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Interaction of leisure-time physical activity with body mass index on the risk of obesity-related cancers: A pooled study

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Abstract

Physical activity (PA) has been associated with a lower risk of some obesity-related cancers, but the combined association and interaction of PA and body weight on obesity-related cancer risk is less clear. We examined the association of leisure-time PA (high/low) and its combination with body mass index (BMI, <25 [low]/≥25 [high] kg/m^2) on obesity-related cancer risk in 570 021 individuals, aged 43 years on average at baseline, in five Scandinavian cohorts. We used Cox regression to calculate hazard ratios of obesity-related cancers (n = 19 074) and assessed multiplicative and additive interactions between PA and BMI on risk. High leisure-time PA, recorded in 19% of the individuals, was associated with a 7% (95% confidence interval [CI] 4%-10%) lower risk of any obesity-related cancer compared to low PA, with similar associations amongst individuals with a low and a high BMI (6% [1%-11%] and 7% [2%-11%]). High PA was also associated with decreased risks of renal cell (11% [9%-31%]) and colon cancer (9% [2%-16%]). When high PA and low BMI were combined, the relative risk reduction for all obesity-related cancers was 24% (95% CI 20%-28%); endometrial cancer, 47% (35%-57%); renal cell cancer, 39% (27%-51%); colon cancer, 27% (19%-35%); multiple myeloma, 23% (2%-40%) and pancreatic cancer, 21% (4%-35%), compared to low PA-high BMI. There were no additive or multiplicative interactions between PA and BMI on risk. The result of our study suggests a reduced risk of obesity-related cancer by leisure-time PA in both normal weight and overweight individuals, which further decreased for PA and normal weight combined.

KEYWORDS
body mass index, interaction, leisure-time physical activity, obesity-related cancer

What's new?

Evidence suggests that physical activity lowers risk of certain obesity-related cancers. Whether physical activity and body weight act together to prevent cancer, however, remains unclear. In this study, the authors explored the impact on obesity-related cancer risk of associations and

Abbreviations: 40-y, Age 40-programme; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD-7, International Classification of Diseases, 7th edition; MDCS, Malmö Diet and Cancer Study; MET, metabolic equivalent of task; NCS, Norwegian Counties Study; Oslo, Oslo study 1; PA, physical activity; RERI, relative excess risk due to interaction; RR, relative risk; VIP, Västerbotten Intervention Programme.

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interactions between physical activity and body mass index (BMI). While high leisure-time physical activity and normal weight were individually associated with reduced obesity-related cancer risk, the greatest risk reduction occurred in the presence of both high physical activity and normal weight. No additive or multiplicative interactions were observed. The findings highlight the importance of physical activity in obesity-related cancer prevention.

1 | INTRODUCTION

Cancer is one of the leading causes of death worldwide, and every sixth death in the world is due to cancer, accounting for almost 10 million cancer deaths in 2020.[1,2] Yet around 40% of cancer cases are estimated to be preventable by avoiding modifiable risk factors including lifestyle-related factors.[3-5] For physical activity (PA), the association with risk of most individual cancers remains inconclusive.[6] However, there is strong evidence that PA is associated with a lower risk of colon, postmenopausal breast and endometrial cancer,[6] and a recent study additionally provided evidence for a potential association with other cancers, in particular kidney cancer and liver cancer.[7] These same cancers, and another eight to nine cancers, were in the most recent reviews concluded to be obesity-related with strong evidence.[8,9]

The biological mechanisms through which high PA and normal weight could prevent cancer are likely to be partially shared, for example, through improved immune function, modulated inflammation and enhanced insulin sensitivity.[10] These shared pathways suggest the potential for an interaction between PA and obesity on cancer risk.[11] This, however, has only been investigated in one or a few studies each on cancers of the breast, prostate, pancreas, endometrium or colorectum.[12-22] Some of these studies found a positive multiplicative interaction between low PA and high body mass index (BMI) on risk,[12,14,20] but most did not.[13,15-19,21,22] However, interaction on the additive scale is more informative to identify the group at most benefit for intervention, as it reveals the absolute number of cases that could have been prevented in one group vs another.[11] Additive interaction between PA and BMI on cancer risk has been investigated only in a few studies of various cancers, and these suggested no additive interaction.[12,13,17]

In this pooled cohort study, we investigated the relationship of leisure-time PA and its combined association and multiplicative and additive interaction with BMI, in relation to the risk of obesity-related cancers individually and combined.

