Physically active individuals have a 23% lower risk of any colorectal neoplasia and a 27% lower risk of advanced colorectal neoplasia than their non-active counterparts: systematic review and meta-analysis of observational studies

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ABSTRACT

Background Few studies have examined the associations between physical activity (PA), sedentary behaviour (SB) and risk of colorectal neoplasia (CN).

Methods We systematically searched Medline, Embase, PsyInfo, Cochrane and other sources from their inception to 30 September 2018 for cohort, case-control and cross-sectional studies that evaluated these associations in asymptomatic, average-risk subjects. Random-effect models were used to estimate relative risks (RRs) of any-type CN, advanced CN, and non-advanced CN, respectively, in individuals with the highest versus the lowest level of PA and SB. Dose-response analyses and subgroup analyses were conducted. The I^2 statistic was used to examine heterogeneity among studies.

Results We identified 32 observational studies, including 17 cross-sectional studies, 10 case-control studies and five longitudinal studies. PA (highest vs lowest) was inversely associated with risk for any-type CN (n=23 studies) and advanced CN (n=15 studies), with a RR of 0.77 (95% CI=0.71 to 0.83, I^2=57.5%) and 0.73 (95% CI=0.63 to 0.82, I^2=45.5%), respectively. There was no association between PA and non-advanced CN (n=5 studies). There was an as association between PA and any-type CN in both sexes, and also for the distal colon. We found no dose–response relationship between PA and any-type or advanced CN. Based on three studies identified, SB time (longest vs shortest) was associated with an increased risk of advanced CN (RR=1.24, 95% CI 1.04 to 1.49, I^2=14.4%). No publication bias was detected by Begg's test.

Conclusion We report a 23% lower relative risk of any type of CN and a 27% lower risk of advanced CN in people with the highest level of PA compared with those in the lowest.

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INTRODUCTION

Globally, colorectal cancer (CRC) accounts for 10% of all new cancer cases and 9% of all cancer deaths.[1] Detecting and removing adenomatous polyps (which are not yet cancer) is an important primary objective of CRC screening,[2] and it reduces CRC mortality.[3] We briefly refresh the BJSM reader about several fundamentals of CRC screening biology so the reader can better understand the innovation in this systematic review.

In the past two decades, CRC screening has been expanded to include *precancerous* lesions. In addition to the conventional adenoma (precancer) to carcinoma (cancer) pathway, pathologists have recognised 'serrated lesions' as precursors of one-third of CRCs.[4] There are two classes of precancerous colorectal neoplasia (CN) that are CRC screening targets, that is, conventional adenomas (non-advanced adenoma (NAA) and advanced adenoma) and serrated polyps.[5] These distinctions are relevant for the reader as we have data on how PA is associated with each of these categories of neoplasia (abnormal growth but not necessarily cancer—can be benign or malignant) (figure 1).

PA is inversely associated with the occurrence of CRC.[6] This inverse relationship was also consistent for CRC in the proximal or distal colon for both sexes.[7 8] However, the outcomes were inconsistent with respect to PA in relation to precancerous neoplasias. To our knowledge, only two meta-analyses have explored the relationship between PA and precancerous neoplasias.[9 10] The 2011 review by Wolin *et al*[9] reported an inverse association between PA and colon adenoma (benign at that point), and the association was slightly stronger (more protective) for those (benign) polyps that were larger or more advanced. However, this review only included colon adenoma without consideration of rectal adenoma, some of the selected studies enrolled symptomatic patients or patients who had received polypectomy as study participants,[11 12] some did not define PA,[13] and some used self-reported questionnaires to ascertain the diagnosis of colon adenoma.[14] These factors limit the validity and generalisability of the study findings. Authors could not conduct subgroup analyses due to the small number of selected studies in this meta-analysis, and did not perform quality assessment or evaluate risk of bias.[9] In a 2017 systematic review[10] there was no significant association between PA and serrated polyps (not cancerous at that stage) (relative risk (RR)=0.90, 95% CI 0.78, 1.03). Yet the meta-analysis was restricted by the methodological designs of the original articles selected, and mainly

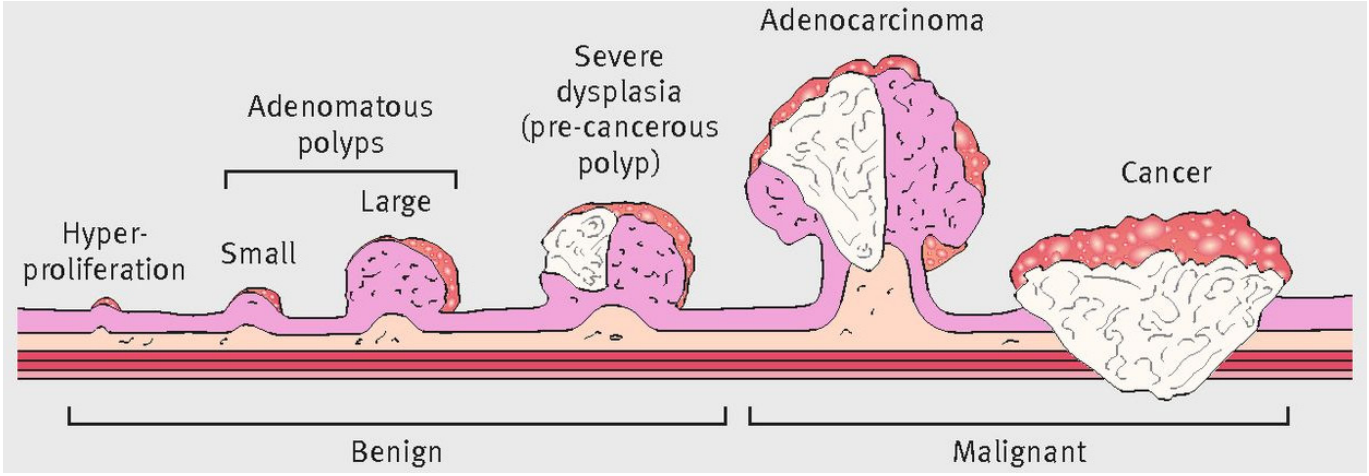


Figure 1 Progression from colorectal polyp to cancer.

focused on serrated lesions.[10] Furthermore, most of the previous meta-analyses considered PA as a binary variable (the most active group vs the least one)[7 9 10 15]; and in dose–response analysis PA level was only analysed against cancerous (not precancerous) lesions.

