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ORIGINAL PAPER

Interplay between exercise and BMI; results from an equal access, racially diverse biopsy study

Jamie Michael[1] · Taofik Oyekunle[2] · Lauren Howard[2] · Amanda De Hoedt[1] · Catherine Hoyo[3] · Delores Grant[4] · Stephen Freedland[1,5]

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Abstract

Purpose It is unclear if exercise and BMI interact to influence prostate cancer (PC) risk. We hypothesized BMI is linked with increased aggressive PC risk but this link will be attenuated with increased exercise.

Methods Men undergoing prostate biopsy completed a questionnaire and metabolic equivalent (MET) hours of exercise was calculated. Of 695 men, 349 had PC; 161 low-grade, and 188 high-grade. We assessed the link between exercise and PC risk, high-grade PC (Gleason 7–10), and low-grade PC (Gleason 2–6) using logistic and multinomial logistic regression. Analysis was stratified by BMI. Link between BMI and PC risk and aggressive PC was similarly tested.

Results On multivariable analysis, there was no link between exercise and PC diagnosis in the entire cohort (p trend = 0.18–0.71) or across BMI groups (p trend = 0.15–0.97). For the entire cohort, higher BMI was linked with increased risk of high-grade PC (OR 1.06, $p = 0.008$). When stratified by exercise groups, the trend for higher BMI and increased risk of high-grade PC remained (OR 1.03–1.15, $p = 0.02$–0.66). There were no interactions between exercise and BMI in predicting PC risk (all $p \geq 0.31$).

Conclusions Regardless of exercise, higher BMI was linked with higher risk of aggressive PC, while exercise was unrelated to PC risk. Confirmatory studies are needed.

Keywords Prostate biopsy · Exercise · BMI · Veterans · Prostate cancer

Introduction

Prostate cancer is the most frequently diagnosed non-skin cancer in men in the United States, and the second leading cause of cancer deaths [1]. It is important to find modifiable risk factors for prostate cancer to alleviate the impact of this disease. Exercise and excess body fat are both modifiable factors and could be key to further understand the epidemiology of prostate cancer.

A 2014 meta-analysis confirmed that high body mass index (BMI) is associated with prostate cancer diagnosis, particularly high-grade disease [2]. On the other hand, results from a 2018 meta-analysis investigating a relationship between physical activity and prostate cancer diagnosis and mortality was inconclusive [3]. Therefore, the association between exercise and prostate cancer remains a promising area of study that requires further research. Despite many studies examining obesity and exercise, to our knowledge, few studies have investigated if exercise and BMI interact to

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✉ Stephen Freedland
Stephen.freedland@cshs.org

[1] Division of Urology, Veterans Affairs Medical Center, Durham, NC, USA

[2] Duke Cancer Institute, Duke University School of Medicine, Durham, NC, USA

[3] Epidemiology and Environmental Epigenomics, North Carolina State University, Raleigh, NC, USA

[4] Department of Biological and Biomedical Sciences, NC Central University, Durham, NC, USA

[5] Cedars-Sinai Medical Center, Los Angeles, CA, USA

influence prostate cancer risk. Specifically, if greater exercise can negate the adverse effects of elevated BMI.

In 2015, a cohort study in Sweden investigated the relationship between physical activity, obesity, and prostate cancer. They found no significant associations, although, their results suggest that an interaction between BMI and exercise during leisure time merits further research [4]. However, we could find no additional studies exploring this relationship.

Some studies have explored an interaction between physical activity and obesity in relation to other diseases. In a study investigating the influence of fitness and BMI on diabetes, Holtermann et al. concluded that higher cardiorespiratory fitness had a stronger protective effect on diabetes among obese men than among normal weight men [5]. Also, Barry et al. found that unfit individuals had twice the risk of mortality regardless of BMI. In addition, they discovered that fit individuals who were overweight or obese had similar mortality risks as fit individuals who were normal weight [6]. These studies imply that fitness may negate the risks associated with obesity.