2 | METHODS

2.1 | Study population

We included participants from three Norwegian cohorts: the Oslo study I (Oslo), the Norwegian Counties Study (NCS) and the Age 40 Programme (40-y), and in two Swedish cohorts: the Västerbotten Intervention Programme (VIP)[23] and the Malmö Diet and Cancer Study (MDCS). All cohorts are population-based and include information from health examinations in individuals performed between 1972 and 2014 (see Table 1). The health examination included measurements of height and weight for participants wearing light indoor clothes and no shoes. BMI was calculated by dividing weight in kilogrammes by the square of height in meters (kg/m^2). Leisure-time PA was assessed with closed-ended question/-s in written questionnaire form. In the Norwegian cohorts, participants were asked to indicate their usual level of leisure-time PA during the year preceding the survey by selecting one of four categories: (1) reading, watching TV or any other sedentary activity, (2) walking, cycling or other activity for at least 4 hours per week, (3) light sports or heavy gardening for at least 4 hours per week and (4) regular, hard exercise or participating in competitive sports several times a week. In the VIP, participants were asked to select one of five categories to indicate their frequency of exercising in changed outfit with the purpose to increase their fitness level or wellbeing during the last 3 months: (1) never, (2) once in a while, (3) 1 to 2 times a week, (4) 2 to 3 times a week and (5) >3 times a week. In the MDCS, participants were asked to fill in the number of minutes spent per week on 17 leisure-time PA types separately per four seasons.[24] A metabolic equivalent of task (MET) value was assigned to each activity. The indicator of PA level is a score calculated as the sum of the number of minutes per week for the four seasons multiplied by MET. Owing to different assessments of PA between the cohorts and, thus, the difficulty to harmonise absolute PA levels between cohorts, in the pooled cohort, we used a similar percentile cut-point for all cohorts to categorise PA level into low or high. We combined levels 1 to 2 (sedentary to light PA) in the Norwegian cohorts and the VIP as the reference group (low PA), which made up around 80% of the respective population and in the MDCS, we cut the continuous PA variable at the 80th percentile (2962 MET-min/week). The remaining around 20% of the respective population made up the high PA group (moderate to hard PA; Table S1).

2.2 | Follow-up

Cancer diagnoses were identified by linking each individual by their unique personal identity number to the respective national Cancer Register in Norway and Sweden. Death and emigration were captured in each national Cause of Death and Population Register, respectively. Follow-up for these linkages ended on 31 December 2012 for the Norwegian cohorts, on 31 December 2014 for the VIP and on 31 December 2019 for the MDCS. Obesity-related cancers were defined as those concluded with strong or highly suggestive evidence

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TABLE 1 Baseline characteristics of the 570 021 individuals in the study

Characteristics	All	Women	Men
Cohort (year of baseline examination), n (%)			
Total (1972-2014)	570 021 (100)	284 928 (100)	285 093 (100)
Oslo (1972-1973)	17 737 (3)	0 (0)	17 737 (6)
NCS (1974-1988)	90 874 (16)	44 618 (16)	46 256 (16)
40-y (1985-1999)	329 943 (58)	171 327 (60)	158 616 (56)
MDCS (1991-1996)	26 723 (5)	16 056 (6)	10 667 (4)
VIP (1985-2014)	104 744 (18)	52 927 (18)	51 817 (18)
Age, years			
Mean (SD)	43 (7.5)	44 (7.6)	43 (7.5)
Category, n (%)			
<30	15 514 (3)	7252 (3)	8262 (3)
30-44	431 219 (76)	218 027 (76)	213 192 (75)
45-59	87 075 (15)	40 647 (14)	46 428 (16)
≥ 60	36 312 (6)	19 002 (7)	17 211 (6)
Smoking status, n (%)			
Never smoker	229 012 (40)	126 638 (45)	102 374 (36)
Ex-smoker	128 526 (22)	56 921 (20)	71 605 (25)
Current smoker	209 822 (37)	100 108 (34)	109 714 (38)
Smoking intensity, pack years, n (%)			
<10	75 880 (36)	45 138 (45)	30 742 (28)
10-19.9	60 240 (29)	30 274 (30)	29 966 (27)
≥20	67 976 (32)	23 487 (24)	44 489 (41)
Pack years missing	5726 (3)	1209 (1)	4517 (4)
Smoking status missing	2661 (1)	1261 (1)	1400 (1)
BMI, kg/m^2			
Mean (SD)	25 (3.8)	25 (4.1)	26 (3.4)
Category, n (%)			
<25 kg/m^2 (low BMI)	310 460 (54)	178 435 (63)	132 025 (46)
≥25 kg/m^2 (high BMI)	259 561 (46)	106 493 (37)	153 068 (54)
Leisure-time PA, n (%)			
Sedentary to light (low PA)	460 382 (81)	248 433 (87)	211 949 (74)
Moderate to hard (high PA)	109 639 (19)	36 495 (13)	73 144 (26)
Combination of BMI and leisure-time PA, n (%)			
High BMI-low PA	212 638 (38)	94 979 (33)	117 659 (41)
High BMI-high PA	46 923 (8)	11 514 (4)	35 409 (13)
Low BMI-low PA	247 744 (43)	153 454 (54)	94 290 (33)
Low BMI-high PA	62 716 (11)	24 981 (9)	37 735 (13)
Follow-up time, years			
Mean (SD)	20 (8.0)	20 (7.7)	20 (8.3)
Category, n (%)			
<10	57 798 (10)	27 361 (10)	30 437 (11)
10-19	201 885 (35)	102 378 (36)	99 507 (35)
20-29	250 214 (44)	128 907 (45)	121 307 (42)
≥30	60 124 (11)	26 282 (9)	33 842 (12)

