cancer risk. Age at baseline in years was used as entry time. Age at complete follow-up, age at cancer diagnosis, or age at death, whichever came first, was used as exit time. The proportional hazards assumption was verified using Schoenfeld residuals. The proportional hazards assumption did not hold in certain models regarding the categorical variables study centre, education, income, smoking behavior or family history of bowel cancer. In such instances, we ran stratified Cox models.

Cardiorespiratory fitness ($PWC_{75\%}$) expressed as W/kg was entered into the model as a continuous variable and log-linearity was checked using restricted cubic splines. We report HRs per interquartile range increase (i.e., 25^{th} to 75^{th} percentile) in $PWC_{75\%}$ [34]. In an alternative analysis, cardiorespiratory fitness was categorized according to age- and gender-specific tertiles (low/intermediate/high) for easier interpretability and better comparability with the previous literature. To increase the statistical power and to reduce potential bias, we applied chained-equation multiple imputation to covariables with missing values [35]. In supplementary models, we considered a complete case model. Separate models were run for each colorectal cancer endpoint (i.e., colorectal cancer, colon cancer, rectal cancer, proximal colon cancer, and distal colon cancer) in the total study population and separately for women and men. Subtype heterogeneity was checked by the Wald statistic using a competing risk approach [36].

We performed numerous sensitivity analyses to assess the extent to which observed associations could be due to bias or confounding. Specially, we calculated the E-Value, which indicates the minimum strength of an association that an unmeasured confounder would need to have with cardiorespiratory fitness and colorectal cancer on the risk ratio scale to account for the observed

exposure-outcome association [37, 38]. Because prevalent diabetes could represent an intermediate variable lying on the causal pathway linking cardiorespiratory fitness to colorectal cancer, models were run with and without adjustment for diabetes. Because habitual physical activity represents the main determinant of cardiorespiratory fitness [39], in a further sensitivity analysis we adjusted for physical activity (MET-minutes/week) to rule out possible confounding by physical activity. To assess the potential for residual confounding by baseline health status, we performed an additional analysis after excluding study participants who rated their health as "poor". In a further sensitivity analysis, we excluded participants who were diagnosed with colorectal cancer within 12 months of baseline to assess the potential for reverse causation.

Our primary analysis was based on all participants with at least two data points during the incremental work load phase. Because an inappropriately brief cardiorespiratory fitness test could lead to differential exposure misclassification, in a supplementary analysis we excluded all participants whose incremental work load phase was shorter than 30 seconds. As only participants with minimal or small risk took part in the incremental cycle ergometer protocol, in an additional sensitivity analysis we imputed missing values for cardiorespiratory fitness data to minimize possible selection bias. We tested for multiplicative effect modification using the Wald test, with Bonferroni correction. A p value < 0.05 was considered statistically significant and all statistical analyses were performed using R Statistical Software version 3.3.2 [40].

Results

During 271,504.5 person-years of follow-up (mean=4.6 years; SD=0.3), we observed 232 colorectal cancer cases, 151 colon cancer cases, 79 rectal cancer cases, 74 cases of proximal colon cancer, and 61 cases of distal colon cancer. Participants in the highest quartile of fitness showed higher levels of education, income, and participation in physical activity, and they were more likely to currently consume alcohol and to smoke than those in the lowest quartile of fitness. Subjects with a high level of fitness also tended to report better health and a history of undergoing bowel cancer screening than their less fit counterparts. By comparison, participants in the highest fitness level showed less

consumption of red meat and they were less affected by adiposity, diabetes, cardiovascular disease, and long-standing illness than those in the lowest fitness level (Table 1).

Increasing level of cardiorespiratory fitness was associated with decreasing risk of colorectal cancer. After adjustment for age, gender, and study centre, the HR of colorectal cancer per interquartile increase in cardiorespiratory fitness was 0.79 (95% CI: 0.65-0.98). Additional control for multiple variables had no impact (HR 0.78, 95% CI: 0.62-0.97). After further adjustment for physical activity, results were also essentially unaltered (HR 0.78, 95% CI: 0.63-0.98). In an analysis adjusted for diabetes, the relation of cardiorespiratory fitness to colorectal cancer remained principally unchanged (HR 0.78, 95% CI: 0.63-0.97)(Table 2).

Because undiagnosed colorectal cancer may have caused lower fitness levels at study baseline, in a sub-analysis we excluded 42 colorectal cancer cases that occurred within 12 months of study baseline. Statistical power was reduced, but results were not materially altered (HR 0.85, 95% CI: 0.67-1.08). Findings were also largely similar when we further minimized any impact that undiagnosed colorectal cancer may have had on fitness levels by additionally excluding subjects who reported poor health at entry (HR 0.78, 95% CI: 0.62-0.97). Because an inappropriately brief cardiorespiratory fitness test could have led to differential exposure misclassification, in an additional analysis we excluded participants with an incremental work load phase < 30 seconds and found that the inverse association remained apparent (HR 0.78, 95% CI: 0.62-0.97).

In additional sensitivity analyses, we found that for an unmeasured confounder to explain the observed HR relating cardiorespiratory fitness to colorectal cancer of 0.78, the unobserved confounder would have to be related to cardiorespiratory fitness and colorectal cancer with a relative risk of 1.9, above and beyond the measured confounders. For an unmeasured confounder to bring the upper confidence limit of 0.97 to above 1.0, the unobserved confounder would have to be related to cardiorespiratory fitness and colorectal cancer with a relative risk of 1.2, above and beyond the measured confounders.

To enhance statistical power and minimize potential selection bias, we conducted supplementary analyses based on imputed values for missing or implausible exposure data. This procedure generated findings that were similar to those observed in the main analysis (Online Resource Table S1). Although statistical power was slightly reduced, results remained largely similar in complete case analyses (Online Resource Table S2). When cardiorespiratory fitness was analysed as a categorical value, the HR of colorectal cancer for high vs. low cardiorespiratory fitness was 0.73 (95% CI: 0.51-1.06).

