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SPECIAL REPORT

Post-diagnosis physical activity and sedentary behaviour and colorectal cancer prognosis: A Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis

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Abstract

Low physical activity and high sedentary behaviour have been clearly linked with colorectal cancer development, yet data on their potential role in colorectal cancer survival is limited. Better characterisation of these relationships is needed for the development of post-diagnosis physical activity and sedentary behaviour guidance for colorectal cancer survivors. We searched PubMed and Embase through 28 February 2022 for studies assessing post-diagnosis physical activity, and/or sedentary behaviour in relation to all-cause and cause-specific mortality and recurrence after colorectal cancer diagnosis. Total and recreational physical activity were assessed overall and by frequency, duration, intensity, and volume using categorical, linear, and non-linear dose–response random-effects meta-analyses. The Global Cancer Update Programme (CUP Global) independent Expert Committee on Cancer Survivorship and Expert Panel interpreted and graded the likelihood of causality. We identified 16 observational studies on 82,220 non-overlapping patients from six countries. Physical activity was consistently inversely associated

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Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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with colorectal cancer morbidity and mortality outcomes, with 13%–60% estimated reductions in risk. Sedentary behaviour was positively associated with all-cause mortality. The evidence had methodological limitations including potential confounding, selection bias and reverse causation, coupled with a limited number of studies for most associations. The CUP Global Expert panel concluded limited-suggestive evidence for recreational physical activity with all-cause mortality and cancer recurrence. Total physical activity and its specific domains and dimensions, and sedentary behaviour were all graded as limited-no conclusion for all outcomes. Future research should focus on randomised trials, while observational studies should obtain objective and repeated physical activity measures and better adjustment for confounders.

KEYWORDS
colorectal cancer survival, evidence grading, meta-analysis, physical activity, systematic review

What's new?

The roles of physical activity and sedentary behaviour in colorectal cancer prognosis are unclear. Here, as part of CUP Global, the authors performed a systematic review and meta-analysis on the associations of post-diagnosis physical activity and sedentary behaviour with all-cause and cause-specific mortality and recurrence among colorectal cancer survivors. Whilst the evidence was graded as limited, it suggested that a physically active lifestyle and avoidance of sedentary behaviour may be associated with longer overall survival. The study highlights the importance of more consistent and objective exposure assessment in future studies and the need for randomised trials to provide stronger evidence.

1 | INTRODUCTION

Colorectal cancer is the third leading cause of cancer incidence and the second leading cause of cancer-related mortality worldwide, with an estimated >1.9 million incident cases and >0.9 million deaths, respectively, in 2020.[1] The effectiveness of early detection via cancer screening programmes in reducing mortality[2–4] coupled with better cancer treatment options have led to increased survival rates among individuals diagnosed with colorectal cancer.[5] The estimated 5-year survival for colorectal cancer is generally over 60% in western populations and high income countries,[5–7] and on average 20% lower in transitioning countries.[8] Among patients diagnosed with earlier stages of the disease, survival rates are even higher, and the 5-year prevalence of the disease is estimated to be over 5.2 million people worldwide, making colorectal cancer the second most prevalent cancer, after breast cancer.[1]

Extensive research has been conducted to identify risk factors affecting the incidence of colorectal cancer. In addition to genetic predisposition and increasing age, several environmental and lifestyle factors have been associated with the development of the disease. Among these, the protective role of physical activity on colorectal cancer risk, specifically on colon cancer, is well-established.[9,10] The Third Expert Report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is convincing evidence that physical activity reduces colon cancer incidence,[9] while the 2018 Physical Activity Guidelines Advisory Committee (PAGAC) Scientific Report[11] graded this association as being supported by strong evidence.

Despite the abundance of evidence on colorectal cancer incidence, evidence regarding the association between physical activity and sedentary behaviour and colorectal cancer prognosis is relatively limited. A small number of meta-analyses investigating the role of post-diagnosis physical activity on outcomes after colorectal cancer[12–18] suggested an inverse association with all-cause mortality. These meta-analyses have primarily focused on the association of categories of physical activity levels with colorectal cancer prognosis, but none explicitly assessed the different dimensions and domains of activity. Moreover, apart from one ongoing trial[19] there is a lack of randomised controlled trials (RCTs) assessing the effect of physical activity on colorectal cancer survival. The role of sedentary behaviour as a distinct risk factor from physical activity, defined as the energy expenditure of less than 1.5 metabolic equivalents of task (METs) while one assumes a sitting or reclining posture,[20] is even less studied.[21]

Due to the lack of strong evidence, physical activity and sedentary behaviour recommendations targeting cancer outcomes tailored to cancer survivors are limited. Formal evaluation of the existing observational evidence base performed by PAGAC concluded moderate evidence strength for all-cause and cancer-specific mortality in colorectal cancer, based on individual studies published until

February 2018.[11] The 2018 American College of Sports Medicine (ACSM) Roundtable also concluded that physical activity is beneficial for survival[22] and other cancer-related health outcomes.[23] However, the precise quantity of physical activity required to effectively reduce cancer-specific or all-cause mortality remains undetermined.[22] The evidence on sitting time as a proxy of total sedentary time and cancer-specific mortality was limited.[22] Currently, colorectal cancer patients and survivors are advised to follow the same recommendations as for cancer prevention.[9,24–26]

The aim of WCRF International's new Global Cancer Update Programme (CUP Global) formerly known as the WCRF/AICR Continuous Update Project[27] is the development of disease- and stage-specific guidance and recommendations. Therefore, as part of CUP Global, we present the findings of a systematic literature review on the association of post-diagnosis physical activity and sedentary behaviour and colorectal cancer prognosis. Evidence on adiposity and diet and outcomes after colorectal cancer, along with an overall summary are presented in the accompanied papers.[28–30]

2 | METHODS

This systematic review is part of the ongoing CUP Global programme and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[31] (Supplementary Table S1). The protocol can be found elsewhere.[32]

2.1 | Search strategy, selection criteria and data extraction

Comprehensive details on the methodology are available in the Supplementary Texts 1 and 2. Briefly, we searched PubMed and Embase through 28th February 2022. We included observational studies, RCTs, or pooled analyses of such studies evaluating post-diagnosis (at or shortly after diagnosis, during treatment, after the end of treatment) physical activity, sedentary behaviour, or their pre-to-post diagnosis or post-diagnosis changes. We included studies with at least 100 participants with primary colorectal cancer or its subtypes diagnosed during adulthood. The term 'colorectal' referred to any colorectal cancer survivor, regardless of cancer subtype, colon or rectum. Outcomes of interest included all-cause, colorectal cancer site and subsite-specific, and cardiovascular-specific mortality, second primary cancer, and cancer recurrence/disease-free survival. Study selection was performed at title and abstract level, followed by full-text review, and supplemented with manual reference screening. If more than one publication from the same population was identified, we included the one with the higher number of events per outcome assessed. Data were extracted into the CUP Global database and included, among others, publication details, study characteristics (number of participants, events, and inclusion and exclusion criteria), exposure and outcome details, relative risks (RR) 95% confidence intervals (CI), standard errors, and/or p-values, and details on adjustment variables. Study selection and data extraction were performed by one reviewer and at least 10% checked by another; disagreements were resolved by consensus.