Abbreviations: 40-y, Age 40-programme; BMI, body mass index; MDCS, Malmö Diet and Cancer Study; NCS, Norwegian Counties Study; Oslo, Oslo study 1; PA, physical activity; VIP, Västerbotten Intervention Programme.

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to be related to obesity in Kyrgio et al.[9] We also reviewed later Continuous Update Project reports on single cancer forms performed by the World Cancer Research Fund for potential redefinition of obesity-related cancers, which, however, remained defined as in Kyrgio et al[9]: oesophageal adenocarcinoma (International Classification of Diseases, seventh/tenth edition [ICD-7/10] code 150/C15, of adenocarcinoma histologic subtype), stomach-cardia (151.1/C16.0), colon (153/C18), rectum/anus (154/C19-21), liver/intrahepatic bile ducts (155.0/C22), gallbladder/biliary tract (155.1-155.3/C23-24), pancreas (157/C25), postmenopausal breast (170/C50, and attained age ≥60 years), endometrium (172/C54), ovary (175.0/C56), renal cell (180.0, 180.9/C64) and multiple myeloma (203/C90). In our study, we use the term "endometrial cancer" to denote the slightly larger group uterine corpus cancer.

2.3 | Selection criteria

Altogether, the cohorts included 655 275 individuals with 832 998 health examinations (observations). After exclusions due to missing information on leisure-time PA and BMI, extreme values of height, weight or BMI, mismatching dates and a prevalent cancer (excluding carcinoma in situ and basaliomas), 570 021 individuals with one observation each were retained in the study (Figure 1).

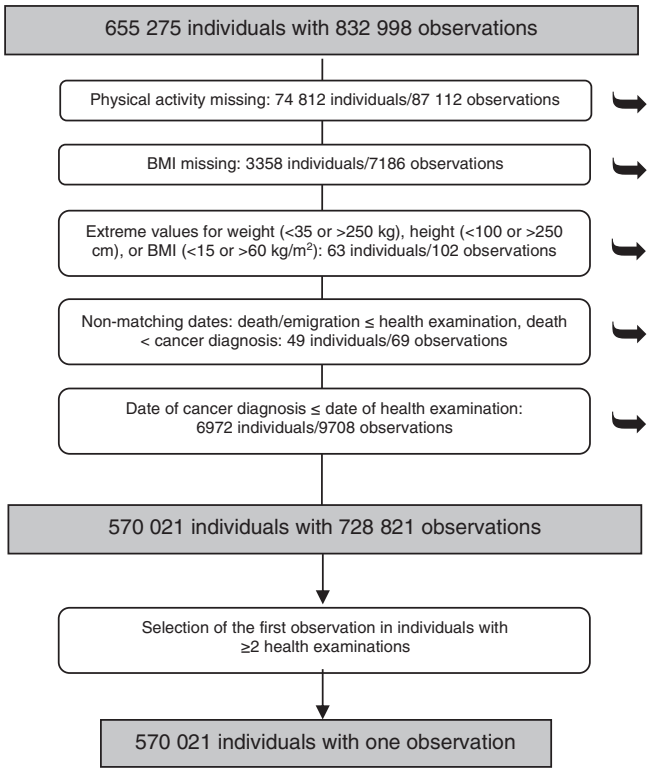

FIGURE 1 Flowchart of exclusions and selections of individuals and observations in the study. ➥ denotes exclusions