Of note, we recently published in a prostate biopsy study that higher BMI correlated with aggressive prostate cancer risk [7]. Moreover, we published that higher self-reported exercise was protective for aggressive prostate cancer, but only in white men, though these findings were several years ago and based upon small numbers ($n = 307$) [8]. Herein, we updated our cohort and assessed the interplay between BMI and exercise on aggressive prostate cancer risk. We hypothesized that BMI is linked with increased aggressive prostate cancer diagnosis; however, this link will be weaker in men who exercise more. We also hypothesized that fit individuals who are obese will have reduced risks compared to unfit obese men.

Materials and methods

Study design

Men undergoing prostate biopsy for an elevated PSA and/or abnormal digital rectal examination (DRE) at the Durham Veterans Affairs Medical Center between January 2007 and January 2018 were recruited to participate in an ongoing biopsy study. Methods for identification and accrual of participants have been described previously [7]. Men were at least 18 years of age, had a PSA test within 12 months prior to enrollment, and had no history of prostate cancer. Of the 1,595 eligible men who underwent biopsy, 1,222 (77%) consented to participate. Of these, we excluded 516 due to incomplete exercise questionnaires and 11 for missing data on BMI, previous biopsy, or TRUS volume, resulting in a study cohort of 695 patients (see Fig. 1). The study was approved by the Institutional Review Board at Durham Veterans Affairs Medical Center and all patients provided written informed consent.

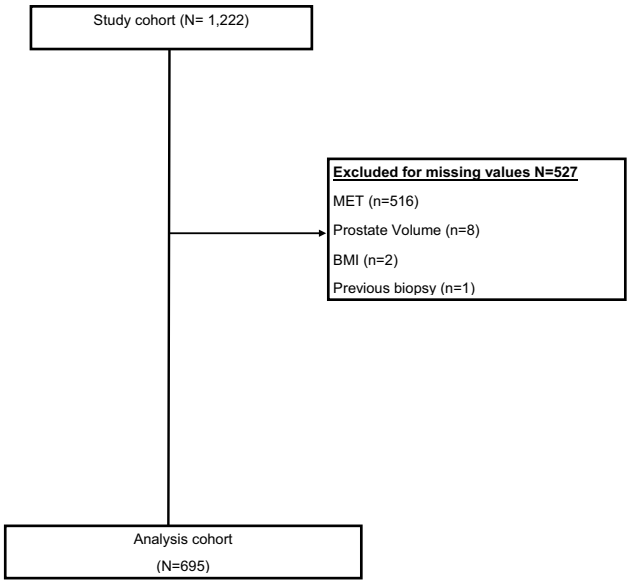

Fig. 1 Consort diagram showing patient selection

Data collection

Patients completed a questionnaire, including demographic, medical, and lifestyle characteristics. Exercise was assessed using the Godin Leisure-Time Exercise Questionnaire [9, 10], which was given to the participant by study personnel on the day of prostate biopsy. The questionnaire instructs patients to "only count exercise that was done during free time," so it does not encompass occupational or household activities. Participants were instructed to complete the questionnaire at home at their convenience and return it to study personnel in a pre-addressed, stamped envelope. It was typically returned prior to the participant knowing the results of his biopsy. The leisure score index contains 3 questions that assess the average frequency of mild, moderate, and strenuous intensity exercise during free time in a typical week. There was also a corresponding question for each of the 3 exercise intensities on the average duration in minutes for a typical session of activity within that exercise intensity.

To calculate the metabolic equivalent (MET) hours of exercise, the frequency of exercise sessions per week in each intensity category was multiplied by the average reported duration in hours, weighted by an estimate of the MET for that intensity, summed across all intensities, and expressed as average total MET hours per week. The weighted values for each exercise intensity were mild (3 METs, e.g.. easy walking, yoga), moderate (5 METs, e.g.. brisk walking, tennis), and strenuous (9 METs, e.g.. running, vigorous swimming).

DRE findings and PSA level were abstracted from urology clinic notes from either the visit at which the biopsy was performed, or the most recent visit prior to biopsy. Prostate volume was taken from the ultrasound-guided biopsy. Height and weight, measured by trained personnel on the day of biopsy, were used to calculate body mass index (BMI).