We investigated cardiorespiratory fitness in relation to anatomic colorectal cancer subsites. Similar to our analysis of overall colorectal cancer, an interquartile increase in cardiorespiratory fitness was associated with decreased risk of colon cancer (HR 0.74, 95% CI: 0.56-0.97). The relation appeared to be somewhat more pronounced for proximal colon cancer (HR 0.70, 95% CI: 0.46-1.06) than distal colon cancer (HR 0.81, 95% CI: 0.53-1.24), and the association was weakest for rectal cancer (HR 0.88, 95% CI: 0.62-1.26; p value for difference between colorectal cancer subsites=0.113)(Table 2).

In analyses stratified by gender, cardiorespiratory fitness was inversely associated with colorectal cancer in men (HR 0.72, 95% CI: 0.55-0.94) but not women (HR 0.99, 95% CI: 0.71-1.38), although the interaction by gender was not statistically significant (p value for interaction by gender=0.192). The relation between cardiorespiratory fitness and colon cancer appeared to be more pronounced for men (HR 0.72, 95% CI: 0.51-1.01) than women (HR 0.84, 95% CI: 0.56-1.26; p value for interaction by gender=0.802)(Table 2). In addition, the association between cardiorespiratory fitness and colorectal cancer was not modified by study centre, education, income, physical activity, sedentary behaviour, waist-to-hip ratio, height, alcohol consumption, smoking behaviour, processed meat intake, past colorectal cancer screening, family history of bowel cancer, prevalent non-gestational diabetes, NSAID use, and hormone replacement therapy (among women), after Bonferroni correction. In analyses stratified by age- and gender-specific tertiles of physical activity, associations between cardiorespiratory fitness and colorectal cancer were not statistically significant (results not shown).

Discussion

In this prospective study of nearly 60,000 women and men followed for up to 5 years, higher cardiorespiratory fitness was associated with lower risk of colorectal cancer. The inverse relation with cardiorespiratory fitness appeared to be most pronounced for proximal colon cancer, it was somewhat weaker for distal colon cancer, and the association was weakest for rectal cancer. When analysed according to gender, cardiorespiratory fitness was more strongly related to decreased risk of colorectal cancer in men than women, although the difference by gender was not statistically significant.

Only six studies examined the association between cardiorespiratory fitness and colorectal cancer risk [3-8]. A recent UK Biobank study found a borderline statistically significant inverse relation of cardiorespiratory fitness to colorectal cancer (HR 0.96, 95% CI: 0.92-1.00) when modelled as a linear association, and a statistically significant relation when modelled as a non-linear association using penalized cubic splines [7]. However, that study did not present associations according to gender or colorectal cancer anatomic subsite [7]. The Kuopio Ischaemic Heart Disease Risk Factor Study reported a HR of gastrointestinal cancer of 0.88 (95% CI: 0.79-0.99) for a one metabolic equivalent of task (MET) increase in cardiorespiratory fitness [5]. Similarly, the Cooper Center Longitudinal Study generated a HR of 0.91 (95% CI: 0.84-0.99) for a 1 MET increase in cardiorespiratory fitness [6]. The Oslo Ischemia Study found a HR of proximal colon cancer of 0.30 (95% CI: 0.13-0.73) for intermediate vs. low cardiorespiratory fitness but detected no association with distal colon cancer [4]. In contrast, the Veterans Exercise testing study and the Copenhagen Male Study did not find a statistically significant association between cardiorespiratory fitness and colorectal cancer [3, 8]. The results of the most recent 4 studies in men were pooled in a meta-analysis and yielded a HR of colorectal cancer of 0.77 (95% CI: 0.62-0.92) for high versus low cardiorespiratory fitness [41].

Most previous studies used a maximal treadmill or cycle ergometer test to measure cardiorespiratory fitness until volitional exhaustion [3-6]. An advantage of that method is that VO_{2max} can be derived

with better accuracy or can even be determined directly if spirometry is conducted during exercise testing [42]. However, maximal exercise tests are highly dependent on participant motivation and they pose greater burden and risk [20, 42]. While MET_{max} can be estimated using a submaximal ergometer test, we chose to use $PWC_{75\%}$, the rationale being that a linear increase assumed by extrapolation is unassured, particularly in elderly individuals [19, 20].

The exact biologic mechanisms underlying the association between cardiorespiratory fitness and colorectal cancer are not established, but several hypotheses exist. Cardiorespiratory fitness is positively associated with insulin sensitivity and inversely related to fasting insulin levels, although those relations have been shown to be partly mediated through changes in body composition, particularly increased fat-free mass [43, 44]. A further etiologic pathway is that moderate exercise training leading to increased VO_{2max} reduces circulating levels of IL-6 and TNF-α and increases levels of IL-10, thereby creating an anti-inflammatory microenvironment [45]. Cardiorespiratory fitness is also positively associated with microbial diversity and butyrate production, which in turn is inversely related to colorectal cancer [46, 47]. Also, higher fitness level is associated with better resilience against oxidative stress due to upregulation of antioxidant enzyme capacity [48].

We noted a more pronounced inverse association between cardiorespiratory fitness and proximal colon cancer than distal colon cancer. Reasons are unknown, but one possible explanation is molecular heterogeneity between colon anatomic subsites. For example, proximal colon tumours more often show microsatellite instability and deficient DNA mismatch repair than distal colon tumours [49]. If part of the beneficial effect of fitness on colon cancer is mediated by elevated DNA repair mechanisms, higher cardiorespiratory fitness would be expected to preferentially benefit colon anatomic subsites that are characterized by diminished DNA repair.