2.4 | Statistical analysis

Survival analyses were conducted for any obesity-related cancer and separately by cancer form and by sex if the number of cases was more than 400. Person-years at risk was calculated from the date of health examination until the diagnosis of any obesity-related cancer or until censoring due to another cancer, death, emigration or until the end of follow-up, whichever came first. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) of cancer by categories of leisure-time PA (as previously described), BMI (<25 and ≥25 kg/m^2) and their combination. Since a small number of individuals and cases were obese (BMI ≥30 kg/m^2) with moderate to hard PA, we analysed obesity and overweight jointly. We used age as underlying time metric and we adjusted for sex, cohort, date of birth in five categories (before 1931, 1931-1938, 1939-1946, 1947-1954, 1955 and later) and smoking in seven categories (never smoker, ex-smoker, current smoker by tertile of pack-years, smokers with pack-years missing and smoking status missing [1% of individuals]). BMI (continuous) was additionally adjusted for in the analysis of PA and cancer risk as a potential confounder and/or mediator, and the analysis of BMI and cancer risk additionally included adjustment for PA (low/high). Results for BMI and obesity-related cancer risk have been reported in greater detail before in a population with large overlap with the present study population.[25,26]

Schoenfeld residuals statistics was used to test the proportional hazards assumption of the Cox models. Sex and cohort violated the proportional hazards assumption in some models but including sex or cohort as a stratum in the Cox models did not alter HRs, so they were not retained as stratum in the models.

The relative excess risk due to interaction (RERI) was calculated to investigate additive interactions between PA and BMI in relation to obesity-related cancer risk. The RERI was based on adjusted HRs representing relative risks (RRs) in the formula: RR11 − RR10 − RR01 + 1, denoting individuals in the low BMI-high PA group (RR11), low BMI-low PA group (RR10), high BMI-high PA group (RR01) and high BMI-low PA group (1, reference group). CIs were calculated using the delta method.[11,27] Multiplicative interactions of PA with BMI, cohort and sex, and a three-way interaction of PA, BMI and sex, were tested by the Wald test of the respective product term in the model. *P*-values for sex-interactions were reported for all analyses.

Absolute risks of all incident obesity-related cancers between 60 and 80 years of age were calculated as described by Gail et al.[28] For this method, the risks of cancer and of dying from other causes than cancer were derived from the cohort for ages 60 to 70 years and 70 to 80 years, respectively.

All analyses were performed using Stata 16.1, (StataCorp LLC., College Station, Texas).

3 | RESULTS

The 570 021 individuals (284 928 women, 285 093 men) in the study had a mean baseline age of 43 years (SD = 7.5) (Table 1).

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TABLE 2 Hazard ratio (95% confidence interval) of obesity-related cancers by level of leisure-time physical activity

Cancer type	Level of leisure time PA[a]	No. at risk/ cases	HR (95% CI)[b] not BMI-adjusted	HR (95% CI)[c] BMI-adjusted	$P_{sex-interaction}$[d]
All obesity-related cancers	All				.67
	Low PA	460 382/16 127	Reference	Reference	
	High PA	109 639/2947	0.93 (0.90-0.96)	0.94 (0.91-0.98)	
	Women				
	Low PA	248 433/10 696	Reference	Reference	
	High PA	36 495/1379	0.93 (0.88-0.98)	0.95 (0.90-1.01)	
	Men				
	Low PA	211 949/5431	Reference	Reference	
	High PA	73 144/1568	0.92 (0.87-0.97)	0.94 (0.89-1.00)	
Colon cancer	All				.67
	Low PA	460 382/3841	Reference	Reference	
	High PA	109 639/779	0.91 (0.84-0.98)	0.92 (0.85-1.00)	
	Women				
	Low PA	248 433/1974	Reference	Reference	
	High PA	36 495/249	0.94 (0.82-1.07)	0.95 (0.84-1.09)	
	Men				
	Low PA	211 949/1867	Reference	Reference	
	High PA	73 144/530	0.89 (0.80-0.98)	0.91 (0.83-1.00)	
Rectal cancer	All				.39
	Low PA	460 382/2336	Reference	Reference	
	High PA	109 639/513	0.93 (0.84-1.02)	0.93 (0.85-1.03)	
	Women				
	Low PA	248 433/1045	Reference	Reference	
	High PA	36 495/141	0.99 (0.83-1.19)	1.01 (0.84-1.20)	
	Men				
	Low PA	211 949/1291	Reference	Reference	
	High PA	73 144/372	0.91 (0.81-1.03)	0.92 (0.82-1.04)	
Pancreatic cancer	All				.92
	Low PA	460 382/1168	Reference	Reference	
	High PA	109 639/221	0.89 (0.77-1.03)	0.90 (0.78-1.04)	
	Women				
	Low PA	248 433/560	Reference	Reference	
	High PA	36 495/65	0.89 (0.69-1.15)	0.90 (0.70-1.17)	
	Men				
	Low PA	211 949/608	Reference	Reference	
	High PA	73 144/156	0.88 (0.74-1.06)	0.89 (0.74-1.06)	
Postmenopausal breast cancer	Women				
	Low PA	171 989/3180	Reference	Reference	
	High PA	22 272/467	0.99 (0.89-1.09)	0.99 (0.90-1.09)	
Endometrial cancer	Women				
	Low PA	248 433/1689	Reference	Reference	
	High PA	36 495/201	0.88 (0.76-1.02)	0.95 (0.82-1.10)	
Ovarian cancer	Women				
	Low PA	248 433/1144	Reference	Reference	
	High PA	36 495/155	1.02 (0.86-1.21)	1.03 (0.87-1.21)	