2.2 | Evidence synthesis

We reviewed total physical activity (defined as any combined activity domain, including occupational, recreational, household, transportation) and the specific domains, irrespective of which physical activity dimension was assessed (frequency, duration, intensity). Specifically for recreational physical activity, the most investigated domain, we further reviewed frequency, duration, and intensity (activity of any intensity and specifically moderate-to-vigorous intensity). We also investigated recreational physical activity volume as a separate dimension, measured in MET-h/week. Furthermore, we performed meta-analyses on sedentary behaviour when its definition was sufficiently consistent across studies (capturing similar types of sedentary behaviours).

We analysed cancer recurrence/disease-free survival as defined by the studies (Supplementary Table S2). When more than one of these outcomes were reported, the one with the highest number of events was included in the meta-analyses.

We performed DerSimonian-Laird random-effects meta-analyses[33] for categorical (highest vs. lowest levels) and linear dose–response comparisons when at least two and three studies provided relevant information, respectively. When at least five studies provided sufficient information, we also performed one-stage non-linear dose–response meta-analyses[34] using restricted cubic splines with knots placed at the 10th, 50th, and 90th percentiles of the exposure distribution. The nonlinear component was tested using a likelihood ratio test.[35]

We assessed the presence of small-study effects (such as publication bias) by visual inspection of the funnel-plots and used the Egger's regression asymmetry test,[36] when at least 10 studies were included in a meta-analysis. If small study effects bias was suggested, we estimated an adjusted summary RR using the trim-and-fill method.[37] Heterogeneity was described by the between-study variation (tau^2) and by the range of study estimates in each meta-analysis. The I^2 metric of inconsistency[38] with cut-offs at $I^2 = 30\%$, 50%, and 75% indicated low, moderate, high, and substantial proportion of total variability in effect estimates due to between-study heterogeneity. The 95% prediction intervals depicted the range of estimates likely to contain the value of a new study.[39]

We performed pre-defined stratified meta-analyses by sex, cancer anatomical subsite and stage, and molecular subtype (based on sequencing or immunohistochemistry approaches). We performed sensitivity meta-analyses by excluding, when possible, survivors with locally advanced and metastatic tumours, to explore potential impact of bias by reverse causation. We also performed leave-one-out sensitivity meta-analyses to assess the magnitude of the effect of exclusion of each study on the summary estimate.[40]

2.3 | Risk of bias assessment

A modified version of the Risk of Bias for Nutrition Observational Studies (RoB-NObs) tool[41] was utilised to assess the risk of bias in the studies included in the meta-analyses. The tool was originally developed by the U.S. Department of Agriculture (USDA) Nutrition Evidence Systematic Review after modifications to the Cochrane's collaboration Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I).[42] The tool underwent further refinement and testing by the Imperial College London (ICL) review team to ensure its suitability for investigating exposure-outcome associations in cancer survivorship studies. This involved adapting the tool's prompting questions and providing additional guidance to encompass adiposity, physical activity, and dietary/nutritional exposures (the working document version dated 11/07/2023 can be found in Supplementary Table S3). The tool consists of seven domains, including confounding, participant selection, exposure classification, departures from intended exposures, missing data, outcome measurement, and selective reporting. In the context of cancer survivorship, we have specifically designated age, adiposity, and cancer stage and treatment as pivotal confounding variables a-priori of the studied associations, due to their substantial impact on both the levels of physical activity and sedentary behaviour engagement along with their recognised role as robust prognostic factors for survival in colorectal cancer patients.

2.4 | Evidence grading criteria

The CUP Global independent Expert Committee on Cancer Survivorship and Expert Panel convened by WCRF International interpreted the findings, independently of ICL. The Expert Committee made the preliminary conclusions, and the Expert Panel made the final conclusions. The quality of the evidence was graded for all exposures as strong (subgrades evaluating likelihood of causality: convincing, probable, substantial effect on risk unlikely) or limited (subgrades evaluating likelihood of causality: limited-suggestive, limited-no conclusion) according to a list of pre-defined criteria assessing the quantity, consistency, magnitude, and precision of the summary estimates, evidence of biological gradient, the study design, risk of bias, generalisability, and biological plausibility of the results (Supplementary Table S4). The grades of the quality of the evidence reflect the independent Expert Committee's and Expert Panel's confidence that the association estimates are correct.

3 | RESULTS

A flowchart of the selection process is presented in Figure 1. We excluded 453 publications on exposures other than physical activity, 64 on pre-diagnosis-only exposures,[43–106] seven on a mixture of pre- and post-diagnosis exposures,[107–113] and one where the outcome was colorectal polyps.[114] Overall, 28 publications met the eligibility criteria. Five publications[115–118] that were superseded by more recent publications and three[119–121] only reporting unadjusted results were excluded from any subsequent analyses. Therefore, a total of 20 publications (16 studies) on post-diagnosis physical activity, pre-to post and post-diagnosis change in physical activity levels, and post-diagnosis sedentary behaviour were included. These pertained to 16 publications of 13 cohort studies[122–137] and four publications of three observational follow-up analyses of patients enrolled in clinical treatment RCTs[138–141] not aiming to evaluate physical activity interventions. The number of publications may differ from the number of studies as several publications from the same study reporting on different exposure-outcome associations were included,[126,131,134–136,139,140] but also one publication included two studies.[123] No primary RCT was identified.

Detailed information on study and participants' characteristics and physical activity definitions and domains are presented in Supplementary Tables S5 and S6. The 16 studies comprised 82,220 non-overlapping patients, of whom about 7800 died of any cause, about 1700 died of colorectal cancer, and about 2100 experienced an additional colorectal cancer event. The median study size was 1640 (range 247–43,596) participants in cohort studies and 1218 (832–1992) participants in secondary analyses of RCTs. Most studies ($n = 9$; 60%) were from the United States,[124,126,128–130,132,135,136,138–141] three were from the Netherlands,[123,137] and one each from Australia,[133] Germany,[127] Japan,[125] and South Korea.[122] Most studies included individuals with stage I–III ($n = 7$[123,126,128,129,131–136]) or I–IV disease ($n = 4$[122,124,127,130]), of which 2 studies reported the percentage of stage IV patients (3.5% and 17%) and another two did not report the %. In addition, two studies included only stage III,[140,141] one included stage 0–IV,[125] and two included only survivors with tumour metastases.[137,138]

Six (38%) studies[123,127,133,137,141] measured physical activity of any type (total, including multiple types such as recreational, occupational, household, and other types of activity), and 12 (75%) studies[122,124–126,128,130–132,134–141] measured recreational physical activity. The results of the two studies that further measured other specific types of activity, such as cycling,[127] gardening,[127] housework,[127] sports,[127] or walking[127,138] were descriptively synthesised. Eight studies (50%)[126,127,131,132,134–139,141] assessed total (low, moderate, and vigorous) intensity of physical activity, seven (44%)[122–124,128,130,133] assessed physical activity of moderate-to-vigorous intensity, while the intensity of physical activity was unclear in one study.[125] Physical activity was self-reported in all studies but only nine (56%) used validated questionnaires.[123,126,127,131–138] Two studies[133,136] examined physical activity changes (pre-to-post-diagnosis or post-diagnosis). Four studies[127–130] assessed sedentary behaviour as daily time spent sitting while watching TV[127–129] or as overall sitting time/day.[130]

Figure 2 and Supplementary Table S7 show a summary of the results of the meta-analyses.