To the best of our knowledge, the current study is the first to present data on women. We noted that the inverse association between cardiorespiratory fitness and colorectal cancer was considerably weaker in women than men. Reasons for this observation are speculative but may involve

differences in hormonal pathways of colorectal carcinogenesis between women and men. For example, the potential benefits of fitness brought about by decreases in insulin resistance may be largely offset by diminished rates of aromatase activity and decreased production of endogenous estrogens in the adipose tissue in fit women [43, 50] . Of note, both exogenous and endogenous estrogens are related to decreased risk of colorectal cancer in postmenopausal women [51, 52]. Also, the 25^{th} to 75^{th} percentile range of cardiorespiratory fitness was wider among men (increment=0.79) than women (increment=0.57). It is possible that such smaller variation and thus, worse discrimination of exposure among women contributed to a less pronounced strength of association in that group.

While adiposity may represent a causal intermediate linking increased physical activity to decreased risk of colorectal cancer, the notion that adiposity acts as a confounder of the association between cardiorespiratory fitness and colorectal cancer also appears possible. Therefore, we adjusted for waist-to-hip ratio in all full models. By comparison, diabetes likely represents an intermediate on the causal pathway between cardiorespiratory fitness and colorectal cancer. Higher levels of cardiorespiratory fitness are associated with lower risk of type 2 diabetes and diabetes is an established risk factor for colorectal cancer [53, 54]. Thus, we did not include diabetes in our full models. We did adjust for diabetes in a sensitivity analysis and results were principally unchanged, indicating that the benefits of fitness on risk for colorectal cancer are not exclusively mediated by insulin sensitivity.

Physical fitness and physical activity are positively correlated and increases in physical activity generally lead to enhanced levels of physical fitness [55, 56]. In addition, both physical fitness and physical activity provide important health benefits and physical activity is an established protective factor for colon cancer [57, 58]. To address the benefit of cardiorespiratory fitness on reducing risk of colorectal cancer independent of the effect of physical activity, in a sensitivity analysis we adjusted for physical activity and found that the inverse association between cardiorespiratory fitness and colorectal cancer was unaltered. This suggests that the exercise-independent element of cardiorespiratory fitness may be most relevant to its anticancer benefit. Although physical activity is strongly positively related to cardiorespiratory fitness, the latter can be also influenced by other

factors such as genetics, smoking, body weight or subclinical disease, indicating that cardiorespiratory fitness is an imperfect proxy for physical activity [59, 11, 60]. An alternative or additional explanation for the observation that adjusting for physical activity did not attenuate the association is that in our study, physical fitness was assessed with greater validity than was physical activity. While cardiorespiratory fitness was measured with an objective method, physical activity was assessed with a subjective questionnaire, a method that is susceptible to measurement errors such as recall or social desirability bias [61]. When performing an analysis stratified by age- and gender-specific tertiles of physical activity, we did not find statistically significant associations between cardiorespiratory fitness and colorectal cancer in any stratum. This could be due to reduced power in stratified analyses.

Our study has several notable strengths. Cardiorespiratory fitness was objectively measured using state-of-the-art methodology, which increased the validity and precision of our findings and helped avoid exposure misclassification. Information on colorectal cancer endpoints was obtained through linkage to national cancer registries, which ensured comprehensive case ascertainment. Particular attention was given to adjusting for a broad range of potential confounding variables, including family history of bowel cancer, history of colorectal cancer screening, NSAID use, smoking behaviour, and red and processed meat intake.

A further important asset of our study is that we performed numerous informative sensitivity analyses to test the robustness of our findings to unobserved confounding. In order to explain away our results, an unobserved confounder would have needed to show a strong relation to both cardiorespiratory fitness and colorectal cancer of the order of magnitude of a relative risk of 1.9, above and beyond the measured confounders. Established colorectal cancer risk factors such as family history of bowel cancer showed a HR of about 1.4 in our dataset, and being male showed a HR of about 1.6. Those variables are among the strongest known colorectal cancer risk factors. It appears unlikely that an unmeasured or unknown confounder would have had a larger impact on colorectal cancer risk than those established risk factors.

Despite numerous advantageous features of our study, one potential limitation is the relatively short follow-up time with a limited number of cases, especially in the subsite analyses, which reduced precision. While our analyses were able to pick up several meaningful and statistically significant relations between cardiorespiratory fitness and colorectal cancer, this does not prove that statistical power was sufficient and an underpowered study also has a greater chance that statistically significant results do not reflect true effects [62]. Still, our results for men are remarkably similar to the results of a recent meta-analysis that used data from 4 separate cohorts with varying methodology (e.g., maximal fitness test, different covariables) [41]. Such agreement implies that our estimates are not overly inflated by the choice of methodology [62, 63]. Further studies with sufficient power are needed to provide additional information regarding the association between cardiorespiratory fitness and colorectal cancer subsites in subgroups of men and women. We were concerned that the short follow-up period may have led to reverse causation. However, findings remained reasonably stable after exclusion of cases that occurred during the initial period of follow-up. An additional potential shortcoming of our study is that only a subsample of the overall UK Biobank cohort was selected for fitness testing, raising concern about potential selection bias. We addressed this issue by imputing data for all participants who were originally intended to undergo fitness testing. Reassuringly, the inverse association between fitness and colorectal cancer seen in the initial analysis persisted in that secondary analysis. Because the latency period between cardiorespiratory fitness and cancer initiation presumably spans many years, we assumed that cardiorespiratory fitness at study entry represents a consistent trait over time, an assumption we were unable to directly verify in the data at hand. Our investigation lacks the causality of a randomized trial, but trial data on the effects of cardiorespiratory fitness on colorectal cancer are currently unavailable. Thus, at present, findings from our and other observational research are needed to help address the question of whether fitness levels predict future colorectal cancer risk.

Conclusion

In summary, our findings suggest that a high level of cardiorespiratory fitness decreases the risk of colorectal cancer. Our results indicate that achieving a high level of fitness by those who are currently unfit represents an important individual-level and public health opportunity to decrease the risk of colorectal cancer.

Compliance with Ethical Standards:

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants

Ethical approval: All procedures performed were in accordance and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and ethical approval was obtained from North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820).

Informed consent:

Informed consent was obtained from all individual participants included in the study.