Outcome ascertainment

Biopsy tissue was assessed by a pathologist per standard of care and prostate cancer grade was abstracted from the resulting pathology report. Grade was assigned using the five-tiered grade group system where low-grade disease was defined as grade group (GG) 1 (Gleason score ≤ 6) and high-grade prostate cancer as GG2-5 (Gleason score ≥ 7).

Statistical methods

MET was categorized as <3, 3–8.9, 9–17.9, and ≥ 18 h per week. These categories correspond with the equivalent of <1, 1–2.9, 3–5.9, and ≥ 6 h of walking at an average pace, consistent with prior analysis of exercise and cancer risk [11]. The Godin Leisure Time questionnaire has been validated previously against activity diaries [9, 10]. BMI was categorized as <25, 25–29.9, ≥ 30 kg/m^2 (normal weight, overweight, obese). The association between the 4-tiered MET hours/week and 3-tiered BMI with baseline characteristics were assessed using Kruskal–Wallis and Chi square for continuous and categorical variables, respectively.

The association between BMI and prostate cancer diagnosis was assessed among the entire cohort using logistic regression, treating BMI as continuous and categorical in separate models. Similarly, multinomial logistic regression was used to test the association between BMI and high-grade and low-grade cancer relative to no prostate cancer (see above for definitions). In addition, these analyses were stratified by MET hours per week (<3, 3–8.9, 9–17.9, ≥ 18). Models were adjusted for age, race (black, non-black), DRE (normal vs. suspicious), family history of prostate cancer (yes, no, unknown), prostate volume (log-transformed), PSA (log-transformed), previous prostate biopsy (yes, no), and MET (categorical; for entire cohort only). We also assessed the association between MET hours per week (categorical) among the entire cohort and prostate cancer diagnosis using logistic regression and the association between MET hours per week and high-grade and low-grade cancer vs. no prostate cancer was tested using multinomial logistic regression. Further, these analyses were stratified by BMI (<25, 25–29.9, ≥ 30 kg/m^2). We tested for trends by entering median MET hours per week for each MET category as a continuous term into the model and evaluating the coefficient by the Wald test. We tested for interactions between MET hours per week and BMI by including both main effect terms as continuous variables and an interaction term, which represented the cross-product of the two main effect terms in the same model. We tested the coefficient of the cross-product term by the Wald test. In secondary analysis, we re-analyzed exercise as tertiles to create groups with larger samples sizes and thus more statistical power. Analyses were performed using SAS 9.4 (SAS Institute, Inc. Cary, NC). Statistical significance was two-sided with a threshold of $p<0.05$.

Results

Patient demographics

Of the 695 men included in our study, 312 (45%) reported exercising <3 MET hours per week, 103 (15%) reported exercising 3–8.9, 90 (13%) reported exercising 9–17.9, and 190 (27%) reported exercising ≥ 18 MET hours per week; 109 (16%) were normal weight; 279 (40%) were overweight and 307 (44%) were obese. Overall, 349 men had prostate cancer, which was low-grade in 161, and high-grade in 188. Median age at biopsy was 64 years (IQR 60–68). Though race ($p=0.001$) and PSA ($p=0.006$) were significantly related to MET, there were no clear trends. Men with lower BMI tended to have higher PSA values ($p=0.057$), smaller prostate volumes ($p<0.001$), and were more likely to be black ($p=0.006$). There was no statistically significant difference in age at biopsy or history of prior biopsy across both MET and BMI groups. Across MET categories, BMI was not statistically significantly different ($p=0.122$). Likewise, there was no difference in the amount of exercise done across BMI groups ($p=0.150$) (Table 1).

Exercise and prostate cancer: whole cohort and by BMI group

In unadjusted analysis, higher MET hours per week was associated with reduced risk of prostate cancer diagnosis (p-trend $=0.02$) and high-grade prostate cancer (p-trend $=0.004$) but there was no association between MET hours per week and low-grade prostate cancer (p-trend $=0.45$) (Supplemental Table 1). After stratification by BMI, there was no association between MET hours per week and prostate cancer diagnosis or prostate cancer aggressiveness within any BMI category (p-trend ≥ 0.05). On adjusted analysis, there was no association between MET hours per week and prostate cancer diagnosis (p-trend $=0.33$), low-grade prostate cancer (p-trend $=0.71$), or high-grade prostate cancer (p-trend $=0.18$) among all men (Table 2). When models were stratified by BMI, again no associations were found between MET hours per week and prostate cancer in any BMI group (p-trend ≥ 0.15) (Table 2).