(Continues)

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TABLE 2 (Continued)

Cancer type	Level of leisure time PA[a]	No. at risk/ cases	HR (95% CI)[b] not BMI-adjusted	HR (95% CI)[c] BMI-adjusted	$P_{sex-interaction}$[d]
Renal cell cancer	All				.11
	Low PA	460 382/1189	Reference	Reference	
	High PA	109 639/237	0.79 (0.69-0.91)	0.82 (0.71-0.95)	
	Women				
	Low PA	248 433/450	Reference	Reference	
	High PA	36 495/37	0.63 (0.45-0.89)	0.66 (0.47-0.93)	
	Men				
	Low PA	211 949/739	Reference	Reference	
	High PA	73 144/200	0.84 (0.72-0.98)	0.87 (0.74-1.02)	
Multiple myeloma	All				.05
	Low PA	460 382/666	Reference	Reference	
	High PA	109 639/168	1.03 (0.87-1.23)	1.05 (0.88-1.25)	
	Women				
	Low PA	248 433/301	Reference	Reference	
	High PA	36 495/32	0.77 (0.53-1.11)	0.77 (0.53-1.11)	
	Men				
	Low PA	211 949/365	Reference	Reference	
	High PA	73 144/136	1.16 (0.95-1.42)	1.19 (0.97-1.45)	
Other obesity-related cancers[e]	All				.07
	Low PA	460 382/955	Reference	Reference	
	High PA	109 639/216	0.95 (0.82-1.11)	0.99 (0.85-1.15)	
	Women				
	Low PA	248 433/373	Reference	Reference	
	High PA	36 495/37	0.73 (0.52-1.03)	0.76 (0.54-1.07)	
	Men				
	Low PA	211 949/582	Reference	Reference	
	High PA	73 144/179	1.03 (0.87-1.22)	1.08 (0.91-1.28)	

Abbreviations: CI, confidence interval; HR, hazard ratio; PA, physical activity.
[a]Low PA: sedentary to light PA, High PA: moderate to hard PA.
[b]Hazard ratios from Cox regression models with age as time scale, adjusted for sex, cohort, baseline age, date of birth in five categories (before 1931, 1931-1938, 1939-1946, 1947-1954, 1955 and later) and smoking status and intensity in seven categories.
[c]Hazard ratios from Cox regression models with age as time scale, adjusted for sex, cohort, baseline age, date of birth in 5 categories (before 1931, 1931-1938, 1939-1946, 1947-1954, 1955 and later), smoking status and intensity in 7 categories and BMI (continuous).
[d]The *P*-value for sex-interaction was based on Wald statistics of the product terms of sex and leisure-time physical activity in the Cox regression model.
[e]Other obesity-related cancers include oesophageal adenocarcinoma, stomach cardia, liver/intrahepatic bile ducts and gallbladder/biliary tract cancer.

Approximately 63% of women and 46% of men had a BMI within the low-to-normal range (<25 kg/m^2), and 13% of women and 26% of men were categorised with moderate to hard PA. After on average 20 years (SD = 8.0) of follow-up, 19 074 obesity-related cancer cases (12 075 in women, 6999 in men) had been recorded.