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Contributions:

AH conducted the data preparation and analysis. AH drafted the manuscript with support from ML and SB. ML and SB conceived the original idea and supervised the project. All authors directly participated in interpretation of the results, provided critical comments to the manuscript and revised the text. All authors of this research paper have read and approved the final version submitted.

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Availability of data and materials:

UK Biobank is an open access resource. Bona fide researchers can apply to use the UK Biobank data set by registering and applying at http://www.ukbiobank.ac.uk/register-apply.

List of abbreviations:

BMI: body mass index; bpm: beats per minute; CI: confidence interval; ECG: electrocardiograph; HR: hazard ratio; ICD: International Classification of Diseases; IPAQ: International Physical Activity Questionnaire; MET: metabolic equivalent of task; MREC: North West Multi-centre Research Ethics Committee; NSAID: nonsteroidal anti-inflammatory drug; $PWC_{75\%}$: physical work capacity at 75% of the maximum heart rate standardised to body mass.

References

1. Mahmood S, MacInnis RJ, English DR, Karahalios A, Lynch BM. Domain-specific physical activity and sedentary behaviour in relation to colon and rectal cancer risk: a systematic review and meta-analysis. Int J Epidemiol. 2017;46(6):1797-813. doi:10.1093/ije/dyx137.
2. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA internal medicine. 2016;176(6):816-25. doi:10.1001/jamainternmed.2016.1548.
3. Vainshelboim B, Muller J, Lima RM, Nead KT, Chester C, Chan K et al. Cardiorespiratory fitness and cancer incidence in men. Annals of epidemiology. 2017;27(7):442-7. doi:10.1016/j.annepidem.2017.06.003.
4. Robsahm TE, Falk RS, Heir T, Sandvik L, Vos L, Erikssen J et al. Cardiorespiratory fitness and risk of site-specific cancers: a long-term prospective cohort study. Cancer medicine. 2017;6(4):865-73. doi:10.1002/cam4.1043.
5. Laukkanen JA, Pukkala E, Rauramaa R, Makikallio TH, Toriola AT, Kurl S. Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men. European journal of cancer (Oxford, England : 1990). 2010;46(2):355-63. doi:10.1016/j.ejca.2009.07.013.
6. Lakoski SG, Willis BL, Barlow CE, Leonard D, Gao A, Radford NB et al. Midlife Cardiorespiratory Fitness, Incident Cancer, and Survival After Cancer in Men: The Cooper Center Longitudinal Study. JAMA oncology. 2015;1(2):231-7. doi:10.1001/jamaoncol.2015.0226.
7. Steell L, Ho FK, Sillars A, Petermann-Rocha F, Li H, Lyall DM et al. Dose-response associations of cardiorespiratory fitness with all-cause mortality and incidence and mortality of cancer and cardiovascular and respiratory diseases: the UK Biobank cohort study. British journal of sports medicine. 2019:bjsports-2018-099093. doi:10.1136/bjsports-2018-099093.
8. Nunez C, Clausen J, Jensen MT, Holtermann A, Gyntelberg F, Bauman A. Main and interactive effects of physical activity, fitness and body mass in the prevention of cancer from the Copenhagen Male Study. Scientific reports. 2018;8(1):11780. doi:10.1038/s41598-018-30280-5.
9. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports. 1985;100(2):126-31.
10. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. Circulation. 2016;134(24):e653-e99. doi:10.1161/cir.0000000000000461.
11. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Medicine and science in sports and exercise. 2001;33(6 Suppl):S379-99; discussion S419-20.
12. McGuire KA, Ross R. Incidental physical activity is positively associated with cardiorespiratory fitness. Medicine and science in sports and exercise. 2011;43(11):2189-94. doi:10.1249/MSS.0b013e31821e4ff2.
13. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG et al. Colorectal cancer. Nature reviews Disease primers. 2015;1:15065. doi:10.1038/nrdp.2015.65.
14. Brenner H, Kloor M, Pox CP. Colorectal cancer. The Lancet. 2014;383(9927):1490-502. doi:https://doi.org/10.1016/S0140-6736(13)61649-9.
15. Trehearne A. Genetics, lifestyle and environment. UK Biobank is an open access resource following the lives of 500,000 participants to improve the health of future generations. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz. 2016;59(3):361-7. doi:10.1007/s00103-015-2297-0.
16. UK Biobank. Cardio Assessment. Version 1.0. 2011. https://biobank.ctsu.ox.ac.uk/crystal/docs/Cardio.pdf.
17. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. Physical therapy. 2000;80(8):782-807.
18. Eng JJ, Dawson AS, Chu KS. Submaximal exercise in persons with stroke: test-retest reliability and concurrent validity with maximal oxygen consumption. Archives of physical medicine and rehabilitation. 2004;85(1):113-8.