Table 1 Demographic and clinicopathologic features of patients undergoing biopsy as a function of MET hours per week and BMI

	Total ($n=695$)	MET hours/week					BMI (kg/m^2)			
		<3 ($n=312$)	3–8.9 ($n=103$)	9–17.9 ($n=90$)	≥ 18 ($n=190$)	p value	Normal weight ($n=109$)	Overweight ($n=279$)	Obese ($n=307$)	p value
Age at biopsy	64 (60, 68)	63 (59, 68)	65 (61, 68)	63 (60, 68)	64 (60, 68)	0.197[b]	62 (60, 67)	65 (60, 68)	63 (60, 67)	0.058[b]
Black	379 (55)	187 (60)	38 (37)	49 (54)	105 (55)	0.001[c]	73 (67)	137 (49)	169 (55)	0.006[c]
PSA at biopsy (ng/mL)	5.7 (4.5, 8.0)	6.2 (4.6, 8.6)	5.5 (4.4, 7.5)	5.1 (4.3, 7.3)	5.8 (4.6, 7.7)	0.006[b]	6.4 (4.6, 10.1)	5.6 (4.5, 7.5)	5.7 (4.4, 8.0)	0.057[b]
TRUS prostate volume (cc)	43.0 (30.0, 60.0)	42.0 (28.0, 55.0)	42.0 (31.2, 64.3)	41.9 (31.0, 58.0)	46.0 (32.0, 62.4)	0.092[b]	37.0 (26.0, 53.0)	40.7 (28.0, 56.0)	47.0 (34.0, 63.0)	<0.001[b]
BMI (kg/m^2)	29.3 (26.4, 33.1)	29.4 (26.7, 33.8)	30.5 (26.5, 33.2)	29.6 (26.5, 33.7)	28.4 (26.3, 31.9)	0.122[b]	23.1 (21.3, 24.2)	27.6 (26.5, 28.9)	33.8 (31.5, 36.5)	<0.001[b]
BMI group						0.074[c]				<0.001[c]
Normal weight	109 (16)	51 (16)	13 (13)	13 (14)	32 (17)		109 (100)	0 (0)	0 (0)	
Overweight	279 (40)	117 (38)	36 (35)	34 (38)	92 (48)		0 (0)	279 (100)	0 (0)	
Obese	307 (44)	144 (46)	54 (52)	43 (48)	66 (35)		0 (0)	0 (0)	307 (100)	
Previous biopsy	107 (15)	47 (15)	13 (13)	14 (16)	33 (17)	0.752[c]	15 (14)	48 (17)	44 (14)	0.551[c]
MET hour/week	4.5 (0.0, 19.0)	0.0 (0.0, 0.0)	5.0 (3.5, 6.5)	12.4 (10.5, 15.0)	34.0 (24.5, 52.5)	<0.001[b]	3.8 (0.0, 27.0)	6.0 (0.0, 24.0)	3.0 (0.0, 14.0)	0.150[b]
MET group						<0.001[c]				0.074[c]
<3	312 (45)	312 (100)	0 (0)	0 (0)	0 (0)		51 (47)	117 (42)	144 (47)	
3–8.9	103 (15)	0 (0)	103 (100)	0 (0)	0 (0)		13 (12)	36 (13)	54 (18)	
9–17.9	90 (13)	0 (0)	0 (0)	90 (100)	0 (0)		13 (12)	34 (12)	43 (14)	
≥ 18	190 (27)	0 (0)	0 (0)	0 (0)	190 (100)		32 (29)	92 (33)	66 (21)	
Suspicious DRE findings	166 (24)	78 (25)	22 (21)	21 (23)	45 (24)	0.898[c]	20 (18)	82 (29)	64 (21)	0.018[c]
Positive biopsy results	349 (50)	171 (54.8)	53 (52)	41 (46)	84 (44)	0.101[c]	60 (55)	138 (50)	151 (49)	0.546[c]
Biopsy Grade Group[a]						0.329[c]				0.357[c]
1	161 (46)	75 (44)	21 (40)	19 (46)	46 (55)		29 (48)	69 (50)	63 (42)	
2–5	188 (54)	96 (56)	32 (61)	22 (54)	38 (45)		31 (52)	69 (50)	88 (58)	