Sedentary behaviour (SB) is 'sitting or in reclining posture' with energy expenditure less than 1.5 times the basal metabolic rate.[16] SB is therefore not a direct measure of physical inactivity. It is possible that individuals who meet the recommendation on PA may still be highly sedentary on the same day, whereas the opposite is also possible—people who do not sit much may perform inadequate levels of PA. Along with PA, SB has been identified as a risk factor for various cancers, including those of the colon and rectum.[17–19] Previous reviews concluded the associations between prolonged SB and elevated risks of cardiovascular disease and cancer mortality.[20–23] A recent large cohort study showed that prolonged SB was associated with an elevated risk of colon cancer; authors reported relative risks as large as 54% greater for increased time on watching television, 24% greater for increased time on occupational sitting and 24% greater for total sitting time.[17] Findings from two meta-analyses indicated that higher SB was associated with an increased risk of colon and rectal cancer.[15 24] However, no existing meta-analysis examined the risk association between SB and precancerous CNs.

Therefore, the objective of our meta-analysis was to synthesise the association between PA, SB and any types of CN. Our innovation was to examine the association between these variables (PA, SB) and 'earlier' pathology in the cancer continuum.

METHODS

Search strategy and selection criteria

A protocol guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[25] was approved by all investigators before this meta-analysis was conducted. We systematically searched Medline, Embase, Cochrane and PsycInfo databases from their inception up to September 2018. All cross-sectional, case control and cohort studies that examined the relationship between PA, SB and any types of CN were retrieved. We included NAA, advanced adenoma, serrated sessile adenoma/polyp (SSA/P) and traditional serrated adenoma (TSA) in retrieval of existing literature (online supplementary appendix 1). All references from related reviews and included studies were accessed for potential inclusion. We also examined grey literature through several resources, such as the Grey Literature Report website and the Directory of Open Access scholarly Resources.

Two reviewers (JJW, LWH) screened all search outcomes independently by title and abstract. Only relevant studies were included for full-text review. During the review process, all eligible studies consisted of risk estimates or data (eg, odds ratios, risk ratios, or hazard ratios) to calculate risk estimates so that the association between PA, SB and any types of CN could be determined. We applied the following eligibility criteria: (1) participants were asymptomatic, average-risk individuals; hence, we excluded studies where participants were symptomatic,[11 26] largely at high-risk,[12 27] and where the study did not include this information; (2) the diagnosis of CN was confirmed with histological or medical records based on colonoscopy performed for screening purposes but not surveillance[28–31]; (3) the study had a clear definition of PA or SB; (4) data were available on the association between PA, SB and any type of CN, presented as relative risks (RRs) with 95% CIs, or equivalent. Publications were excluded if they: (1) were from conference abstracts[32]; (2) reported CRC as the sole outcome without data on any other types of CN, since the association between PA, SB and CRC was already well established[33]; (3) reported data mixed with hyperplastic polyps, because they were not precancerous lesions of CRC.[34] For studies having multiple publications on the same risk factor from a study sample, the most recent article was retained. In case of disagreement, consensus was reached via a third reviewer (WJZ).

Data extraction and quality assessment

All data were extracted by one author (LWH) and double-confirmed by another (JJW). Information on the general characteristics of all selected studies and the measurement methods, domains of PA (overall vs recreational vs occupational), and definition of PA and SB in terms of duration, frequency and category were collected. Their RRs (95% CI) were extracted, based on the lowest level of PA or the lowest degree of SB as a reference group. For studies that presented risk estimates for PA/SB in different assessments, RRs on energy expenditure (eg, MET-hr/week) were preferred to the volume of PA (eg, hours/day) or frequency (eg, times/week).[35] Regarding the same assessment of PA/SB, if more than one set of classifications were reported, RRs with more quantified categories were chosen considering the feasibility of dose–response analysis.[36] Data regarding lesions in

the sigmoid colon were included in the 'distal colon' subgroup.[37] Baseline data were used for studies that contained both baseline and follow-up data on PA or SB.[38 39] Some studies on advanced colorectal neoplasia (ACN) reported the outcomes combining advanced adenoma and invasive cancer.[38 40 41] We categorised those lesions as into the ACN category. The Newcastle-Ottawa Scale was employed to evaluate the quality of the selected studies (online supplementary appendix 2).

Statistical analysis

The statistics work was performed in a two-stage process. First, four sets of meta-analyses were conducted among various types of CN, including any type CN, ACN, NAA and SSA/P (also TSA). The RRs from the highest level of the PA or SB level were pooled, using the lowest level as a reference group. If a separate risk estimate was presented for males and females, both values were included in the meta-analysis as they indicated the risk estimates in independent samples.[42 43] A pooled RR was employed for those studies that investigated more than one PA domain[44] or several anatomical subsites.[45] A random effects model was applied since PA or SB exposure was highly varied. Subgroup analyses were performed for any type CN, comparing estimated RRs according to sex (female and male), domains of PA and SB (overall, recreational, occupational and commute), measurement instruments of PA and SB (validated and not validated measures), PA assessment methods (PA energy expenditure, duration and frequency), location within the colorectum (proximal colon, distal colon and rectum), number of adjustment factors (upper, intermediate and lower tertile), adjustments for various confounders (family history, obesity, smoking and diet behaviours), study design (cross-sectional, case-control and cohort studies), sample size (n≥3000 and n<3000) and study setting (national programme, multiple centres and single centre).

In the second stage, we employed generalised least squares methods to perform a dose–response analysis among those selected studies having more than three categories with respect to the cumulative volume of PA,[46] quantified using metabolic equivalents per week (MET-hour/week). If several sets of PA classification were presented in one study,[36] direct MET-hour/week data were used. For studies that reported the cumulative volume in weekly hours (hour/week) with different activity intensities, we converted them into MET-hour/week using the following criteria: the weekly hours were multiplied by four METs for moderate activity, by eight METs for vigorous activity and by six METs for moderate-to-vigorous PA (MVPA).[47] For each study, we chose the median PA volume of each category to the corresponding RR if available[35]; otherwise the midpoints of the upper and lower cut-off values of each category were used. For the open boundary, we assumed the same width of the interval with the nearest category and calculated the central dose.[48] The dose–response analysis followed Orsini's protocol to test non-linear and linear regression in a step-by-step process.[49] If linear regression was applicable, the change of RR by increasing every 10 MET-hours/week was reported, which is according to the levels recommended by the WHO.[50] Dose–response analysis was also performed for studies on SB and CN. Given the similar energy expenditure of various SBs, the cumulative volume of SB was quantified by hours per day, without transformation to MET.