19. Gore CJ, Booth ML, Bauman A, Owen N. Utility of pwc75% as an estimate of aerobic power in epidemiological and population-based studies. Medicine and science in sports and exercise. 1999;31(2):348-51.
20. Hollmann W, Strüder H, Predel H-G, Tagarakis C. Spiroergometrie. Kardiopulmonale Leistungsdiagnostik des Gesunden und Kranken. Schattauer; 2006.
21. Batcho CS, Thonnard JL, Nielens H. PWC 75%/kg, a fitness index not linked to resting heart rate: testing procedure and reference values. Archives of physical medicine and rehabilitation. 2012;93(7):1196-200. doi:10.1016/j.apmr.2012.02.021.
22. Finger J, Gößwald A, Härtel S, Müters S, Krug S, Hölling H et al. Measurement of cardiorespiratory fitness in the German Health Interview and Examination Survey for Adults (DEGS1). Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz. 2013;56(5-6):885-93. doi:10.1007/s00103-013-1694-5.
23. Finger J, Krug S, Gößwald A, Härtel S, Bös K. Cardiorespiratory fitness among adults in Germany. Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung; 2013.
24. Baumeister SE, Ricci C, Kohler S, Fischer B, Topfer C, Finger JD et al. Physical activity surveillance in the European Union: reliability and validity of the European Health Interview Survey-Physical Activity Questionnaire (EHIS-PAQ). The international journal of behavioral nutrition and physical activity. 2016;13:61. doi:10.1186/s12966-016-0386-6.
25. Niedermann K, Sidelnikov E, Muggli C, Dagfinrud H, Hermann M, Tamborrini G et al. Effect of cardiovascular training on fitness and perceived disease activity in people with ankylosing spondylitis. Arthritis care & research. 2013;65(11):1844-52. doi:10.1002/acr.22062.
26. Nagashima J, Musha H, Takada H, Takagi K, Mita T, Mochida T et al. Three-month exercise and weight loss program improves heart rate recovery in obese persons along with cardiopulmonary function. Journal of cardiology. 2010;56(1):79-84. doi:10.1016/j.jjcc.2010.03.001.
27. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. Journal of the American College of Cardiology. 2001;37(1):153-6.
28. Reifman A, Keyton K. Winsorize. In N. J. Salkind (Ed.), Encyclopedia of Research Design (pp. 1636-1638). Thousand Oaks, CA: Sage; 2010.
29. World Health Organization (WHO). ICD-9 : international statistical classification of diseases and related health problems / World Health Organization. Geneva: World Health Organization; 1978.
30. World Health Organization (WHO). ICD-10 : international statistical classification of diseases and related health problems / World Health Organization. Geneva: World Health Organization; 2004.
31. VanderWeele TJ, Shpitser I. A New Criterion for Confounder Selection. Biometrics. 2011;67(4):1406-13. doi:10.1111/j.1541-0420.2011.01619.x.
32. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International Journal of Epidemiology. 2016;45(6):1887-94. doi:10.1093/ije/dyw341.
33. Hernán MA, Robins JM. (2019). Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming.
34. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Springer International Publishing; 2015.
35. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011;45(3):1-67. doi:10.18637/jss.v045.i03.
36. Wang M, Spiegelman D, Kuchiba A, Lochhead P, Kim S, Chan AT et al. Statistical methods for studying disease subtype heterogeneity. Stat Med. 2016;35(5):782-800. doi:10.1002/sim.6793.
37. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the e-value. Annals of internal medicine. 2017;167(4):268-74. doi:10.7326/M16-2607.
38. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. JAMA. 2019;321(6):602-3. doi:10.1001/jama.2018.21554.
39. McKinney J, Lithwick DJ, Morrison BN, Nazzari H, Isserow S, Heilbron B et al. The health benefits of physical activity and cardiorespiratory fitness. BCMJ. 2016;58(3):131-7.
40. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.
41. Pozuelo-Carrascosa DP, Alvarez-Bueno C, Cavero-Redondo I, Morais S, Lee IM, Martínez-Vizcaíno V. Cardiorespiratory fitness and site-specific risk of cancer in men: A systematic review and meta-

analysis. European Journal of Cancer. 2019;113:58-68. doi:https://doi.org/10.1016/j.ejca.2019.03.008.
42. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 9th Edition. edn. Baltimore: Wolters Kluwer Health/Lippinoctt, Williams & Wilkins; 2014.
43. Lee S, Bacha F, Gungor N, Arslanian SA. Cardiorespiratory fitness in youth: relationship to insulin sensitivity and beta-cell function. Obesity (Silver Spring, Md). 2006;14(9):1579-85. doi:10.1038/oby.2006.182.
44. Vella CA, Van Guilder GP, Dalleck LC. Low Cardiorespiratory Fitness Is Associated with Markers of Insulin Resistance in Young, Normal Weight, Hispanic Women. Metabolic syndrome and related disorders. 2016;14(5):272-8. doi:10.1089/met.2015.0135.
45. Santos RV, Viana VA, Boscolo RA, Marques VG, Santana MG, Lira FS et al. Moderate exercise training modulates cytokine profile and sleep in elderly people. Cytokine. 2012;60(3):731-5. doi:10.1016/j.cyto.2012.07.028.
46. Estaki M, Pither J, Baumeister P, Little JP, Gill SK, Ghosh S et al. Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. Microbiome. 2016;4(1):42. doi:10.1186/s40168-016-0189-7.
47. Ahn J, Sinha R, Pei Z, Dominianni C, Wu J, Shi J et al. Human gut microbiome and risk for colorectal cancer. Journal of the National Cancer Institute. 2013;105(24):1907-11. doi:10.1093/jnci/djt300.
48. Traustadottir T, Davies SS, Su Y, Choi L, Brown-Borg HM, Roberts LJ, 2nd et al. Oxidative stress in older adults: effects of physical fitness. Age (Dordrecht, Netherlands). 2012;34(4):969-82. doi:10.1007/s11357-011-9277-6.
49. Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25(10):1995-2001. doi:10.1093/annonc/mdu275.
50. Song M, Hu FB, Spiegelman D, Chan AT, Wu K, Ogino S et al. Long-term status and change of body fat distribution, and risk of colorectal cancer: a prospective cohort study. International journal of epidemiology. 2016;45(3):871-83. doi:10.1093/ije/dyv177.
51. Murphy N, Strickler HD, Stanczyk FZ, Xue X, Wassertheil-Smoller S, Rohan TE et al. A Prospective Evaluation of Endogenous Sex Hormone Levels and Colorectal Cancer Risk in Postmenopausal Women. Journal of the National Cancer Institute. 2015;107(10):djv210. doi:10.1093/jnci/djv210.
52. Limsui D, Vierkant RA, Tillmans LS, Wang AH, Weisenberger DJ, Laird PW et al. Postmenopausal hormone therapy and colorectal cancer risk by molecularly defined subtypes among older women. Gut. 2012;61(9):1299-305. doi:10.1136/gutjnl-2011-300719.
53. Tarp J, Stole AP, Blond K, Grontved A. Cardiorespiratory fitness, muscular strength and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetologia. 2019;62(7):1129-42. doi:10.1007/s00125-019-4867-4.
54. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. World journal of gastroenterology. 2015;21(19):6026-31. doi:10.3748/wjg.v21.i19.6026.
55. Jackson AS, Sui X, Hebert JR, Church TS, Blair SN. Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. Archives of internal medicine. 2009;169(19):1781-7. doi:10.1001/archinternmed.2009.312.
56. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Medicine and science in sports and exercise. 2011;43(7):1334-59. doi:10.1249/MSS.0b013e318213fefb.
57. Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services, 2018.
58. Rezende LFM, Sa TH, Markozannes G, Rey-Lopez JP, Lee IM, Tsilidis KK et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. British journal of sports medicine. 2018;52(13):826-33. doi:10.1136/bjsports-2017-098391.