The main associations of leisure-time PA with cancer risk showed a lower risk of all obesity-related cancers combined amongst individuals with moderate to hard PA as compared to individuals with sedentary to light PA (HR: 0.93 [95% CI 0.90-0.96]) (Table 2). This association was similar between individuals with low-to-normal weight (HR: 0.94 [95% CI 0.89-0.99]) and with overweight or obesity (BMI ≥25 kg/m^2, HR: 0.93 [95% CI 0.88-0.99]). The inverse association for high PA was also found for colon cancer (HR: 0.91 [95% CI 0.84-0.98]) and renal cell cancer (HR: 0.79 [95% CI 0.69-0.91]) (Table 2). Adjusting for BMI minimally attenuated these associations. The associations between PA and obesity-related cancers risk did not differ between men and women (Table 2) or between cohorts (Table S2). Associations between the original four or five categories of PA in the Norwegian cohorts and in the VIP, and of quartiles of PA in the MDCS, and all obesity-related cancer risk is shown in Table S3.

Low-to-normal weight compared to overweight or obesity was associated with a lower risk of all obesity-related cancers combined (HR: 0.81 [95% CI 0.79-0.83]), and of all separate cancers, but only weakly for ovarian cancer for which the confidence interval crossed one (Table S4).

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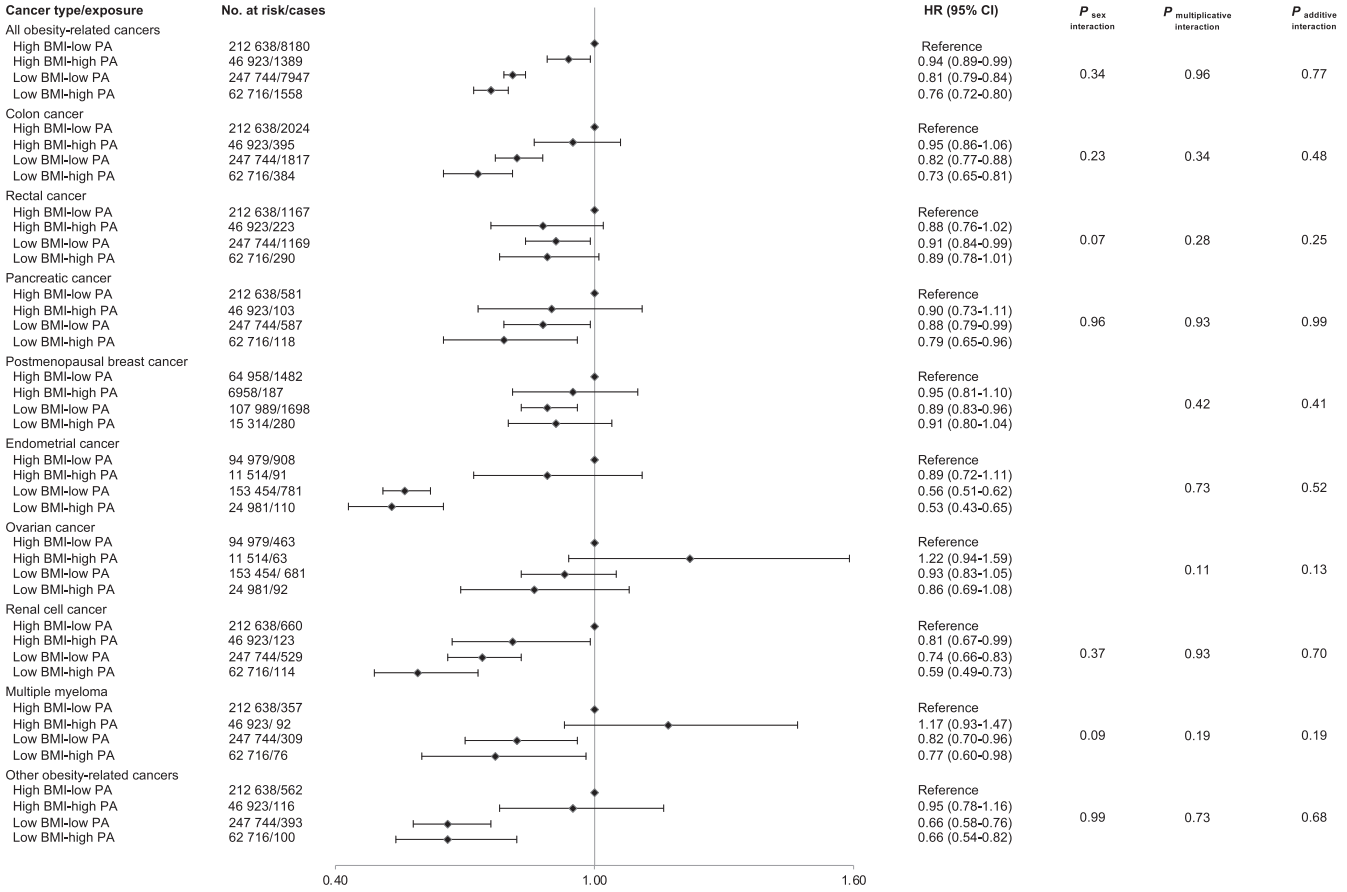