Sensitivity analyses were evaluated by the random effects model, analysing the effect of any one single study on the pooled RR. Heterogeneity was examined by I^2 statistics and the respective p values. A p value >0.05 indicated that acceptable heterogeneity was low when I^2=0%–30% and moderate when I^2=30%–60%.[51]

Publication bias was explored in funnel plots and assessed by Begg's test. All statistical tests were evaluated two-sided, and a p value <0.05 was recognised as statistically significant. All data analysis was performed by Stata software (V.14.0), using metan, metafunnel and glst commands.

RESULTS

Study characteristics

A total of 32 studies met the selection criteria (figure 2). The only study on the relationship between PA and SSA was excluded because the full text was unavailable.[32] The general characteristics of all these studies are summarised in table 1.[35–45 52–72] Among them, 14 studies were from North America, nine from European, eight from Asia and one from Australia. There were 17 cross-sectional studies, 10 case-control studies and five cohort studies in total. Over half of all the selected studies (17 out of 32; 53%) were published after the previous meta-analysis[9] since 2011. Most studies were assessed as having high quality (21 out of 32; 66%) (online supplementary appendix 2).

Among all the selected studies, 15 studies (46%) reported overall PA and 18 studies (55%) considered recreational PA as predominant indicators (table 2). Only two articles[52 63] reported data on occupational PA. To assess PA, 10 studies (30%) applied validated instruments, including the Cambridge Physical Activity Index,[62]the Framingham index,[41] IPAQ,[36 57] other PA index[61] and validated questionnaires.[44 54 58 59] Direct and converted MET-hour/week information was available in only 36% of all the selection studies (12 out of 32).

Only three eligible studies were identified to assess the association between duration of SB in relation to occurrence of CN, and all were from North America.[36 54 72] Among them, one study reported overall SB,[36] while two studies used recreational SB[54] as the domain of SB. Regarding different types of CN, three articles[36 54 72] had data on ACN, while one article presented data on CN[54] (table 2).

Primary analyses

PA had an inverse relationship with any type of CN (n=23, RR=0.77, 95% CI 0.71 to 0.83, I^2=57.5%, $P_{heterogenity}$<0.01) and ACN (n=15, RR=0.73, 95% CI 0.63 to 0.82, I^2=45.5%, $P_{heterogenity}$<0.01), but not with NAA (n=5, RR=0.92, 95% CI 0.69 to 1.15, I^2=10.9%, $P_{heterogenity}$=0.03) (figure 3A–C). Based on the three studies identified, SB had an increased risk for ACN (RR=1.24, 95% CI 1.04 to 1.49, I^2=14.4%, $P_{heterogenity}$=0.31) (figure 3D).

Subgroup and sensitivity analysis

Subgroup analyses (table 3) showed that for both sexes, PA had a significant inverse association with any type of CN at low degrees of heterogeneity (both $P_{heterogeneity}$>0.05, I^2=0%) (graph in online supplementary appendix 3). A similar relationship was detected for overall PA, also with moderate heterogeneity. The inverse association was demonstrated for PA and neoplasia in the colon (OR=0.79, 95% CI 0.67 to 0.91), especially in distal colon (RR=0.76, 95% CI 0.59 to 0.92), not in proximal colon and rectum though the heterogeneity level was high ($P_{heterogeneity}$=0.01, I^2=64%) (graph in online supplementary appendix 4). When various measurement instruments for PA, assessment methods, study design, and settings were examined in subgroup analyses, no significant difference was found. Neither any significant difference was detected using adjustments for family history,