59. DeFina LF, Haskell WL, Willis BL, Barlow CE, Finley CE, Levine BD et al. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? Progress in cardiovascular diseases. 2015;57(4):324-9. doi:10.1016/j.pcad.2014.09.008.
60. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Medicine and science in sports and exercise. 2001;33(5):754-61. doi:10.1097/00005768-200105000-00012.
61. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. The international journal of behavioral nutrition and physical activity. 2008;5:56. doi:10.1186/1479-5868-5-56.
62. Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ et al. Power failure: why small sample size undermines the reliability of neuroscience. Nature Reviews Neuroscience. 2013;14:365. doi:10.1038/nrn3475.
63. Ioannidis JP. Why most discovered true associations are inflated. Epidemiology (Cambridge, Mass). 2008;19(5):640-8. doi:10.1097/EDE.0b013e31818131e7.

Fig. 1 Flow chart of UK Biobank participants for the analysis of cardiorespiratory fitness and colorectal cancer associations

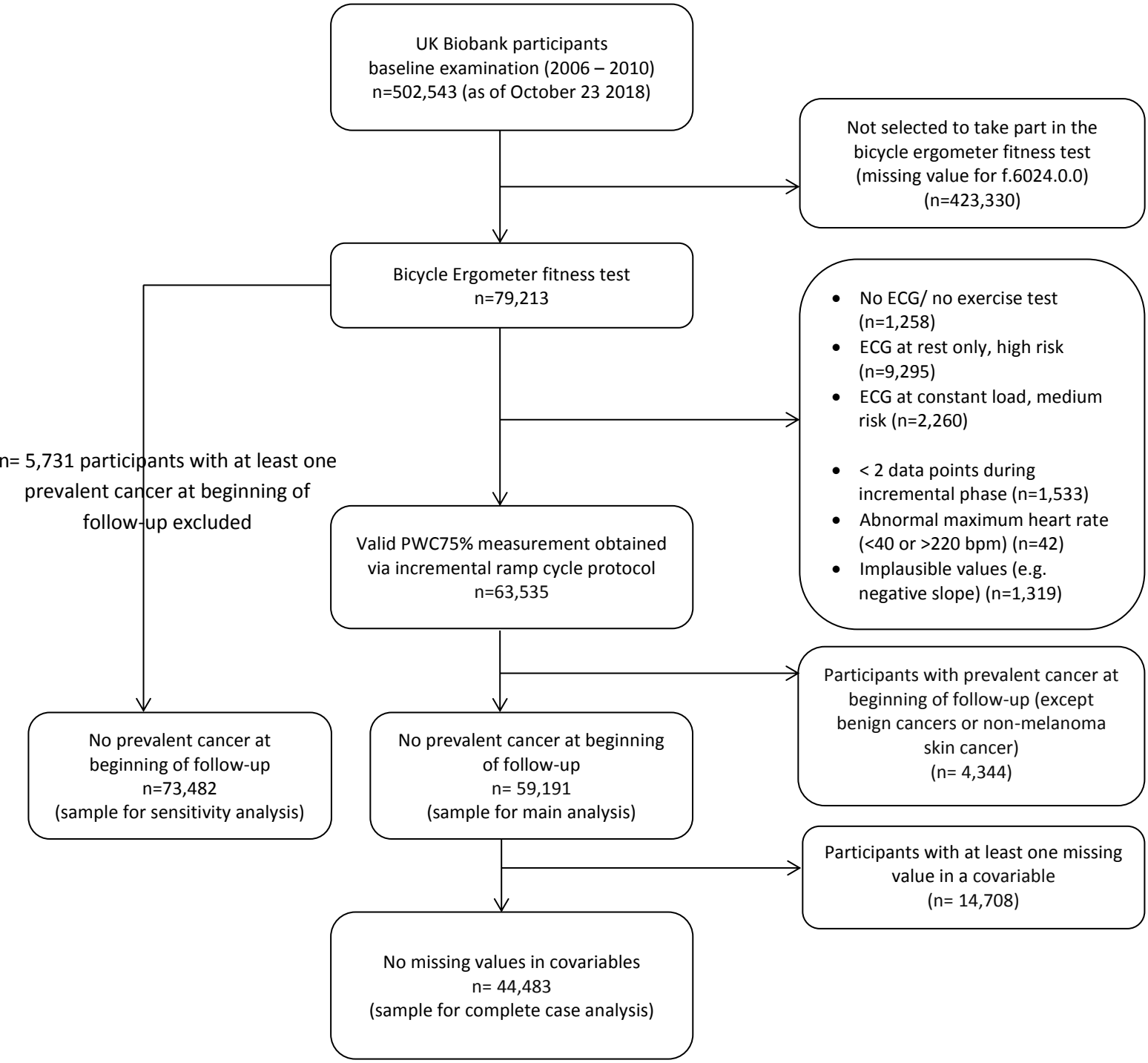

Fig. 2 Distribution of cardiorespiratory fitness ($PWC_{75\%}$, winsorized at 1st and 99th percentile), stratified by gender