3.1 | Physical activity

3.1.1 | Total physical activity

Six studies (five publications) were identified.[123,127,133,137,141] The category with the highest versus lowest levels of total physical activity was inversely associated with all-cause mortality (RR = 0.70; 95% CI = 0.55–0.89; $I^2 = 47\%$; $tau^2 = 0.03$; RRs range = 0.48–0.80; six

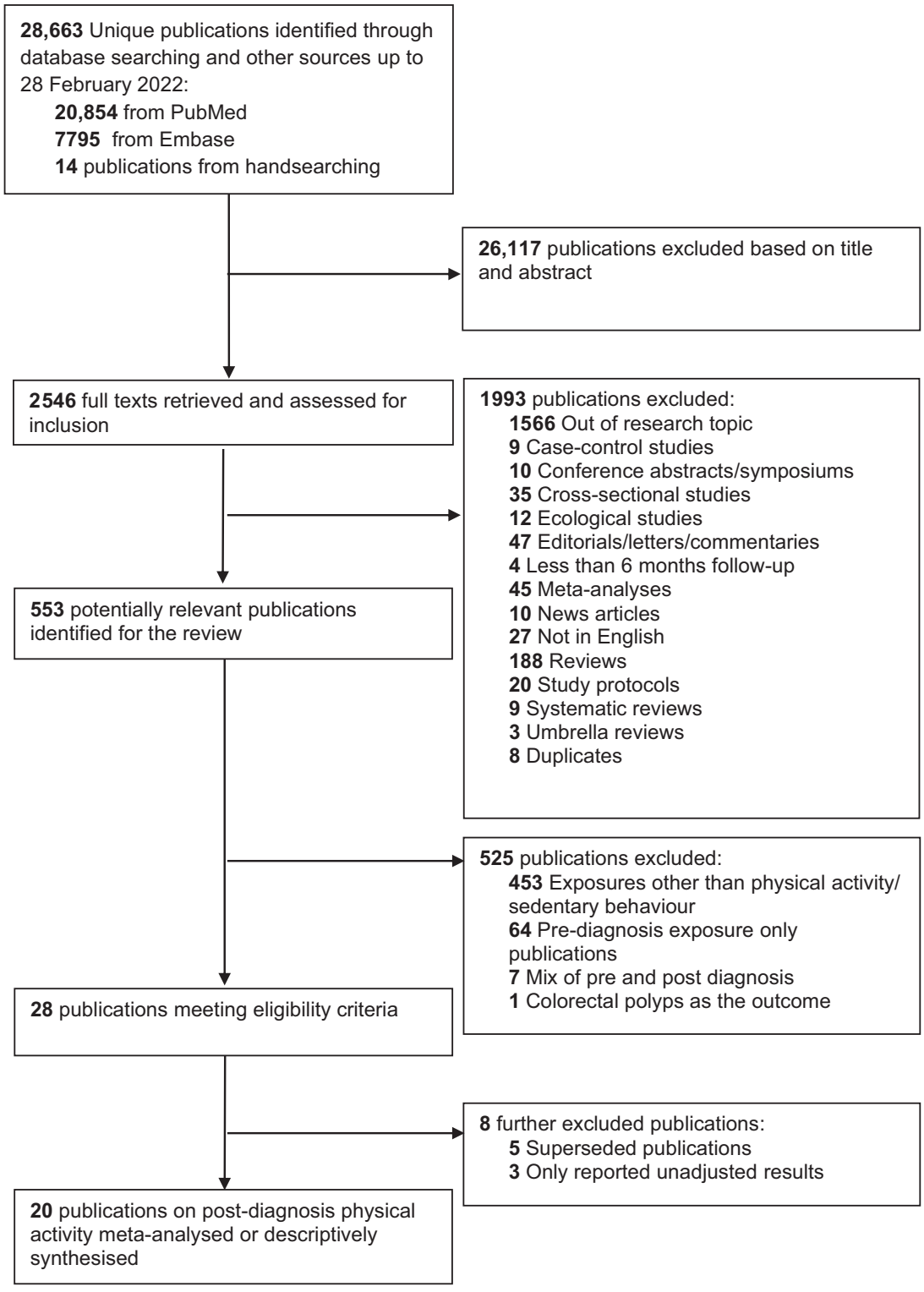

FIGURE 1 Flowchart of study selection process.

studies; 1443 deaths),[123,127,133,141] but the evidence for cancer recurrence/disease-free survival was weak (RR = 0.87; 95% CI = 0.63–1.20; I^2 = 0%; RRs range = 0.75–0.99; two studies; 762 deaths)[123,141] (Supplementary Figure S1). Dose–response meta-analysis could not be conducted due to insufficient data.

When excluding survivors with locally advanced and metastatic tumours, the summary RR for all-cause mortality was similar but with lower heterogeneity than when including all colorectal cancer patients (RR = 0.70; 95% CI = 0.56–0.87; I^2 = 21%; tau^2 = 0.09; RRs range = 0.53–0.80; four studies, three publications)[123,127,133]