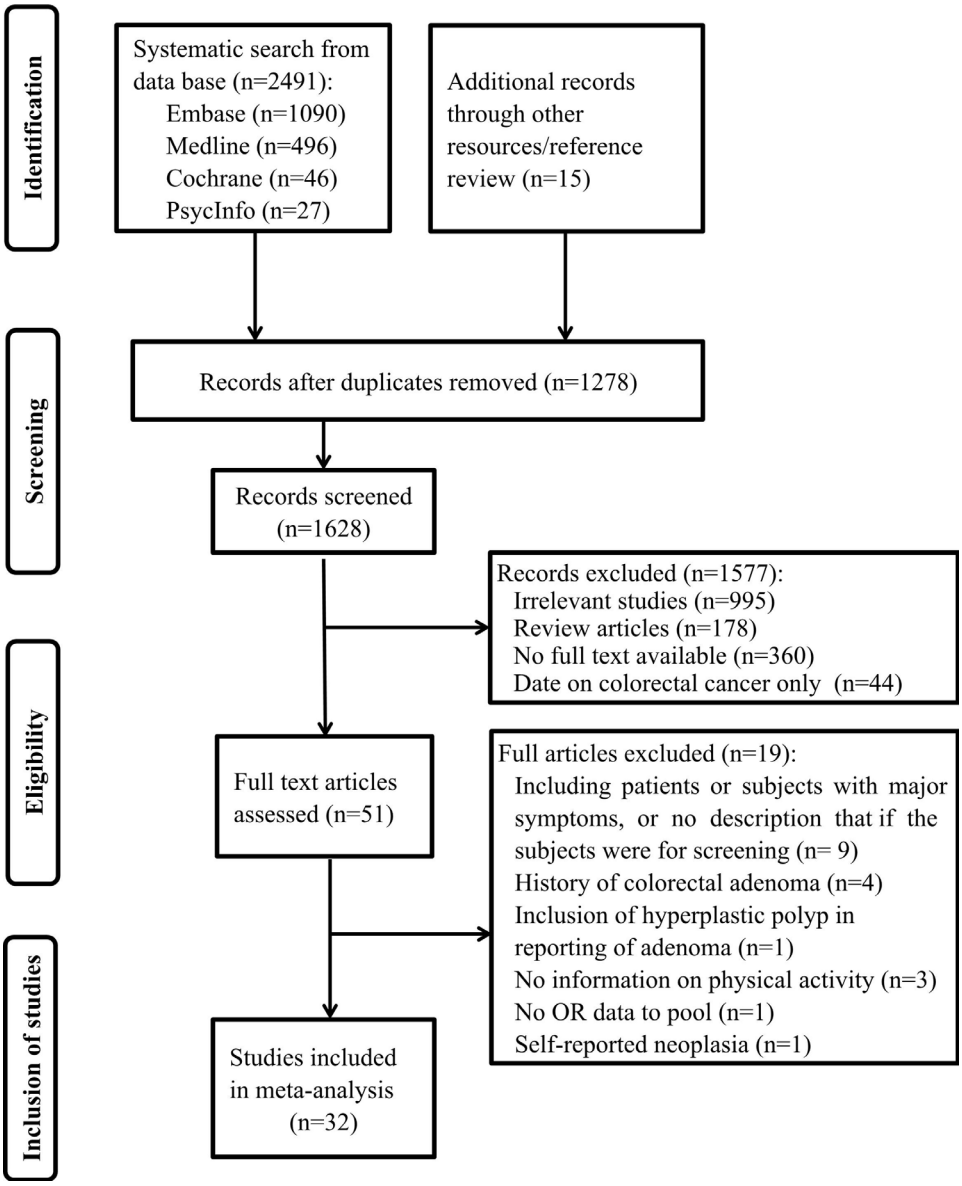


Figure 2 Selection diagram of literature research.

obesity, smoking and alcohol, and diet behaviours. In contrast, studies with large sample size (n≥3000) had a significant lower OR than those with small sample size (n<3000). Sensitivity analyses excluding any individual studies did not change the association markedly. The subgroup analyses for ACN, NAA and SB were not presented because of the small number of the relevant studies in the according groups.

Dose–response analysis

Four studies provided data on the amount of PA that allowed analysis for dose–response relationship,[44 55 59 65] and four studies contributed to dose–response analysis for CAN.[41 44 54 59] Linear regression was found to be applicable to examine the dose–response relationship after non-linear regression modelling. The linear regression showed that there was no significant association between the dose of PA (in MET-hours/week), and ACN and CN (the RR was 0.94 (95% CI 0.87 to 1.02) and 0.97 (95% CI 0.94 to 1.00), respectively). Dose–response analysis for PA and NAA, SB and any type of CN could not be performed due to the small number of eligible studies.[42 44]

Publication bias

No publication bias was detected from both funnel plots (online supplementary appendix 5) and the Begg's tests (p=0.83 and 0.72 for CN and ACN, respectively). We were not able to conduct a publication bias test for NAA and SB related studies because of the limited number of included studies.

DISCUSSION

From our SR, we report an inverse associations between PA and any type of CN and ACN, and the RRs were similar to that for CRC as reported in a previous meta-analysis.[7] A 23% risk reduction of any type of CN was detected between the most physically active individuals and those who were the least active (RR=0.77, 95% CI 0.71 to 0.83). Subgroup analyses showed that this association was consistent irrespective of sex, measurement instruments of PA, domains of PA, study design, sample size and study setting with moderate levels of heterogeneity with no publication bias detected for all analyses. Our synthesis of SB evidence is preliminary as we only identified three eligible

Table 1 Characteristics of selected studies (n=32)

Study	Site	Data collection	Study design	Sample size	Male (%)	Age (years)	Median age (years)	Detection methods	Setting	Adjustments	Adjusted confounders						
											Age	Sex	History of family	BMI	Smoking	Diet	Quality
Blanks *et al* 2015[39]	UN	2006–2010	1	628976	0	60–69	65.2	TC, FS, CTC	1	Y	√	/		√	√		Low
Boutron-Ruault *et al* 2001[52]	France	NA	2	1269	52.3	30–79	NA	TC	2	Y	√	√					Low
Botteri *et al* 2016[38]	Italy	2007–2009	1	750	51.2	50–69	64	TC	2	Y	√	√			√	√	High
Brenner *et al* 2018[36]	Canada	2008–2015	1	2496	53.8	50–74	NA	TC	2	Y	√	√	√	√	√		High
Burnett-Hartman *et al* 2013[53]	USA	1998–2007	2	2506	NA	20–79	NA	TC	2	Y	√	√	√	√	√		High
Cao *et al* 2015[54]	USA	1998–2008	1	22851	21.4	40–75	NA	Record	1	Y	√	/	√	√	√	√	High
Cao* *et al* 2015[72]	USA	1998–2008	1	31065	100	40–75	NA	TC	1	Y	√	/	√	√	√	√	High
Carr *et al* 2017[55]	Germany	2005–2014	1	15950	49.4	55–	63.3	TC	1	N							Low
Chia *et al* 2007[56]	USA	1999–2003	2	348	42.8	30–79	NA	TC	3	N							Low
Enger *et al* 1997[35]	USA	1991–1993	2	976	66.6	50–74	62	FS	2	Y				√	√	√	High
Frantz *et al* 2013[57]	USA	2006–2008	1	934	49.6	30–80	55	TC	3	Y	√	√					High
Giovannucci *et al* 1995[58]	USA	1986–1992	3	47723	100	40–75	NA	TC, FS	1	Y	√	/	√		√	√	High
Giovannucci *et al* 1996[59]	USA	1986–1992	3	13057	0	40–65	NA	Record	1	Y	√	/	√		√	√	Low
Hauret *et al* 2004[60]	USA	1995–1997	2	405	46.7	30–74	58.2#	TC	2	Y	√	√	√		√	√	High
Hermann *et al* 2009[61]	Germany	1994–2007	3	25540	63.6#	35–65	NA	Record	1	Y	√	√	√	√	√	√	High
Jung *et al* 2015[40]	Korea	2010–2011	1	28 504	80.9	30–59	NA	TC	3	Y		√	√	√	√		High
Karaginni *et al* 2010[62]	Greec e	2008–2009	2	104	61.5	30–77	60#	TC	3	Y	√	√		√	√	√	High
Kato *et al* 1990[45]	Japan	1986–1990	2	1324	64.9	NA	NA	TC	3	Y	√	√					High
Kim *et al* 2011[63]	Korea	1998–2007	3	1562	69.7	20–	NA	FS	3	Y	√	√					Low
Knudsen *et al* 2016[64]	Norway	2012–2013	1	14 832	48.5	50–74	62	FS	1	Y	√	√		√	√	√	Low
Kono *et al* 1999[65]	Japan	1995–1996	1	803	100	47–55	NA	Record	2	Y		/			√		Low
Larsen *et al* 2006[66]	Norway	1999–2002	1	6961	NA	50–64	NA	FS	1	Y	√	√		√	√	√	High
Liberman *et al* 2003[41]	USA	1994–1997	1	3121	95.8	50–75	NA	TC	2	Y	√						High
Little *et al* 1993[67]	France	1981–1988	2	476	NA	50–	NA	Record	2	Y	√	√					Low
Lubin *et al* 1997[68]	Israel	NA	2	392	57	21–75	♂63♀60#	TC	3	Y						√	High
Massa *et al* 2014[69]	USA	1991–2007	3	43641	0	42–62	NA	TC	1	N		/					High
Morimoto *et al* 2002[42]	USA	1991–1994	2	1502	46.5	30–74	NA	TC	2	Y	√	/		√	√	√	High
Scnchez *et al* 2012	USA	2002–2010	1	982	41.8	45–	NA	TC	3	Y	√	√		√			High
Shinchi *et al* 1994[37]	Japan	1991–1992	1	2228	100	49–55	NA	TC, FS	2	Y		/			√		Low
Song *et al* 2013[44]	Korea	2008–2010	1	1526	57.2	21–78	49.2	TC	3	Y	√	√	√	√	√		High
Waldmann *et al* 2016[43]	Austria	2008–2012	1	25 409	49.2	40–	60	TC	1	Y	√	/					High
Yang *et al* 2017[71]	Korea	2003–2012	1	70 812	69.4	NA	41.6	TC	2	N							Low