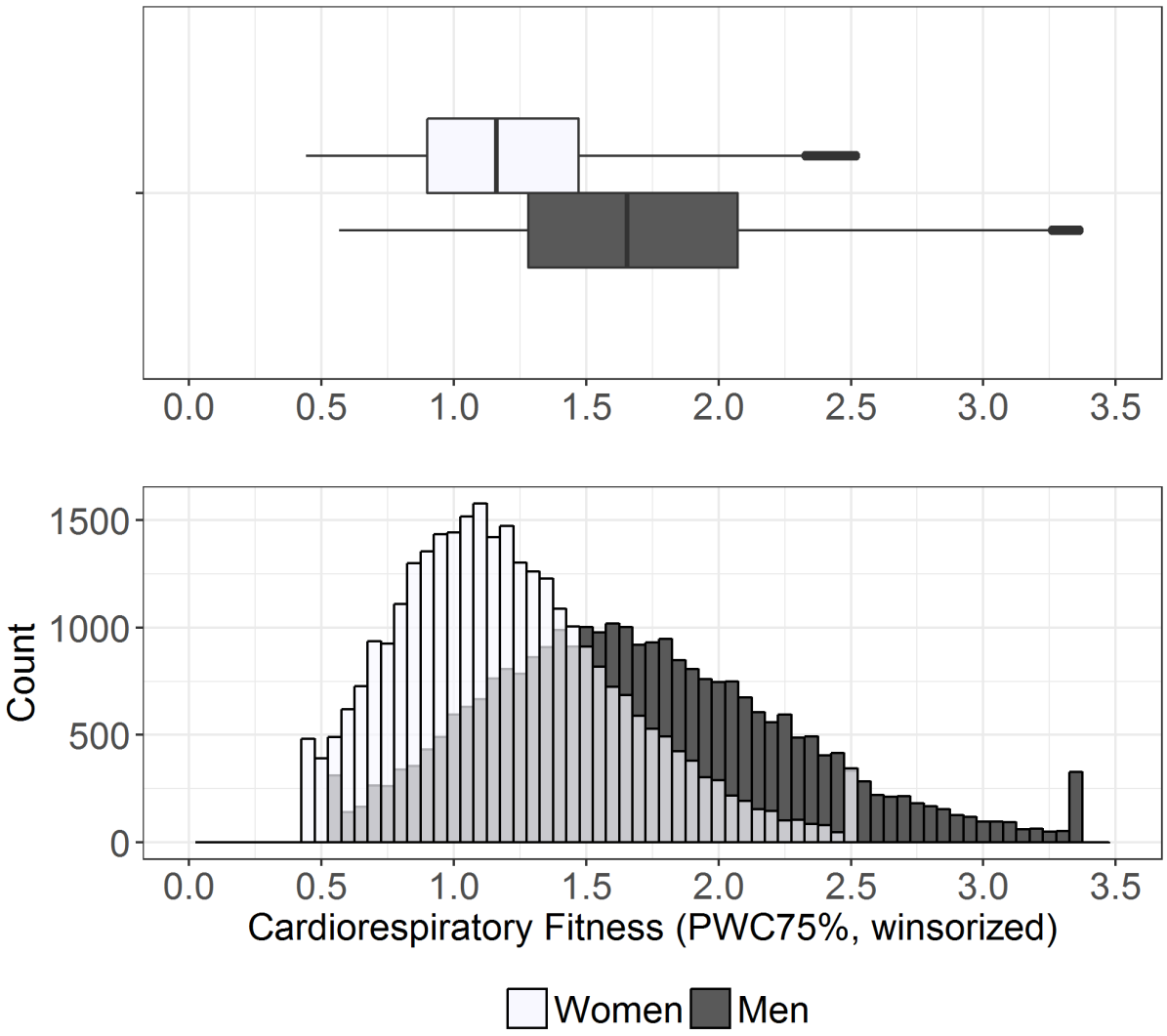

Table 1: Age-standardised baseline characteristics of the study population by quartiles of cardiorespiratory fitness ($PWC_{75\%}$).

	Gender-specific quartile of $PWC_{75\%}$[a]				
	1st Quartile Lowest fitness	**2nd Quartile**	**3rd Quartile**	**4th Quartile Highest fitness**	**Missing**
Number of participants	**14,798**	**14,798**	**14,797**	**14,798**	
Cardiorespiratory fitness ($PWC_{75\%}$ in W/kg; winsorized at inner 98%)					0
	0.86	1.25	1.57	2.14	
Age at baseline (yrs)					0
	56.66	56.32	56.03	55.75	
Gender					0
Women	52.02	51.69	51.34	49.04	
Men	47.98	48.31	48.66	50.96	
Ethnic background					1,607
White	87.70	92.15	94.31	95.87	
Mixed, Other	3.27	2.62	2.08	1.85	
Asian, British Asian, Chinese	2.17	1.65	1.43	1.10	
Black or Black British	6.86	3.58	2.18	1.17	
UK Biobank assessment centre					0
Sheffield	23.47	24.14	25.56	26.16	
Liverpool	8.32	8.39	8.08	6.99	
Hounslow	16.69	18.27	19.25	20.41	
Croydon	22.58	23.24	24.14	26.46	
Birmingham	28.95	25.96	22.98	19.99	
Education					678
University, College degree	29.19	34.41	39.11	45.28	
A-levels, AS-levels, NVQ, HND, HNC or equivalent or other professional qualification	24.43	24.44	23.57	22.62	
O-levels, CSEs or equivalent	29.88	28.60	26.72	23.54	
None of the above	16.51	12.54	10.61	8.56	
Average total household income before tax					7,754
< 31,000 £	53.10	45.26	39.81	34.56	
31,000 £ - 51,999 £	25.89	26.63	27.61	27.10	
> 51,999 £	21.00	28.12	32.57	38.34	
Physical activity (MET-minutes/week)					11,547
	2512.02	2721.16	2938.61	3330.50	
TV watching time (hrs/day)					531
	3.09	2.74	2.53	2.31	
Waist-to-hip ratio					3
	0.90	0.88	0.87	0.86	
Body mass index (kg/m^2)					0
	29.70	27.53	26.44	25.52	