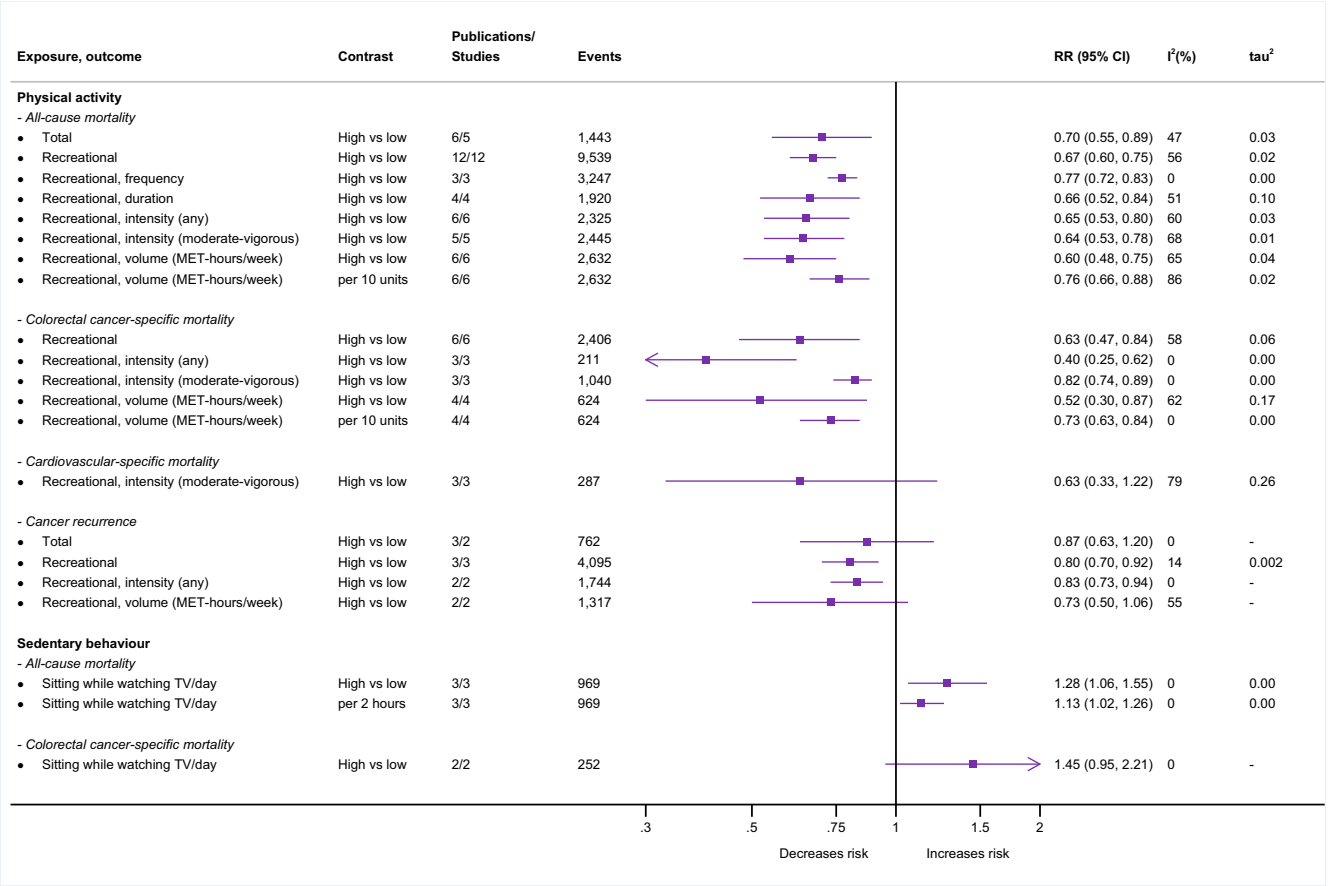

FIGURE 2 Summary risk ratios (RRs) and 95% confidence intervals (95% CI) for post-diagnosis physical activity and sedentary behaviour and outcomes after colorectal cancer. CI, confidence interval; MET, metabolic equivalent of task; RR, relative risk.

(Supplementary Figure S2). The leave-one-out sensitivity analyses did not identify any influential studies (Supplementary Figure S3).

3.1.2 | Recreational physical activity

Twelve studies (12 publications) were identified.[122,124,125,128,130,132,135–139,141] Most studies investigated volume of recreational activity (MET-h/week).[125,130,132,135,136,138–140] Four studies measured duration of recreational activity[124,128,137,138] and three measured physical activity frequency.[122,125,141] The primary analysis on recreational physical activity included all studies, irrespective of the dimension of activity measured, however, due to heterogeneity across definitions and dimensions measured, meta-analyses are also presented by specific dimensions.

A lower risk of all-cause mortality was observed when comparing the highest with the lowest levels of recreational physical activity (any dimension) (RR = 0.67; 95% CI = 0.60–0.75; I^2 = 56%; tau^2 = 0.02; RRs range = 0.39–0.85; 12 studies; 9539 deaths)[122,124,125,128,130,132,135–139,141] (Supplementary Figure S4). We found evidence of small-study effects from visual inspection of the funnel plot and the Egger's test (p = .002) (Supplementary Figure S5). The trim and fill sensitivity analysis suggested that after adjusting for six potentially missing studies, the summary RR would be RR = 0.76 (95% CI = 0.68–0.86) (Supplementary Figure S6).

The highest versus lowest levels of recreational physical activity (any dimension) were associated with a lower risk of colorectal cancer-specific mortality (RR = 0.63; 95% CI = 0.47–0.84; I^2 = 58%; tau^2 = 0.06; RRs range = 0.29–0.83; six studies; 2406 deaths)[122,128,130,132,135,136] and cancer recurrence (RR = 0.80; 95% CI = 0.70–0.92; I^2 = 14%; tau^2 = 0.002; RRs range = 0.52–0.83; three studies, all secondary analyses of RCTs; 4095 events).[138,140,141] (Supplementary Figure S4).

Since studies often included patients with various cancer stages, the predefined subgroup meta-analyses by stage could not be performed. When excluding survivors with locally advanced and metastatic tumours, the summary RR and heterogeneity for all-cause mortality were similar to the results including all colorectal cancer patients (RR = 0.65; 95% CI = 0.56–0.75; tau^2 = 0.02; RRs range = 0.41–0.78; I^2 = 54%; eight studies)[122,124,125,128,130,132,135,136] (Supplementary Figure S7). The leave-one-out sensitivity analyses did not identify any influential studies (Supplementary Figure S8).

3.1.3 | Recreational physical activity frequency

Three studies (three publications) were identified.[122,125,141] The highest versus lowest levels of physical activity frequency showed an inverse association with all-cause mortality (RR = 0.77; 95%

CI = 0.72–0.83; I^2 = 0%; tau^2 = 0.00; RRs range = 0.75–0.78; three studies; 3247 deaths)[122,125,141] (Supplementary Figure S9). Dose–response meta-analyses were not possible due to limited data.

In subgroup meta-analyses by cancer subsite, the highest versus lowest levels of recreational physical activity frequency were inversely associated with all-cause mortality risk in both colon (RR = 0.77; 95% CI = 0.71–0.84; I^2 = 0%; tau^2 = 0.00; RRs range = 0.66–0.79; three studies; 2502 deaths) and rectal (RR = 0.76; 95% CI = 0.67–0.86; RRs range = 0.75–0.86; I^2 = 0%; two studies; 1135 deaths)[122,125] cancer survivors (Supplementary Figure S10).

3.1.4 | Recreational physical activity duration

Four studies (four publications) were identified.[124,128,137,138] Highest versus lowest recreational physical activity duration (minutes or h/week) was inversely associated with the risk of all-cause mortality (RR = 0.66; 95% CI = 0.52–0.84; I^2 = 51%; tau^2 = 0.03; RRs range = 0.39–0.80; three studies; 1820 deaths)[124,128,137,138] (Supplementary Figure S11). Dose–response meta-analysis was not possible due to insufficient data.

3.1.5 | Recreational physical activity intensity

Six studies (six publications) assessed total recreational physical activity intensity.[132,135,136,138,139,141] Highest versus lowest levels of recreational activity intensity (total) were inversely associated with all-cause (RR = 0.65; 95% CI = 0.53–0.80; I^2 = 60%; tau^2 = 0.03; RRs range = 0.41–0.85; six studies; 2325 deaths)[132,135,136,138,139,141] and colorectal cancer-specific mortality (RR = 0.40; 95% CI = 0.25–0.62; I^2 = 0%; tau^2 = 0.00; RRs range = 0.29–0.47; three studies; 211 deaths)[132,135,136] and cancer recurrence (RR = 0.83; 95% CI = 0.73–0.94; I^2 = 0%; RRs range = 0.82–0.83; two studies; 1744 events)[138,141] (Supplementary Figure S12).

When excluding survivors with locally advanced and metastatic tumours, the summary RR for all-cause mortality was 0.51 (95% CI = 0.39–0.67) with no heterogeneity (I^2 = 0%; tau^2 = 0.00; RRs range = 0.41–0.59; three studies)[132,135,136] (Supplementary Figure S13).

Five studies (five publications) assessed moderate-to-vigorous intensity of recreational physical activity.[122,124,128,130,137] Highest versus lowest levels of recreational physical activity (moderate-to-vigorous) were associated with lower risk of all-cause (RR = 0.48; 95% CI = 0.53–0.78; I^2 = 68%; tau^2 = 0.03; RRs range = 0.39–0.78; four studies; 2445 deaths)[122,124,128,130,137] and colorectal cancer-specific mortality (RR = 0.82; 95% CI = 0.74–0.89; I^2 = 0%; tau^2 = 0.00; RRs range = 0.53–0.82; three studies; 1040 deaths).[122,128,130] There was weak (and likely underpowered) evidence of an association with cardiovascular disease-specific mortality (RR = 0.63; 95% CI = 0.33–1.22; I^2 = 79%; tau^2 = 0.26; RRs range = 0.36–0.89; three studies; 287 events)[122,128,130] (Supplementary Figure S14).