Study design: 1, cross-sectional; 2, case-control; 3, cohort. Neoplasia related: 1, all adenoma; 2, advanced colorectal neoplasia; 3, non-advanced adenoma. Setting: 1, national screening programme/large cohort study; 2, multiple centres; 3, single hospital/site.

♂, male; /, not applicable due to homogenous study population; ♀, female; #, case group; CTC, CT colonography; FS, flexible sigmoidoscopy; N, no; TC, total colonoscopy; Y, yes.

Table 2 Measurement of physical activity (PA)/sedentary behaviours (SB) and relations to colorectal neoplasia (CN) in selected studies

Study	Measurement instrument of PA/SB	Domains of PA/SB	Category of PA/SB	Relationship between PA/SB (highest versus lowest) and CN	Dose–response effect
Physical activity (n=32)					
Blanks *et al* 2015[39]	Qs	REC	<1 versus≥1 times/week	CN (+)	/
Boutron-Ruault *et al* 2001[52]	Qs	OA, REC, OCC	Low versus median versus high PA	ACN (–), NAA (–)	ACN (+),[46] NAA (–)
Botteri *et al* 2016[38]	Qs	OA	Low and moderate versus High	ACN (–)	/
Brenner *et al* 2018[36]	Qs (IPAQ)*	REC	MVPA: 0 versus 0–1 versus 1–3 versus >3 hours/week; WHO, AICR/WCRF guideline: no versus yes	ACN (–)	ACN (–)
Burnett-Hartman *et al* 2013[53]	Interview	REC	0 versus 0–1 versus 1–2 versus 2–6 versus ≥6 hours/week	CN (+), ACN (+), NAA (–)	Not reported
Cao *et al* 2015[54]	Qs*	REC	Low versus moderate versus high	ACN (+)	ACN (–)
Cao[#] *et al* 2015[72]	Qs*	REC	Lowest versus highest quintile in MET-hours/week	CN (+), ACN (+), NAA (–)	/
Carr *et al* 2017[55]	Qs	OA	<48.2 versus 48.2–91.0 versus 91.0–150.4 versus >150.4 MET-hours/week	CN (+)	Not reported
Chia *et al* 2007[56]	Qs	REC	0–17.4(M)/11.4(F) versus>17.4(M)/11.4(F) MET-hours/week	CN: M, F (–)	/
Enger *et al* 1997[35]	Interview	REC	VPA: <3 versus ≥3 times/week	CN (–)	/
		REC	VPA: 0 versus 1–13 versus ≥14 MET-hours/week	CN (–)	CN (–)
		REC	1–4 quartiles in MET-hours/day	CN (–)	CN (–)
Frantz *et al* 2013[57]	Qs (IPAQ) *	OA	1–3 tertile in MET-min/week	CN (+)	Not reported
Giovannucci *et al* 1995[58]	Qs*	REC	1–5 quintiles in MET-hours/week	CN: D, R (–)	CN: D, R (–)
Giovannucci *et al* 1996[59]	Qs*	REC	0–1 versus 2–4 versus 5–9 versus10–18 versus19 MET-hours/week	CN: D (+), R (–)	CN: D (+), R (–)
Hauret *et al* 2004[60]	Qs (PPAQ)*	OA	0–17.1 versus 17.2–28.3 versus 28.4–40 versus >40 MET-hours/day	CN (–)	CN (–)
Hermann *et al* 2009[61]	Qs (PA index)*	OA	Inactive versus moderately inactive versus moderately active versus active	CN (–); CN: P, D, R (–); CN: M, F (–)	CN (–); CN: P, D, R (–); CN: M, F (–)
Jung *et al* 2015[40]	Qs	OA	<1 versus ≥1 times/week	CN (–), ACN (–)	/
Karaginni *et al* 2010[62]	Qs *	OA	Inactive versus moderately active and active	ACN (+)	/
Kato *et al* 1990[45]	Qs	REC	<1 versus ≥1–2 times/week	CN: P (–); D, R (+)	/
	Qs	OCC	Low and moderate versus High	CN: P, D (+); R (–)	/
Kim *et al* 2011[63]	Qs	REC	Never versus irregular versus regular (≥1 times/week)	CN: D (–)	Not reported
Knudsen *et al* 2016[64]	Qs	OA	30 min PA: light (<7) versus moderate and high (≥7 times)	ACN (–)	/
Kono *et al* 1999[65]	Qs	REC	<4 versus 4–14 versus15–36 versus >36 MET-hours/week	CN (–) (colon)	CN (–) (colon)
	Qs	REC	≤ 30th versus 31–60th versus 61–90th versus >90th MET-hours/week	CN (–) (colon); P (+), D (–)	Not reported
Larsen *et al* 2006[66]	Qs	REC	PA score: 2–4 versus 5 versus 6 versus 7–12	ACN (–), NAA (–)	ACN (–), NAA (–)
Liberman *et al* 2003[41]	Qs (Framingham index)*	OA	PA index: 24–28 versus 29–36 versus >36	ACN (+)	Not reported
	Qs	OA	<7 versus 7–24 versus 25–48 versus 49–94 versus >94 MET-hours/week	ACN (–)	ACN (–)
Little *et al* 1993[67]	Qs	OA	0 versus 1 versus >1–2 versus 2 times/week	CN (–)	CN (–)
Lubin *et al* 1997[68]	Interview	OA	MVPA: <4.0 versus 4.0–5.5 versus >5.5 hours/day	CN (+)	CN (+)