Standing height (cm)					0
	167.81	168.96	169.71	170.93	
Alcohol consumption					204
Never	6.89	4.78	3.60	2.54	
Previous	3.54	3.59	2.68	2.43	
Current	89.57	91.63	93.73	95.04	
Smoking behaviour					333
Never	59.18	56.71	55.64	54.98	
Previous	32.40	33.90	35.16	35.85	
Current	8.42	9.39	9.20	9.16	
Consumption of red and processed meat					168
< 2 times per week	13.68	14.70	15.08	16.65	
2 - 3 times per week	41.35	44.08	46.32	47.61	
> 3 times per week	44.97	41.21	38.60	35.74	
Ever had bowel cancer screening					949
No	59.78	58.98	58.35	58.31	
Yes	40.22	41.02	41.65	41.69	
Family history of bowel cancer					7,142
No	90.08	89.68	89.29	89.26	
Yes	9.92	10.32	10.71	10.74	
Prevalent diabetes					318
No	93.70	96.63	97.66	97.86	
Yes	6.30	3.37	2.34	2.14	
Prevalent cardiovascular disease					263
No	63.65	74.42	78.36	78.46	
Yes	36.35	25.58	21.64	21.54	
Subjective health rating					314
Excellent	8.89	13.42	17.18	23.85	
Good	57.96	62.12	63.93	61.48	
Fair	28.66	21.58	17.04	13.37	
Poor	4.49	2.88	1.84	1.31	
Longstanding illness					1,449
No	66.21	72.37	75.47	76.44	
Yes	33.79	27.63	24.53	23.56	
Regular intake of NSAIDs					796
No	74.19	76.04	76.09	76.46	
Yes	25.81	23.96	23.91	23.54	
Ever had hormone replacement therapy					28,677
No	65.16	63.60	63.39	66.73	
Yes	34.84	36.40	36.61	33.27	

Age-standardisation was performed by direct standardisation to the baseline age distribution of the cohort.

[a] $PWC_{75\%}$: Physical Work Capacity at 75% of maximum heart rate. Gender-specific quantiles of cardiorespiratory fitness were defined by the following distribution (25^{th} quantile, median, 75^{th} quantile):

For women: 25^{th} quantile=0.9005; median=1.1618; 75^{th} quantile=1.4725

For men: 25^{th} quantile=1.2813; Median=1.6537; 75^{th} quantile=2.0730

Table 2: Association between cardiorespiratory fitness and risk of colorectal cancer

	Total		Men		Women		
Number of participants[a]	**59,191**		**28,483**		**30,708**		
Person years[b]	**271,505**		**130,447**		**141,058**		
	HR (95% CI)	**overall p**	**HR (95% CI)**	**overall p**	**HR (95% CI)**	**overall p**	**p interaction by gender**
Colorectal cancer (C18-C20): n=232/144/88[c]							
Basic model	0.79 (0.65-0.98)	0.030	0.74 (0.57-0.94)	0.015	0.99 (0.72-1.36)	0.942	
Full model	0.78 (0.62-0.97)	0.024	0.72 (0.55-0.94)	0.015	0.99 (0.71-1.38)	0.969	0.192
Full model + physical activity	0.78 (0.63-0.98)	0.030	0.73 (0.56-0.96)	0.023	0.98 (0.70-1.36)	0.891	
Full model + diabetes	0.78 (0.63-0.97)	0.028	0.72 (0.56-0.94)	0.017	1.00 (0.71-1.39)	0.976	
Colon cancer (C18, C18.0-C18.9): n=151/85/66[c]							
Basic model	0.75 (0.57-0.98)	0.033	0.73 (0.53-1.01)	0.054	0.82 (0.56-1.21)	0.319	
Full model	0.74 (0.56-0.97)	0.032	0.72 (0.51-1.01)	0.058	0.84 (0.56-1.26)	0.404	0.802
Rectal cancer (C19, C20): n=79/57/22[c]							
Basic model	0.91 (0.65-1.27)	0.568	0.78 (0.53-1.15)	0.215	1.55 (0.88-2.72)	0.129	
Full model	0.88 (0.62-1.26)	0.495	0.76 (0.50-1.15)	0.193	1.47 (0.81-2.65)	0.204	0.027
Proximal colon cancer (C18.0-C18.5): n=74/39/35[c]							
Basic model	0.68 (0.46-1.01)	0.055	0.63 (0.38-1.03)	0.067	0.81 (0.47-1.39)	0.449	
Full model	0.70 (0.46-1.06)	0.096	0.64 (0.38-1.08)	0.097	0.83 (0.47-1.46)	0.509	0.769
Distal colon cancer (C18.6-C18.7): n=61/36/25[c]							
Basic model	0.87 (0.58-1.30)	0.489	0.92 (0.58-1.48)	0.742	0.78 (0.41-1.45)	0.428	
Full model	0.81 (0.53-1.24)	0.342	0.92 (0.56-1.53)	0.758	0.77 (0.39-1.49)	0.433	0.801

p for subtype heterogeneity (full model)			
proximal vs. distal vs. rectum cancer	0.113	0.659	0.310
colon vs. rectum cancer	0.056	0.683	0.199

Multivariable adjusted Cox proportional hazards regression with age as time scale. Cardiorespiratory fitness ($PWC_{75\%}$) was entered as a continuous variable. Associations were modelled linearly. Hazard ratios were calculated for an interquartile range increase (i.e., 25^{th} to 75^{th} percentile).
Basic models were adjusted for UK Biobank assessment centre and in the total group were additionally adjusted for gender.
Full models were additionally adjusted for education, income, sedentary behaviour, waist-to-hip ratio, height, alcohol consumption, smoking behaviour, consumption of red and processed meat, bowel cancer screening, family history of bowel cancer, and regular intake of NSAIDs. Models containing only women were further adjusted for hormone replacement therapy.
[a] Participants with observed valid cardiorespiratory fitness measures. Missing covariables were imputed.
[b] Person years: Follow-up time was calculated as time from baseline examination to complete follow-up, diagnosis of colorectal cancer, or death, whichever occurred first.
[c] Number of cases that occurred in the total group/ in the subgroup of men/ in the subgroup of women.