Median (IQR) is displayed for continuous variables

MET metabolic equivalent, *BMI* body mass index, *IQR* interquartile range, *PSA* prostate specific antigen, *DRE* digital rectal examination

[a]Biopsy grade group are only indicated for patients with positive biopsy result

[b]Kruskal-Wallis

[c]Chi-square

Table 2 Adjusted odds ratios for the association between exercise (MET) and odds overall prostate cancer, low-grade prostate cancer (Gleason < 7), and high-grade prostate cancer (Gleason ≥ 7) vs. no cancer among the entire cohort and stratified by BMI

	Cohort ($n=695$)		BMI (kg/m^2)					
			Normal weight ($n=109$)		Overweight ($n=279$)		Obese ($n=307$)	
	OR (95% CI)	$^{\S}p$	OR (95% CI)	$^{\S}p$	OR (95% CI)	$^{\S}p$	OR (95% CI)	$^{\S}p$
Overall prostate cancer (prostate cancer vs. no cancer)								
MET hours/week		0.33		0.76		0.15		0.60
< 3	Reference		Reference		Reference		Reference	
3–8.9	1.22 (0.72–2.05)		2.20 (0.40–12.15)		1.27 (0.52–3.09)		0.98 (0.46–2.07)	
9–17.9	0.92 (0.54–1.58)		0.97 (0.22–4.27)		0.79 (0.31–2.05)		0.91 (0.41–1.99)	
≥ 18	0.85 (0.56–1.29)		0.93 (0.35–2.52)		0.66 (0.34–1.28)		0.83 (0.41–1.69)	
Low grade vs. no cancer								
MET hours/week		0.71		0.92		0.28		0.97
< 3	Reference		Reference		Reference		Reference	
3–8.9	1.03 (0.55–1.91)		2.66 (0.39–18.35)		0.81 (0.28–2.33)		0.91 (0.37–2.24)	
9–17.9	0.86 (0.46–1.62)		1.12 (0.20–6.23)		0.75 (0.27–2.09)		0.82 (0.31–2.13)	
≥ 18	0.92 (0.57–1.48)		1.05 (0.34–3.24)		0.67 (0.32–1.39)		0.98 (0.44–2.19)	
High grade vs. no cancer								
MET hours/week		0.18		0.52		0.18		0.34
< 3	Reference		Reference		Reference		Reference	
3–8.9	1.52 (0.81–2.87)		1.43 (0.15–13.52)		2.72 (0.88–8.45)		1.03 (0.42–2.55)	
9–17.9	1.03 (0.52–2.03)		0.83 (0.12–5.83)		0.97 (0.26–3.68)		0.96 (0.37–2.52)	
≥ 18	0.76 (0.44–1.31)		0.67 (0.17–2.62)		0.69 (0.28–1.67)		0.65 (0.27–1.59)	

CI confidence interval, *MET* metabolic equivalent, *BMI* body mass index, *OR* odds ratio, *p* *p*-value

Adjusted for: Age, race, DRE, family history of PC, prostate volume (log transformed), PSA (log transformed), previous prostate biopsy, and BMI (for entire cohort only)

$^{\S}p$ is *p*-value for trend obtained by entering the median MET hour/week for categories (< 3, 3–8.9, 9–17.9, and ≥ 18) as continuous term in the model

In secondary analysis, when exercise was examined in tertiles, results were unchanged in that while odds ratios were generally < 1 in the highest tertile, exercise remained not significantly related to prostate cancer risk overall or of low- or high-grade disease (Supplemental Tables 2 and 3).