Continued

Table 2 Continued

Study	Measurement instrument of PA/SB	Domains of PA/SB	Category of PA/SB	Relationship between PA/SB (highest versus lowest) and CN	Dose–response effect
Massa *et al* 2014[69]	Qs	OA	<14.5 versus ≥14.5 MET-hours/week	CN (+)	/
Morimoto *et al* 2002[42]	Qs	OA	<12.3 versus 12.3–24.7 versus 24.8–46.9 versus ≥47.0 MET-hours/week	CN: M, F (–)	CN: M, F (–)
Sanchez *et al* 2012[70]	Qs	REC	<1 versus ≥1 hours/week	CN (+)	/
Shinchi *et al* 1994[37]	Qs	REC	0 versus 1–3 versus 4–5 versus 7 times/week	CN (–) (sigmoid)	Not reported
Song *et al* 2013[44]	Qs*	REC	12.05 versus 12.06–31.25 versus >31.25 MET-hours/week	CN (+), ACN (+), NAA (+); CN: P (–); D (+); R (–);	CN (+); ACN (+); NAA (+); CN: P (–); D (+); R (–);
	Qs*	OCC	Active versus sedentary	CN (–), ACN (–), NAA (–); CN: P (–); D (–); R (–);	/
Waldmann *et al* 2016[43]	Qs	REC	None versus occasional versus regular	CN: M, F (+); ACN: M, F (+)	CN: M, F (+); ACN: M, F (+)
Yang *et al* 2017[71]	Qs	REC	No exercise versus exercise	ACN (–)	/
Sedentary behaviour (n=3)					
Brenner *et al* 2018[36]	Qs (IPAQ)*	OA	0–14 versus 14–35 versus 35–70 versus >70 hours/week	ACN (–)	ACN (–)
Cao *et al* 2015[54]	Qs	REC	Watching TV: <0.5 versus 0.5–2 versus >2 hours/day	ACN (–)	ACN (+)
Cao* *et al* l2015[72]	Qs	REC, COM	Sitting while watching TV: 0–6 versus 7–13 versus14–20 versus ≥21 hours/week	CN (–); CN: P, D, R (–)	CN (+); CN: P (+), D (–), R (+)
			Sitting at work driving: 0–6 versus 7–13 versus14–20 versus ≥21 hours/week	CN (–)	CN (–)
			Other sitting at home: 0–6 versus 7–13 versus14–20 versus ≥21 hours/week	CN (–)	CN (+)
			Watching TV: <6 versus 7–13 versus14–20 versus ≥21 hours/week	ACN (–), NAA (–)	ACN (+), NAA (–)

*Validated questionnaire; domain of physical activity/sedentary behaviour.
/, not applicable; (–), non-significant association; (+), significant association; dose–response effect; ACN, advanced colorectal neoplasia; AICR/WCR, American Institute for Cancer Research/World Cancer Research Fund; COM, commute type; category of PA/SB; CPA, Cambridge Physical Activity Index; D, distal colon; F, females; IPAQ, International Physical Activity Questionnaire; M, males; MET, metabolic equivalent; relation of PA/SB to CN; MVPA, moderate-to-vigorous physical activity; NAA, non-advanced adenoma; OA, overall physical activity/sedentary behaviour; OCC, occupational physical activity/sedentary behaviour; P, proximal colon; PPAQ, Paffenbarger Physical Activity Questionnaire; Qs, questionnaire; R, rectum; REC, recreational PA/SB; VPA, vigorous physical activity.

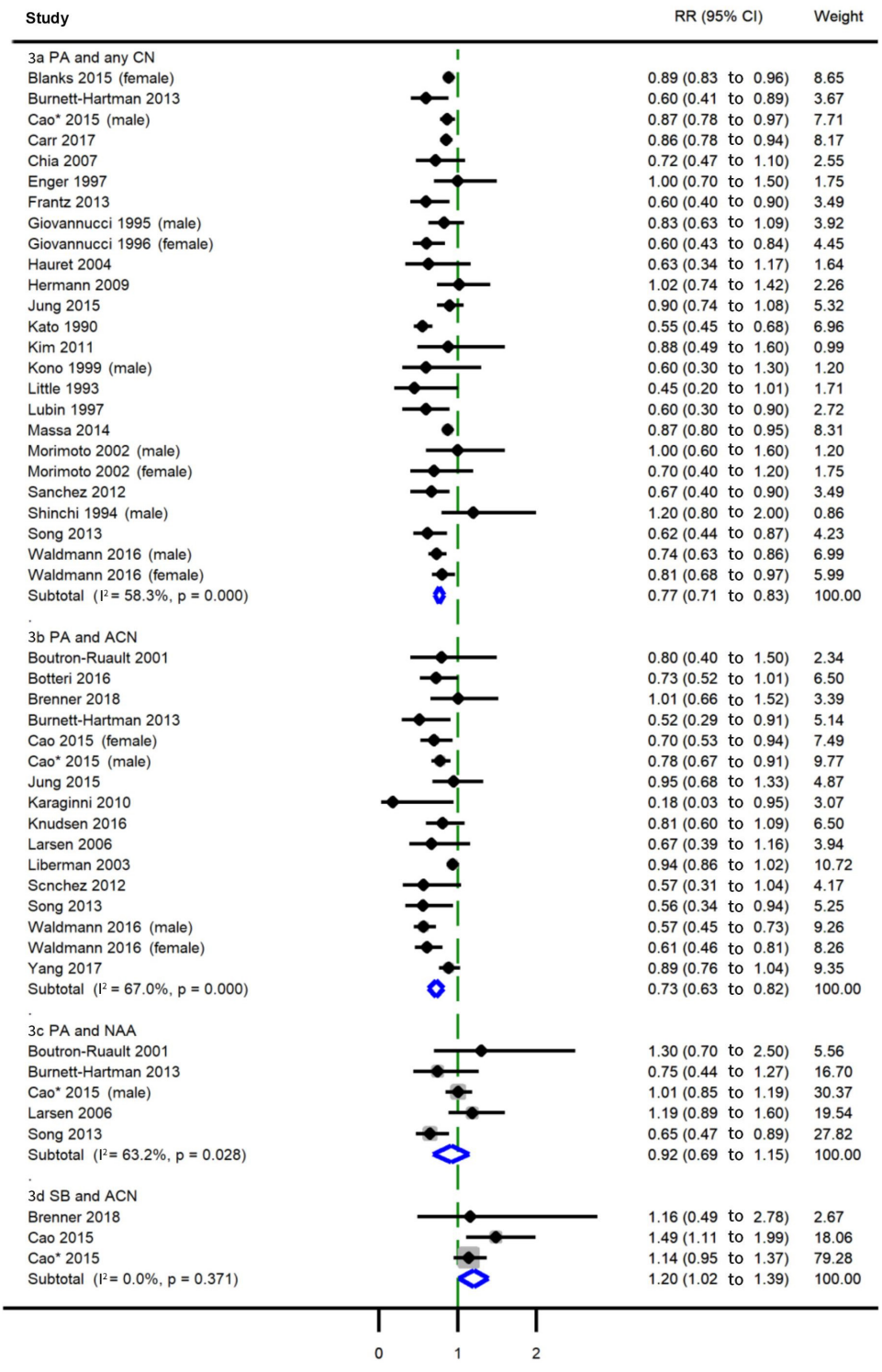
studies. We found a positive association between SB and ACN at a low heterogeneity level.