3.1.6 | Recreational physical activity volume

Six studies (seven publications) were identified.[130,132,135,136,138–140] Highest compared to lowest volumes of recreational physical activity were associated with decreased risk of all-cause (RR = 0.60; 95% CI = 0.48–0.75; I^2 = 65%; tau^2 = 0.04; RRs range = 0.41–0.85; six studies; 2632 deaths)[130,132,135,136,138,139] and colorectal cancer-specific mortality (RR = 0.52; 95% CI = 0.30–0.87; I^2 = 62%; tau^2 = 0.17; RRs range = 0.29–0.87; four studies; 624 deaths).[130,132,135,136] The summary RR for high versus low volumes of recreational physical activity and cancer recurrence was 0.73 (95% CI = 0.50–1.06; I^2 = 56%; RRs range = 0.55–0.83; two studies; 1317 events)[136,138] (Supplementary Figure S15).

In the sensitivity analysis excluding survivors with locally advanced and metastatic tumours, the summary RR for all-cause mortality was similar but with no heterogeneity (RR = 0.55; 95% CI = 0.47–0.65; I^2 = 0%; tau^2 = 0.00; RRs range = 0.41–0.59; four studies)[130,132,135,136] (Supplementary Figure S16).

In the linear dose–response meta-analyses, an increase of 10 MET-h/week of recreational physical activity was associated with decreased risk of all-cause (RR = 0.76; 95% CI = 0.66–0.88; I^2 = 86%; tau^2 = 0.02; RRs range = 0.53–0.94; six studies; 2632 deaths)[130,132,135,136,138,139] and colorectal cancer-specific mortality (RR = 0.73; 95% CI = 0.63–0.84; I^2 = 0%; tau^2 = 0.00; RRs range = 0.63–0.84; four studies; 624 deaths)[130,132,135,136] (Supplementary Figure S17). Linear dose–response meta-analysis was not possible for the other outcomes due to limited data.

In the sensitivity analysis excluding survivors with locally advanced and metastatic tumours, the results for all-cause mortality were similar to the analysis including all colorectal cancer patients (RR = 0.68; 95% CI = 0.55–0.84; I^2 = 76%; tau^2 = 0.03; RRs range = 0.53–0.83; four studies) (Supplementary Figure S18). Sequential omission of each study did not change the results (Supplementary Figure S19).

Non-linear dose–response analysis was only possible for all-cause mortality. The evidence from six studies was suggestive of a non-linear inverse association ($P_{non\text{-}linearity}$ = .07; 2408 deaths)[130,132,135,136,138,139] indicating a consistent inverse association up to 20 MET-h/week and remained relatively constant for higher activity levels (Supplementary Figure S20). There was no strong evidence of non-linearity ($P_{non\text{-}linearity}$ = .27; four studies; 1075 deaths) when excluding survivors with locally advanced and metastatic tumours, but the data were sparce[130,132,135,136] (Supplementary Figure S21).

Subgroup analyses by sex were only possible for all-cause mortality, with high versus low volumes of recreational physical activity showing inverse associations for both men (RR = 0.65; 95% CI = 0.52–0.80; I^2 = 0%; RRs range = 0.59–0.68; two studies; 540 deaths)[130,135] and women (RR = 0.55; 95% CI = 0.34–0.88; I^2 = 57%; tau^2 = 0.10; RRs range = 0.41–0.81; three studies; 411 deaths)[130,132,136] (Supplementary Figure S22).

Stratified analyses by molecular subtypes were only performed in subsets of participants (n = 371–605) of the Nurses' Health Study & Health Professionals Follow-Up Study,[126,131,134] so we descriptively

summarise these results. In general, most molecular subtypes did not show evidence of interaction, except for *IRS1*, *CTNNB1*, *PTGS2*, and *P27* and only for colorectal cancer-specific mortality but not for overall survival (Supplementary Figures S23 and S24).

3.1.7 | Other types of physical activity

A pattern of inverse associations with all-cause mortality was observed across the different types of physical activities analysed (walking, bicycling, gardening, housework, and sport) (RRs ranged from 0.34 to 0.90, with the 95% CI not including the null in two out of the six comparisons)[127,138] (Supplementary Figure S25). No evidence of association was observed in the only study analysing walking and cancer recurrence.[138]

3.2 | Physical activity change

Two studies (two publications)[133,136] were identified, which investigated changes in physical activity levels around the time of diagnosis. A meta-analysis was not performed due to large methodological differences, but we descriptively synthesised these results. In one study,[133] increases of total physical activity by >0–2 h/week and by ≥2 h/week from pre-diagnosis to 5 months post-diagnosis compared to no change or decreased levels showed no strong evidence of association with all-cause mortality (RR = 1.27; 95% CI = 0.88–1.83 and RR = 1.06; 95% CI = 0.65–1.71, respectively). There was some weak evidence that a post-diagnosis increase (from 5 to 12 months) by 0–2 h/week was associated with a lower risk of all-cause mortality (RR = 0.79; 95% CI = 0.59–1.04), while an increase by ≥2 h/week was associated with a lower risk of all-cause mortality (RR = 0.69; 95% CI = 0.50–0.94) compared to no change or decreased activity levels. In the Nurses' Health Study,[136] an increase of at least one level of recreational physical activity (defined as categories of MET-h/week) from a median of 6 months before to a median of 22 months post-diagnosis compared to no change in activity levels over this period was associated with lower all-cause mortality risk (RR = 0.53; 95% CI = 0.30–0.85), while a decrease of physical activity by one level compared to no change showed no association (RR = 1.23; 95% CI = 0.79–1.91).

3.3 | Sedentary behaviour

Four studies (four publications) of self-reported sedentary behaviour were identified.[127–130] We performed a meta-analysis of the three that estimated time sitting while watching TV. Highest versus lowest levels of time sitting while watching TV were associated with 28% higher risk of all-cause mortality (RR = 1.28; 95% CI = 1.06–1.55; $I^2 = 0\%$; $tau^2 = 0.00$; RRs range = 1.16–1.45; three studies; 969 deaths)[127–129] and showed imprecise evidence of a higher risk of colorectal cancer-specific mortality (RR = 1.45; 95% CI = 0.95–2.21; $I^2 = 0\%$; RRs range = 1.45–1.45; two studies; 252 deaths)[128,129] (Supplementary Figure S26). Linear dose–response meta-analysis was only possible for all-cause mortality. An increase of 120 min/day of sitting while watching TV was associated with higher risk of all-cause mortality (RR = 1.13; 95% CI = 1.02–1.26; $I^2 = 0\%$; $tau^2 = 0.00$; RRs range = 1.09–1.40; three studies; 969 deaths) (Supplementary Figure S27).