FIGURE 2 Hazard ratios (95% confidence interval) of obesity-related cancers in single and combined according to combinations of leisure-time physical activity and body mass index level. Hazard ratios were calculated by use of Cox regression using age as time scale, adjusted for sex, cohort, baseline age, date of birth and smoking status and intensity. Multiplicative interactions of PA and BMI, and a three-way interaction of PA, BMI and sex, were tested by the Wald test of the respective product term in the model. Additive interactions of PA and BMI were investigated by calculating the Relative Excess Risk for interaction (RERI) as RR11 − RR10 − RR01 − RR00 + 1, for which the delta method was used to obtain confidence interval. BMI, body mass index; CI, confidence interval; HR, hazard ratio; PA, physical activity. Low PA: sedentary to light exercise, High PA: moderate to hard exercise, Low BMI: <25 kg/m^2, High BMI: ≥25 kg/m^2

The associations of a two-by-two categorical combination of leisure-time PA and BMI with the risk of obesity-related cancers, and *P*-values from additive and multiplicative interaction tests, are shown in Figure 2. Compared to overweight or obese individuals with low PA, individuals with low-to-normal weight and high PA had a lower risk of all obesity-related cancers (HR: 0.76 [95% CI 0.72-0.80]), colon cancer (HR: 0.73 [95% CI 0.65-0.81]), pancreatic cancer (HR: 0.79 [95% CI 0.65-0.96]), endometrial cancer (HR: 0.53 [95% CI 0.43-0.65]), renal cell cancer (HR: 0.59 [95% CI 0.49-0.73]), multiple myeloma (HR: 0.77 [95% CI 0.60-0.98]) and of the combination of "other" obesity-related cancers composed of oesophageal adenocarcinoma, stomach-cardia cancer, liver cancer and gallbladder cancer (HR: 0.66 [95% CI 0.54-0.82]). BMI appeared to be a stronger driver than PA in their joint association with all obesity-related cancers, endometrial cancer, multiple myeloma and "other" obesity-related cancers. There were no additive or multiplicative interactions between PA and BMI for all obesity-related cancers or specific cancer types. There were no sex-interactions in the associations; however, sex-specific results are reported in Figure S1.

In absolute terms, the risk of all incident obesity-related cancer over a 20-year period for 60-year-old women of low-to-normal weight with moderate to hard leisure-time PA, and with overweight or obesity with sedentary to light leisure-time PA, was 8.4% and 10.7%, respectively. In men, the corresponding absolute risks were 3.8% and 5.0%, respectively.

4 | DISCUSSION

In this pooled cohort study, we found that moderate to hard leisure-time PA compared to sedentary to light leisure-time PA was associated with a lower risk of all obesity-related cancers, colon cancer and renal cell cancer. Moderate to hard PA and a BMI in the low-to-normal range jointly contributed to a lower risk of obesity-related cancers and several separate cancers. No additive or multiplicative interaction was found between PA and BMI, and the risk reduction of all obesity-related cancer by PA was similar amongst low-to-normal weight and overweight or obese individuals.

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There is strong evidence to support a role of leisure-time PA in reducing the risk of some cancers, including colon, postmenopausal breast and endometrial cancer.[6] The evidence for other cancers is less conclusive, but accumulating evidence suggests an association also for other cancers including kidney cancer,[7,29] which is further supported by the results of our study. Our study did not confirm an association between PA and postmenopausal breast and endometrial cancer risks; however, the results of previous studies have been heterogenous and, for postmenopausal breast cancer, they have shown modest effect sizes.[6] The heterogenous findings between studies are likely affected by different assessments and cut-points of PA. For example, the risk of postmenopausal breast cancer has been shown to reduce already with light exercise such as walking,[30] which could not have been captured in our study due to the higher cut-point of PA. Moreover, for cancers with a dose-response effect of PA, such as postmenopausal breast cancer,[6,7] the effect size will be larger when comparing PA levels in the two ends excluding a middle section than using one single cut-point such as in our study.