BMI and prostate cancer: whole cohort and by MET group

In unadjusted analysis, there was no association between BMI and odds of prostate cancer diagnosis or prostate cancer aggressiveness among all men or when stratified by MET group (all $p \geq 0.17$) (Supplemental Table 4). BMI was not associated with prostate cancer diagnosis (OR 1.03, 95% CI 0.99–1.06, $p = 0.13$) or low-grade prostate cancer (OR 1.00, 95% CI 0.96–1.04, $p = 0.95$) on adjusted analysis (Table 3). A similar trend of no association between BMI and prostate cancer or low-grade prostate cancer was observed across groups of MET hours per week ($p \geq 0.09$). However, higher BMI was associated with increased odds of high-grade prostate cancer among all men after adjustment (OR 1.06, 95% CI 1.01–1.10, $p = 0.008$). This trend was seen across all MET groups with all OR > 1, although with reduced power after stratification, it was not always significant (OR 1.03–1.15, $p = 0.02$–0.66). Similar trends were seen when BMI was treated as a categorical variable. There were no interactions between exercise and BMI in predicting either total prostate cancer risk or low-grade or high-grade prostate cancer (all *p*-interactions ≥ 0.31) (Table 3). In secondary analysis, when models were stratified by tertiles of exercise, results remained unchanged (Supplemental Tables 5 and 6).

Discussion

Obesity is a modifiable risk factor for prostate cancer and research suggests that exercise may also be a potential protective factor for prostate cancer diagnosis and mortality, though the associations with exercise are less clear [2, 3]. Whether BMI and exercise interact to influence prostate cancer risk is unknown. Specifically, it is possible that exercise may negate the increased risk of prostate cancer for obese

Table 3 Adjusted odds ratios for the association between BMI and odds of overall prostate cancer, low-grade prostate cancer (Gleason < 7), and high-grade prostate cancer (Gleason ≥ 7) vs. no cancer among the entire cohort and stratified by MET

	Cohort ($n=695$)		MET (hours/week)							
			< 3 ($n=312$)		3–8.9 ($n=103$)		9–17.9 ($n=90$)		≥ 18 ($n=190$)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Overall prostate cancer (prostate cancer vs. no cancer)										
BMI[a] kg/m^2	1.03 (0.99–1.06)	0.13	1.01 (0.97–1.06)	0.59	1.01 (0.93–1.10)	0.75	1.05 (0.93–1.19)	0.40	1.06 (0.99–1.14)	0.09
BMI group										
Normal weight	Reference		Reference		Reference		Reference		Reference	
Overweight	1.03 (0.61–1.73)	0.91	1.38 (0.63–3.02)	0.42	0.90 (0.16–5.23)	0.91	1.34 (0.23–7.93)	0.75	0.76 (0.29–1.98)	0.58
Obese	1.29 (0.77–2.17)	0.33	1.53 (0.72–3.25)	0.28	0.77 (0.13–4.58)	0.77	1.85 (0.32–10.66)	0.49	1.40 (0.50–3.88)	0.52
Low grade vs. no cancer										
BMI[a] kg/m^2	1.00 (0.96–1.04)	0.95	0.99 (0.94–1.05)	0.82	1.00 (0.90–1.11)	0.93	1.01 (0.88–1.16)	0.89	1.03 (0.95–1.12)	0.48
BMI group										
Normal weight	Reference		Reference		Reference		Reference		Reference	
Overweight	1.03 (0.58–1.83)	0.93	1.54 (0.64–3.69)	0.34	0.42 (0.06–2.95)	0.38	1.97 (0.27–14.48)	0.51	0.73 (0.26–2.09)	0.56
Obese	1.00 (0.55–1.80)	1.00	1.21 (0.51–2.87)	0.67	0.40 (0.06–2.92)	0.37	1.52 (0.20–11.44)	0.68	1.10 (0.36–3.41)	0.87
High grade vs. no cancer										
BMI[a] kg/m^2	1.06 (1.01–1.10)	0.008	1.04 (0.98–1.10)	0.21	1.03 (0.92–1.14)	0.66	1.15 (0.97–1.36)	0.10	1.12 (1.02–1.23)	0.02
BMI group										
Normal weight	Reference		Reference		Reference		Reference		Reference	
Overweight	1.07 (0.55–2.09)	0.84	1.10 (0.41–2.99)	0.85	2.34 (0.27–21.88)	0.43	0.57 (0.05–6.99)	0.66	0.83 (0.23–3.02)	0.78
Obese	1.85 (0.96–3.57)	0.07	1.95 (0.76–5.03)	0.16	1.67 (0.18–15.29)	0.65	2.95 (0.27–32.07)	0.37	2.16 (0.55–8.50)	0.27