3.4 | Risk of bias

Around 37% of the publications on physical activity had moderate RoB in confounding, 21% had serious, and around 42% had critical RoB by failing to adjust for important confounders (i.e., age, stage, cancer treatment). Participation in all the studies was conditional on survival and self-selection cannot be excluded, therefore, all publications had a serious RoB in this domain, except for one that utilised data from a national registry thus accounting for selection bias.[122] Most publications (74%) had a moderate RoB in exposure misclassification, mainly due to the very detailed information provided on exposure assessment, despite many utilising non-validated tools. All publications had a critical RoB in departures from intended exposures as time-varying analyses were not performed, except for one that partially accounted for deviations of the intended measurements.[139] Most publications (58%) had a serious RoB in missing data and 21% had a low RoB either due to no missingness or because appropriate statistical methods were utilised to account for missingness. Most publications (84%) had a low RoB in outcome measurement; the rest did not provide sufficient information for assessment. All publications had a moderate RoB in selective reporting (Supplementary Figures S28 and S29).

For sedentary behaviour, 75% had a critical RoB in confounding by not adjusting for all important confounders, all had serious RoB in participant selection, all had either serious or critical RoB in exposure misclassification, all had critical RoB in departures from the intended exposures, all but one[128] which accounted for missingness had a serious RoB due to missing data, all had low RoB in outcome measurement and all had moderate RoB in selective reporting (Supplementary Figures S28 and S29).

3.5 | Evidence grading

Table 1 reports the evidence grading. Relatively sparce data, methodological and clinical considerations, inconsistencies in the assessment of physical activity, increased likelihood of residual confounding from comorbidities and other factors, and potential for reverse causation were among the reasons that led to limited conclusions on the likelihood of causality for the existing evidence. The evidence on post-diagnosis recreational physical activity and all-cause mortality and cancer recurrence received the limited-suggestive sub-grade. A limited-no conclusion sub-grade was given to recreational physical activity and other outcomes apart from all-cause mortality and cancer

TABLE 1 Summary of the judgement of the Independent WCRF Expert Panel.

		Physical activity and sedentary behaviour and survival in colorectal cancer				
					Summary of findings	
		Exposure	Exposure contrast	Outcomes	*N* studies, *N* events; RR (95% CI); I^2 (%); tau^2; Egger's *p*-value[a]	Conclusions
Strong evidence	Convincing	–	–	–	–	–
	Probable	–	–	–	–	–
Limited evidence	Limited—suggestive	**Decreases risk**				
		Recreational physical activity				
		Any definition	Highest vs. lowest	All-cause mortality	12 studies, 9539 deaths, 0.67 (0.60, 0.75), I^2 = 56%, tau^2 = 0.02, P_{Egger} < 0.01	The evidence is modest, substantial heterogeneity was observed along with evidence of publication bias, and possible methodological issues.
				Cancer recurrence	3 studies, 4095 events, 0.80 (0.70, 0.92), I^2 = 14%, tau^2 = 0.002	The evidence rises from three secondary analyses of randomized controlled trials which were relatively consistent in terms of populations (advanced and metastatic cases) and timing of exposure measurement and with low heterogeneity.
	Limited—no conclusion	Total physical activity				The evidence for total physical activity and recreational physical activity dimensions is sparse, often with substantial heterogeneity, and is generally limited by methodological issues including heterogeneity in exposure definition and timing of measurement, and quality issues including increased risk of survival and reverse causation bias.
		Any definition	Highest vs. lowest	All-cause mortality	6 studies, 1443 deaths, 0.70 (0.55, 0.89), I^2 = 47%, tau^2 = 0.03	
				Cancer recurrence	3 studies, 762 events, 0.87 (0.63, 1.20), I^2 = 0%, tau^2 = NA	
		Recreational physical activity				
		Any definition	Highest vs. lowest	Colorectal cancer mortality	6 studies, 2406 deaths, 0.63 (0.47, 0.84), I^2 = 58%, tau^2 = 0.06	
		Frequency	Highest vs. lowest	All-cause mortality	3 studies, 3247 deaths, 0.77 (0.72, 0.83), I^2 = 0%, tau^2 = 0.00	
		Duration	Highest vs. lowest	All-cause mortality	4 studies, 1920 deaths, 0.66 (0.52, 0.84), I^2 = 51%, tau^2 = 0.03	
		Intensity (any)	Highest vs. lowest	All-cause mortality	6 studies, 2325 deaths, 0.65 (0.53, 0.80), I^2 = 60%, tau^2 = 0.03	
				Colorectal cancer mortality	3 studies, 211 deaths, 0.40 (0.25, 0.62), I^2 = 0%, tau^2 = 0.00	
				Cancer recurrence	2 studies, 1744 events, 0.83 (0.73, 0.94), I^2 = 0%, tau^2 = 0.00	
		Intensity (moderate-to-vigorous)	Highest vs. lowest	All-cause mortality	5 studies, 2445 deaths, 0.64 (0.53, 0.78), I^2 = 68%, tau^2 = 0.03	

(Continues)

TABLE 1 (Continued)

Physical activity and sedentary behaviour and survival in colorectal cancer				
			Summary of findings	
Exposure	**Exposure contrast**	**Outcomes**	***N* studies, *N* events; RR (95% CI); I^2 (%); tau^2; Egger's *p*-value[a]**	**Conclusions**
		Colorectal cancer mortality	3 studies, 1040 deaths, 0.82 (0.74, 0.89), I^2 = 0%, tau^2 = 0.00	
		CVD mortality	3 studies, 287 deaths, 0.63 (0.33, 1.22), I^2 = 79%, tau^2 = 0.26	
Volume	Highest vs. lowest	All-cause mortality	6 studies, 2632 deaths, 0.60 (0.48, 0.75), I^2 = 65%, tau^2 = 0.04	
	10 MET-hours/week		6 studies, 2632 deaths, 0.76 (0.66, 0.88), I^2 = 86%, tau^2 = 0.02	
	Highest vs. lowest	Colorectal cancer mortality	4 studies, 624 deaths, 0.52 (0.30, 0.87), I^2 = 62%, tau^2 = 0.17	
	10 MET-hours/week		4 studies, 624 deaths, 0.73 (0.63, 0.84), I^2 = 0%, tau^2 = 0.00	
	Highest vs. lowest	Cancer recurrence	2 studies, 1317 events, 0.73 (0.50, 1.06), I^2 = 55%, tau^2 = NA	
Physical activity change				The evidence for changes in physical activity is weak, heterogeneous, and inconsistent, and likely affected by biases.
Pre-to-post diagnosis	Highest vs. lowest	All-cause mortality	3 RRs from 2 studies for moderate and high increases vs no change, no meta-analysis. 2 RRs ranging 1.06 to 1.27, both CIs crossing the null & 1 RR=0.53, CI not crossing the null.	
Post-diagnosis	Highest vs. lowest	All-cause mortality	2 RRs from 1 study for moderate and high increases vs no change, no meta-analysis. 2 RRs ranging 0.69 to 0.79, 1 CI crossing the null.	
Sedentary behaviour				The body of evidence is weak showing higher risk of all-cause mortality and indicating a higher risk for colorectal cancer-specific mortality with higher levels of sedentary behaviour, which may be influenced by reverse causation and other biases.
Sitting while watching TV	Highest vs. lowest	All-cause mortality	3 studies, 969 deaths, 1.28 (1.06, 1.55), I^2 = 0%, tau^2 = 0.00	
	120 min/week		3 studies, 969 deaths, 1.13 (1.02, 1.26), I^2 = 0%, tau^2 = 0.00	
	Highest vs. lowest	Colorectal cancer mortality	2 studies, 252 deaths, 1.45 (0.95, 2.21), I^2 = 0%, tau^2 = NA	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; NA, not applicable; RR, relative risk.
[a]Estimated when at least 10 studies were available.

recurrence, and to recreational physical activity dimensions (volume, frequency, intensity, duration), total physical activity, change of physical activity, and sedentary behaviour.