Strengths and limitations

This meta-analysis has several strengths. First, we set stringent criteria to establish the eligibility for study selection so the findings could represent asymptomatic individuals in population-based CRC programme. Most studies were of high quality, and the more robust methodology as compared with the previous meta-analyses enhances the generalisability of the study findings. In addition, it is the most comprehensive study focusing on the relationship between PA and CN, and we conducted pilot dose–response analyses between PA and CN. Our work also had some limitations. First, the design of most included studies (n=27) was either cross-sectional or case-control, and hence we could not draw a conclusion on the cause–effect relationship between PA/SB and CN. Moreover, although nearly two third of these cross-section studies were of high quality (18 in 27, 66.7%), and subgroup analysis showed that those cross-sectional studies generated a similar RR as that of cohort studies; selection bias could not be completely avoided. Future research with a prospective study design is required to quantify the odds of PA and SB in reducing CN or ACN. Our synthesis of the SB evidence is only preliminary as we could only identify three studies. Furthermore, nearly all included studies used self-reported measures to collect PA and SB data. Future studies should use validated objective instruments to measure PA and SB. The number of eligible studies was small and no serrated lesions studies were enrolled in the current pooling process; accordingly, issues related to heterogeneity should be acknowledged. We are not able to perform a meta-regression due to the limited number of studies. Finally, the pooled estimates are confounded as some individual ORs are unadjusted and others are not known to be fully adjusted, confounding bias may still remain even after adjustment using external estimates of confounding.[73]

PA and CN

This meta-analysis provides robust evidence for the role of PA against colon adenomas, while the effect was slightly stronger for ACN (RR=0.73, 95% CI 0.63 to 0.82). This conclusion was consistent with findings on colon adenoma (RR= 0.84, 95% CI 0.77 to 0.92) and advanced polyps (RR=0.70, 95% CI 0.56 to



ACN: advanced colorectal neoplasia; CI: confidential interval; CN: colorectal neoplasia; NAA: non-advanced adenoma; PA: physical activity; RR: relative risk; SB: sedentary behavior.

Figure 3 Physical activity (PA) and sedentary behaviour (SB) in relation to colorectal neoplasia (CN). (A) PA and any type of CN; (B) PA and advanced colorectal neoplasia (ACN); (C) PA and non-advanced adenoma (NAA); (D) SB and ACN. RR, relative risk.

0.88) from Wolin's previous meta-analysis.[9] A similar pattern was reported by continuous update project's (CUP) systematic review on the relationship between PA and CRC in 2016.[33] There was a 20% risk reduction of colon cancer (RR=0.80, 95% CI 0.72 to 0.88) when their occurrence was compared between individuals with the highest and lowest overall PA levels (12 studies), with a moderate level of heterogeneity ($P_{heterogeneity}$=0.06, I^2=39%). No significant association between PA and rectal cancer reported (RR=1.04, 95% CI 0.92 to 1.08), $P_{heterogeneity}$=0.36, I^2=9.2%) in CUP's review. Similar conclusion has also been raised by Harriss' meta-analysis between leisure-time PA and CRC (14 studies).[74]

Table 3 Subgroup analyses for colorectal neoplasia (random effect)

Subgroup	Category	n	RR (95% CI)	$P_{heterogeneity}$ (I^2 statistics)
Sex	Female	7	0.84 (0.77 to 0.91)	0.15 (36%)
	Male	7	0.82 (0.75 to 0.89)	0.64 (0%)
Domains of PA	overall	9	0.82 (0.74 to 0.90)	0.13 (35%)
	recreational	14	0.75 (0.68 to 0.82)	0.01 (52%)
	occupational	2	0.49 (0.30 to 0.68)	0.12 (49%)
Measurement instrument of PA	validated	7	0.74 (0.62 to 0.87)	0.04 (54%)
	invalidated	16	0.78 (0.71 to 0.85)	<0.01 (61%)
PA assessment methods	PA energy expenditure	12	0.85 (0.76 to 0.88)	0.21 (24%)
	PA duration	3	0.63 (0.48 to 0.78)	0.91 (0%)
	PA frequency	9	0.77 (0.66 to 0.89)	<0.01(75%)
Location	Colon	10	0.79 (0.67 to 0.91)	<0.01 (60%)
	Rectum	6	0.80 (0.54 to 1.07)	0.07 (50%)
Anatomical subsites	Proximal	7	0.85 (0.67 to 1.02)	0.06 (51%)
	Distal	9	0.76 (0.59 to 0.92)	0.01 (64%)
	Rectum	6	0.80 (0.54 to 1.07)	0.07 50%)
Study design	Cross-sectional	10	0.81 (0.75 to 0.87)	0.05 (45%)
	Case-control	8	0.62 (0.53 to 0.70)	0.42 (2%)
	Cohort	5	0.82 (0.69 to 0.95)	0.14 (43%)
Number of adjustment factors	Upper tertile (10-17)	7	0.83 (0.74 to 0.91)	0.05 (52%)
	Intermediate tertile (4-8)	8	0.73 (0.61 to 0.85)	0.51 (0%)
	Lower tertile (0–3)	8	0.73 (0.63 to 0.82)	<0.01(73%)
Adjustments for family history	No	15	0.77 (0.69 to 0.84)	<0.01 (63%)
	Yes	8	0.77 (0.66 to 0.88)	0.04 (52%)
Adjustments for obesity	No	14	0.73 (0.65 to 0.81)	<0.01 (61%)
	Yes	9	0.83 (0.75 to 0.91)	0.09 (40%)
Adjustments for smoking and alcohol use	No	10	0.72 (0.63 to 0.82)	0.01 (57%)
	Yes	13	0.81 (0.74 to 0.88)	0.02 (48%)
Adjustments for diet behaviours	No	16	0.75 (0.68 to 0.82)	<0.01 (67%)
	Yes	7	0.82 (0.72 to 0.92)	0.25 (23%)
Sample size	n≥3000	9	0.85 (0.80 to 0.89)	0.16 (31%)
	n<3000	14	0.63 (0.56 to 0.70)	0.55 (0%)
Study setting	National programme	8	0.84 (0.79 to 0.89)	0.12 (37%)
	Multiple centres	7	0.72 (0.56 to 0.88)	0.28 (19%)
	Single hospital/unit	8	0.67 (0.57 to 0.78)	0.10 (42%)