Cancers conclusively or suggestively associated with PA are confirmed to be obesity-related.[10] Several biological mechanisms whereby obesity, PA and sedentary behaviour may influence cancer risk have been proposed. For example, obesity and physical inactivity contribute to energy imbalance, which may be linked to cancer through oxidative stress, DNA repair and telomere length.[31] PA and weight regulation are determinants of energy balance. Maintaining an optimal level of energy balance (caloric expenditure relative to caloric intake) can reduce systemic and adipose tissue inflammation and angiogenesis, alter endogenous hormone metabolism and adipokine levels and improves insulin sensitivity, which are strongly hypothesised biological mechanisms in the development of cancer.[10,32] These potential joint pathways for PA and obesity on cancer suggest the potential for interaction, that is, a risk or relative risk increase or reduction that only occurs in the presence of both factors.[11]

Few studies have investigated such interaction on cancer. Consistent with our findings, a Danish study showed no interaction between BMI and PA on all cancer incidence.[21] Similarly, in relation to individual cancer forms, no multiplicative interaction between BMI and PA has been found for cancer of the endometrium,[18,19] postmenopausal breast,[17,20] pancreas,[15,16] and colon,[14,33] and three studies of breast cancer assessing the additive interaction between BMI and PA on risk found no interaction.[13,17,34] The modest association between PA and cancer risk in our study may be a reason for why no interaction with BMI was found. Despite this lack of interaction, however, moderate to hard PA and low-to-normal weight both contributed to a reduced cancer risk in our study, totalling a 24% relative risk reduction compared to that of inactive, overweight or obese individuals, and an absolute 20-year risk reduction between 60 and 80 years of age of around 1% to 2%. For all obesity-related cancers, we observed that BMI was a stronger driver in the joint association with PA on risk than was PA, which was also observed for some separate cancers, especially endometrial cancer. However, the strengths of these associations and individual contribution of PA and BMI in the associations heavily depend on the chosen cut-points, as previously discussed, and the specific markers used for PA and adiposity.

Our study has some strengths and limitations. Firstly, by use of unique personal identity numbers in Norway and Sweden, we could link individuals to national registers with high completeness and validity.[35-37] Furthermore, the large sample size and long follow-up, which enabled the investigation also of rarer cancer forms, although for some of these, there were less than 100 cases in certain subgroups limiting statistical power to reach significance. The main limitation of our study, like in the vast majority of observational studies of PA, is the once-only and self-reported form of leisure-time PA, which may include both random and systematic misclassifications[38-40] potentially causing diluted or biased results. Furthermore, the different classifications of PA in each cohort restricted the options for categorisation of PA after pooling. Access to information on MET minutes in all cohorts, instead of in only one of our included cohorts, would have facilitated more options for categorisation and the investigation of a dose-response relationship. We also lacked information on potentially important confounders for some cancer forms, including dietary intake and, in women, information on reproductive and hormone-related factors. However, the information on smoking—an important potential confounder for most of the cancers investigated—was virtually complete for both smoking status and pack-years in current smokers.

In conclusion, our study showed a reduction in obesity-related, colon and renal cell cancer risk with moderate to hard leisure-time PA. Higher PA jointly with low-to-normal weight was associated with a further reduced risk contributed by both factors, but without evidence of an interaction. Collectively, these findings underscore the importance of PA in the prevention of obesity-related cancer irrespective of an individual's body weight.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ming Sun: Conceptualization, Formal analysis, Funding acquisition, Investigation and Writing-original draft. Tanja Stocks: Conceptualization, Data curation, Funding acquisition, Investigation and Writing-review & editing. Tone Bjørge: Data curation, Investigation and Writing-review & editing. Stanley Teleka, Anders Engeland, Patrik Wennberg, Christel Häggström: Investigation and Writing-review & editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

ETHICS STATEMENT

The study was approved by Ethics Committees in Norway (Regionale komiteer for medisinsk og helsefaglig forskningsetikk, no 2012/2271/

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REK sør-øst) and Sweden (EPN Umeå, no 2012-354-31M and no 2015-7-32M and EPN Lund, no 2014/830). Written informed consent was obtained from participants in the MDCS. Participants in the VIP provided written informed consent for a blood draw, taken at the health examination, to be donated for future research. In Norway, the participants were invited to the health survey and a questionnaire was sent together with the invitation. An attendance to the health examination where the participants delivered their filled in questionnaire has been accepted by the Data Inspectorate as an informed consent, but not a written consent. Written consent was obtained from 1994 onwards.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author conditional on permission from the involved cohort committees and national registers.

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