4 | DISCUSSION

This systematic literature review showed that higher levels of recreational physical activity and its different dimensions were consistently inversely associated with major clinical outcomes in colorectal cancer patients. Due to methodological limitations leading to increased likelihood of biases, small number of studies, and often high between-study variability due to heterogeneity, the CUP Global independent Expert Committee and Expert Panel concluded that the evidence on post-colorectal cancer diagnosis physical activity and sedentary behaviour and survival-related outcomes was limited. The association of recreational physical activity with all-cause mortality that was supported by a relatively larger number of studies and without high levels of between-study heterogeneity, along with the evidence on cancer recurrence that was supported by relatively more consistent studies in terms of population characteristics and timing of exposure measurement reached a limited-suggestive conclusion for the likelihood on causality.

The evidence on recreational physical activity volume also suggested an inverse non-linear relationship with all-cause mortality up to 20 MET-h/week (roughly equivalent to 5 h of moderate-intensity physical activity/week[142]) compared to zero MET-h/week, which plateaued for higher volumes, although no evidence of non-linearity was found in a sensitivity analysis excluding survivors with locally advanced and metastatic tumours. There was less available evidence for total activity, dimensions of recreational activity, change in activity, and sedentary behaviour on survival-related outcomes and no conclusion could be reached. The evidence base was limited and did not allow for comprehensive evaluation of most of the a-priori defined subgroup analyses.

A plethora of mechanisms have been proposed to explain the link between physical activity and colorectal carcinogenesis,[143] such as changes in the gastrointestinal transit time, immune function, bile acid secretion, lipid and hormone profiles, and insulin and insulin-like growth factor (IGF) alterations. Some of these mechanisms including changes to the IGF-axis and immune response have also been hypothesised to affect colorectal cancer survival, albeit supported by less data,[144–146] while new proposed pathways of action include exercise-induced shear stress, extracellular vesicles, and systemic milieu alterations.[144] Increased blood pressure and heart rate during exercise leads to higher blood flow and shear pressure,[147] which may reduce the number of circulating tumour cells by immediate cell necrosis promotion.[148,149] The beneficial role of physical activity in body composition and its anti-inflammatory effects via enhancement of skeletal muscle has also been proposed.[150–152] For example, exercise leads to increased levels of serum adiponectin and decreased levels of insulin and leptin, which may lead to reduced proliferation and enhanced apoptosis of tumour cells, although evidence specifically in colorectal cancer patients is currently limited.[153] Extracellular vesicles, small membrane-surrounded structures which transfer molecules across cells, are an emerging target for treatment of various cancers.[154,155] Physical activity enhances skeletal muscle mass, which increases extracellular vesicle secretion in blood, leading to increased circulation of beneficial myokines, cytokines and peptides released from muscle cells, such as interleukin-6 (IL-6). Exercise-induced myokine secretion has been shown to have an anti-inflammatory role in various chronic diseases.[156] Physical activity also promotes immune cell mobilisation, which, coupled with increased exercise-induced IL-6 circulation, may lead to increased immune cell tumour infiltration and enhance anti-cancer immunity.[157] Finally, IGF-I and -II and IGF binding protein 3 (IGFBP-3) have been linked with colorectal tumour severity.[158–160] Despite the inconsistent response of IGFs to physical activity in healthy individuals, limited evidence supports the beneficial role of exercise on colorectal cancer mortality via IGF pathway alterations.[65,66] Nevertheless, the diverse mechanisms though which physical activity is linked to outcomes after cancer may be influenced by the interplay between activity and treatment in cancer survivors, while the existence of comorbidities may also affect the observed effects through similar biological pathways.

To the best of our knowledge, our analysis is the most comprehensive evaluation of the existing body of evidence on post-diagnosis physical activity and sedentary behaviour and colorectal cancer outcomes. Our results are in line with the findings of previous reviews and meta-analyses of physical activity in the field[12–18] in both direction and magnitude. However, in the previous meta-analyses, studies assessing total and recreational physical activities were frequently combined. The most recent analysis pooling studies of both post-diagnosis total and recreational physical activity found a 37% and a 21% reduced risk of all-cause mortality for highest versus lowest levels (10 studies, any dimension) and for 10 MET-h/week increase (seven studies),[18] respectively. Those results were similar in magnitude to ours on recreational physical activity volume (40% and 24%, respectively). Half to two-thirds of the studies within these meta-analyses employed validated instruments for the quantification of physical activity, reducing the probability of exposure misclassification and consequently enhancing the reliability of the findings. Change in physical activity has been previously meta-analysed using the same two identified studies.[15] In the present work, due to the high clinical and methodological heterogeneity across studies, including largely different definitions and timeframes of assessment, we decided against a quantitative synthesis. We identified one meta-analysis on post-diagnosis sedentary behaviour and colorectal cancer-specific mortality showing similar results to ours, however sitting while watching TV and overall sitting time were analysed together.[21]

Apart from the updated evidence base, our review is the first to assess specific physical activity domains and dimensions in relation to colorectal cancer outcomes to increase homogeneity of exposure assessment, as well as to evaluate non-linearity. Furthermore, the totality of the evidence was evaluated by the CUP Global independent Expert Committee and Expert Panel following a rigorous evaluation using pre-defined standardised grading criteria. Nevertheless, the

results presented should be interpreted considering certain limitations. Cancer survivorship studies of observational nature are subject to a range of methodological limitations, survivor bias for instance, which could not be excluded in most studies. In addition, there was an increased RoB due to incomplete confounding adjustment in most studies. Studies often did not adjust for important confounders such as treatment and/or stage, factors which can have a large effect on both the exposures and outcomes of interest, while most studies did not account for the presence of comorbidities, which may have an important impact on the ability to participate in physical activity and survival. Finally, the literature search ended on 28 February 2022. Thereby, any relevant studies published after this date were not included. Nonetheless, given the pivotal role RCTs in our evidence grading framework, we performed a comprehensive literature review targeting RCTs published subsequently and until August 31, 2023. However, we did not identify any published physical activity trial among colorectal cancer survivors, apart from the currently ongoing CHALLENGE trial. That trial has an estimated completion date in late 2030.[19,161] As such, we anticipate that the conclusions would remain unaltered.

There are complexities in determining the feasibility of trials for survival-related outcomes. Deciding whether mortality should be the primary focus is not a straightforward decision. To conduct intention-to-treat analyses, participants should ideally remain actively engaged until reaching the primary endpoint. Additionally, selecting and maintaining the appropriate level of activity for the comparison group is challenging, particularly considering existing recommendations for physical activity for cancer survivors and the potential for contamination between groups. The evidence, however, is supported by studies of different designs including clinical treatment trials with a secondary aim of evaluating the impact of physical activity on cancer outcomes. The populations of these studies were more homogeneous, composed of individuals with advanced and metastatic tumours and the timing of exposure measurement was also more consistent, capturing activity close to treatment.