A number of biological mechanisms have been hypothesised to explain the protective role of PA on CRC. One fundamental explanation included alteration of hormone mediation, such as insulin, insulin-like growth factors, and adipokines.[75] PA has also been linked to a lower risk of colon cancer by shortening the gastrointestinal transit time, which could reduce the stimulation of colonic contents, faecal bile acid concentrations, and decrease the exposure of carcinogens to intestinal epithelia.[76] This study indicated the positive effect of PA on ACN, but did not show an association between PA and NAA. In combination of previous reports on insignificant association between PA and colon polyps,[12] these findings imply that PA might play an inhibitory role in the progression of adenoma to carcinoma. Our negative findings for rectal neoplasia were based on data from six studies, where five of these studies did not demonstrate significant relationships. Neither was the association between proximal neoplasia and PA (RR=0.85, 95% CI 0.67 to 1.02). Few studies have been conducted to explore the underlying mechanism. This may be due to the limited number of studies included in the present meta-analysis, and that the missing rate of proximal neoplasia is comparatively higher than that for distal neoplasia in most screening studies.

The subgroup analyses in this meta-analysis showed a mixed finding of the association between PA and CN. A potential explanation may be due to the variability of the instruments for measuring PA. In the selected studies, PA was measured in various ways by volume (METs per week or hours per week), duration (hour per time), frequency (times per week) and domains (recreational, occupational or overall PA). Less than one-third of all studies (seven in 23, 30.4%) used formally validated measures. However, in studies that adopted validated instruments, some reported a PA index without quantifying activity levels (eg, inactive vs moderately active and very active group.[62] Ideal instruments for measuring PA should collect comprehensive data on frequency, intensity and duration to generate the volume of PA as one composite variable. Furthermore, the diverse range in cut-off levels may lead to mixed results in studies that reported PA volume. The thresholds of PA varied from 6.0 to 17.4 METs-hours/wk in different studies.[36 56 69] These different classifications could influence the association estimate of PA on CN as reported by original studies. Universal cut-off levels were suggested for further studies so as to benchmark the association between PA and any types of CN. For instance, moderate intensity activity for at least 150 min each week (≥10 METs-hours/

wk), 210 min each week (≥14 METs-hours/wk) and 300 min per week (≥20 METs-hours/wk) could be adopted as different categories according to the recommendations of the WHO and the World Cancer Research Fund/American Institute for Cancer Research. Notably, all studies collected data on PA through subjective methods, such as self-administered questionnaires or interviews. It was found that the imprecision of measurement was related to the attenuation of risk associations.[77] Given the inherent bias of self-reported measures, objective methods (eg, accelerometers) are warranted in future studies to attain a more precise association.

Any forms of PA that include occupational, recreational activity, transportation and household chores could increase energy expenditure. Recreational activity, known as leisure-time activity, is a well-established modifiable lifestyle determinant for multiple health outcomes.[6 78] The subgroup analyses on domain-specific PA in this study showed that the risk estimates among the most active adults compared with the least active individuals were similar between the studies assessing single recreational domain and those with overall PA. The two studies included in this review with occupational PA also showed an inverse association with CN/ACN.[45 52] However, due to the limited number of studies, this meta-analysis on occupational and commute PA was not performed. It is likely that most adult populations spend the majority of their time performing physical activities in occupational settings. From the National Health Interview Survey in USA, half of the adults who reported leisure-time activities had occupational activities with at least 1 hour per day.[79] The effect of occupational activities, independent of leisure-time activities, on the risk of CRC has also been demonstrated. We have instead suggested capturing all domains of PA in future studies.

SB and CN

SB has adverse effects on cardiovascular disease and cancer mortality, especially in those with low levels of PA.[20] Numerous epidemiological studies have linked SB with chronic disease-related risk factors, such as central adiposity, decreased insulin and increased blood glucose, and other metabolic biomarkers.[80] Obesity and diabetes may mediate the associations between SB and cancer.[81] Consistent with the association between SB and CRC,[15 82] and despite the very limited body of evidence we synthesised, our review demonstrated a positive association between SB and ACN.

What is already known

- Few studies synthesised robust evidence on the relationship between physical activity (PA), SB (SB) and colorectal neoplasia (CN).
- Only two meta-analyses explored the association between PA and colon adenoma (precancer); no meta-analysis examined the association between SB and CN (which may include non-cancerous or precancerous tissue).

What are the new findings

- There is an inverse association between PA and (1) any-type or (2) advanced, CN. We detected no publication bias.
- Subgroup analysis according to sex, measurement instruments of PA, domains of PA, study design, sample size and study setting also demonstrated the association.
- Based on the very small number of studies we identified, SB was associated with an increased risk of advanced CN.

CONCLUSION

PA was inversely associated with any type of CN in both men and women. The prevalence of CN in the average-risk population over 50 years old is as high as 25%,[83] Our data are consistent with an active lifestyles being associated with a lower risk of both colorecatal neoplasia and ACN. Our findings support the utility of including PA when developing and evaluating risk stratification algorithms for CN/ACN. We make a preliminary report of a positive association between SB and ACN at a low heterogeneity level, based on a small number of studies.

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