Physical activity was not consistently assessed across observational studies, as they used different tools for measuring activity levels, measured different types of activity, and assessed different aspects. Our review explicitly assessed several different aspects of physical activity, including frequency, intensity, volume, and duration to enhance definition homogeneity, but studies did not mutually adjust for any of these factors. All studies utilised self-report questionnaires, of which only around half have been validated. Although all studies provided comprehensive descriptions of exposure assessment, physical activity is an umbrella term that describes a breadth of complex behaviours, often inhibiting direct comparability across studies. Even within the same domain or dimension, the comprehensiveness of the assessment varied across studies. Furthermore, self-reported physical activity and sedentary behaviour have been shown to have poor agreement with accelerometer-based measurements generally,[162] and specifically in colon cancer patients,[163] leading to an increased likelihood of exposure misclassification. This misclassification is expected to be non-differential which may result in attenuated associations. The wide range of tools used for exposure assessment and the inclusion of cancer patients of any stage may partly contribute to the heterogeneity of the results across studies. Finally, while TV viewing time was used as a surrogate measure of sedentary behaviour, the two are not directly equivalent, since other sedentariness aspects such as occupational sedentary time are not captured in TV viewing time.

The literature is primarily focused on the assessment of recreational activity. Evidence on total activity is sparse while there is some limited evidence on other types of activity, such as household activities. The timing of physical activity measurement differed across studies, ranging from immediately after diagnosis to over 10 years post-diagnosis. Individuals are more likely to engage in lower levels of activity during and short-term after cancer treatment,[164,165] and their attitudes towards exercise engagement during this period are mixed.[166,167] In contrast, studies on long-term survivors, that usually exclude patients with relapse or with most aggressive or treatment-resistant disease, indicate good proportions of adherence to physical activity recommendations.[168,169] Such inconsistencies across the timing of measurement may contribute to the observed heterogeneity and aggravate direct comparisons across studies but due to the large differences and low number of studies, subgroup analyses were not feasible. Moreover, almost all studies used a single measurement as the exposure. Colorectal cancer patients have inconsistent levels of activity throughout the course of the disease, and it has been suggested that even if patients engage in a short-term physical activity intervention they tend to revert to their less-active lifestyle.[170] Due to the limited number of studies reporting on specific subgroups, we could not perform a comprehensive evaluation of possible sources of heterogeneity, as originally planned.

Our systematic literature review also highlighted a lack of evidence in the literature, particularly in examining the associations of both subjectively and objectively measured sedentary behaviour with outcomes following colorectal cancer, as well as for non-recreational physical activity domains. To enhance our understanding of the impact of both physical activity and sedentary behaviour on colorectal cancer survival, future research should prioritise the assessment of these currently understudied areas.

In consideration of the current evidence base and its methodological limitations, the CUP Global Expert Panel conservatively categorised most of the evidence as limited-no conclusion. Despite the indication of associations across the breadth of the performed analyses, the current evidence is not sufficient to support robust conclusions on causality. The inverse association between recreational activity and all-cause mortality was concluded as limited-suggestive despite being subject to the same biases as the remaining associations, due to the high number of studies providing consistent results (10/11 supported an inverse association, 1 indicative), which was further supported by the results of the linear dose–response meta-analysis. In most cases dose–response meta-analyses could not be performed due to low number of studies, lack of information, and use of a mixture of domains and dimensions assessed, only high versus low levels of activity were compared utilising heterogeneous cut-offs

across studies. Previous assessments, such as those from the ACSM[22] that considered the effect of activity across different types of cancer survivors, have concluded a protective effect of physical activity on cancer mortality, albeit with unknown dose required for tangible benefits. However, the CUP Global Expert Panel, focusing specifically on the benefit of activity on survival outcomes of colorectal cancer patients, acknowledged the limitations of the current literature on the field and concluded that the evidence lacks a consistent basis for further recommendations for this specific population. An overview of limitations of cancer survival studies and future research recommendations is presented in the summary manuscript, Box 1[30] of the current manuscript series on colorectal cancer survivors.

Cancer survivors as well as their social network members are open to receiving lifestyle advice from healthcare providers.[171–173] The CUP Global Expert Panel recognises that the limitations of the evidence represent an opportunity for further research to clarify the nature of the associations between measures of physical activity and sedentary behaviour and cancer-related outcomes. Furthermore, the panel recognises a need to better inform cancer patients about the links between physical activity and sedentariness and cancer survivorship, beyond making firm recommendations based on high quality evidence.

5 | CONCLUSIONS

Our work indicates that the accumulated evidence on the putative beneficial association of physical activity with outcomes after colorectal cancer is still limited and impacted by methodological limitations frequently present in observational survivorship studies, such as measurement error, residual confounding, reverse causation, and survival bias. As physical activity is a multi-faceted exposure, additional observational research using standardised assessment and ideally repeated objective measures, is of utmost importance to minimise biases and accurately capture its relationship with outcomes after colorectal cancer. Moreover, future high-quality trials focusing on specific physical activity dimensions and domains are essential for formulating robust conclusions, which could form the base for specific lifestyle guidance for colorectal cancer survivors. Nevertheless, even in the absence of strong evidence, there is potential to use this evidence as guidance for colorectal cancer patients and their health professionals to show that a physically active lifestyle and avoidance of sedentary behaviour may be associated with longer overall survival after a colorectal cancer diagnosis.

AUTHOR CONTRIBUTIONS

Konstantinos K. Tsilidis and Doris S. M. Chan are co-principal investigators of CUP Global at Imperial College London (ICL). Doris S. M. Chan and Konstantinos K. Tsilidis implemented the study according to the protocol reviewed by the CUP Global Protocol Expert Group (PEG). Katia Balducci and Sonia Kiss performed the literature search. Katia Balducci, Nerea Becerra-Tomás, Margarita Cariolou, Sonia Kiss, and Rita Vieira performed the study selection and data extraction. Georgios Markozannes performed the study selection, data extraction, and checked, analysed, and interpreted the data. Dagfinn Aune was a WCRF International CUP Global ICL team member who revised the manuscript. Darren C. Greenwood was a statistical adviser. Amanda J Cross was a CUP Global advisor at Imperial College London. Marc J. Gunter was a CUP Global collaborator on biological processes and provided input into the biological mechanism citations in the manuscript. Ellen Copson was a PEG member, Chair of CUP Global Expert Committee on Cancer Survivorship, and Expert Panel member. Wendy Demark-Wahnefried and Galina Velikova were PEG, OACD, and CUP Global Expert Committee members. Andrew G. Renehan was a PEG member and Deputy Chair of CUP Global Expert Committee on Cancer Survivorship. John Krebs, Matty P. Weijenberg, Monica L. Baskin, Sarah J. Lewis, Jaap Seidell, Rajiv Chowdhury, and Lynette Hill were CUP Global Expert Panel members. Anne M. May, Anne Tjonneland, Karen Steindorf, Martijn Bours, Melissa M. Hudson, Roderick Skinner, and Folakemi T. Odedina were CUP Global Expert Committee members. All members of the CUP Global Expert Committee and Expert Panel provided input into the judgements on the evidence and advised on the interpretation of the review, the public representative (Lynette Hill) did not contribute to the final decisions made by the Panel. Georgios Markozannes drafted the original manuscript. All authors reviewed and provided comments on the manuscript. Doris S. M Chan is the guarantor and has full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Ellen Copson declared research support from Seca. Galina Velikova declared honoraria from Pfizer, Novartis, and Eisai, an institutional grant from Pfizer, and advisory board and consultancy fees from AstraZeneca, Roche, Novartis, Pfizer, Seagene, Eisai, and Sanofi. All other authors have no conflict of interest related to this work.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study. Data sources and handling of these data are described in the materials and methods section. Further details are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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