Adjusted for: Age, race, DRE, family history of PC, prostate volume (log transformed), PSA (log transformed), previous prostate biopsy, and MET (for entire cohort only)

All *p*-value for interaction between MET and BMI were ≥ 0.31

CI confidence interval, *MET* metabolic equivalent, *BMI* body mass index, *OR* odds ratio, *p* *p*-value

[a]BMI as continuous variable

men. However, to the best of our knowledge, few studies have investigated this interaction. To address this, we investigated the interaction between BMI and exercise on prostate cancer risk among men undergoing a prostate biopsy. In our data, there was no link between exercise and prostate cancer diagnosis or aggressiveness. In contrast, we found higher BMI was linked with increased risk of high-grade prostate cancer. Importantly, we found no interactions between exercise and BMI in predicting prostate cancer risk or aggressiveness. If confirmed in future studies, our findings suggest that exercise does not negate the increased risk of aggressive prostate cancer among obese men.

Although few studies have investigated a link between exercise, BMI, and prostate cancer risk, many have reported an association between BMI and prostate cancer risk. A meta-analysis from 2014 concluded that high body mass index is positively associated with prostate cancer diagnosis, particularly aggressive prostate cancer [2]. Our data confirm the adverse effects of BMI on high-grade prostate cancer risk. We feel that the consistency among our results and the results of this meta-analysis lends credibility to our study data.

Several studies have investigated exercise and prostate cancer, yielding mixed results. In a similar study in 2013 using data from some of the men in this study, our team found evidence of an inverse association between moderate exercise and prostate cancer risk among white men, particularly high-grade disease [8]. However, these results were based on a small sample size and required further investigation. A 2011 meta-analysis of exercise and prostate cancer risk found a small inverse association between physical activity and prostate cancer risk [12]. However, a more recent meta-analysis in 2018 concluded that evidence of an association between exercise and prostate cancer is inconclusive [3]. We found a null association, in line with the most recent meta-analysis. Of note, the meta-analysis suggested potential benefits for progression among men with prostate cancer, something that we were unable to test due to the limits of our study design and lack of follow-up information after the biopsy.

We found one study which investigated the relationship between exercise, BMI, and prostate cancer. In 2015, Grotta et al. followed a cohort of men for 13 years, investigating self-reported physical activity and BMI at baseline and prostate cancer incidence [4]. They found no significant associations between exercise and prostate cancer or BMI and prostate cancer. However, their results suggested that increased leisure time exercise may significantly increase risk of localised prostate cancer among obese men, a result we did not find. This study only gathered baseline lifestyle information and BMI was self-reported among their cohort. In contrast, our exercise questionnaires were given at time of biopsy and BMI was measured.

As we found no interaction between exercise and BMI, this suggests that exercise does not negate the negative effects of higher BMI on high-grade prostate cancer risk. This conflicts with previous research investigating the protective effect of exercise on obesity and risk of other diseases. In 2017, Holtermann et al. found that cardiorespiratory fitness was significantly inversely associated with diabetes. In addition, on stratified multi-variable analysis, they found a significantly stronger reduced risk of diabetes per 10-unit increase of cardiorespiratory fitness among the obese, compared to a weaker association among overweight and normal weight patients [5]. Additionally, on a meta-analysis of an association of cardiorespiratory fitness, weight, and all-cause mortality, researchers found that risk of death was dependent upon fitness and not BMI. Interestingly, they found that fit and overweight and obese individuals had similar mortality risk as their normal weight counterparts, suggesting that exercise can negate some of the mortality risks associated with higher BMI [6]. The reason for discrepancy in findings between our study focused on prostate cancer and other studies focused on other health outcomes is unknown. It is possible that prostate cancer (or cancer in general) is unique relative to other diseases such as diabetes and overall survival. Alternatively, physical activity may not be strongly associated with prostate cancer in general and, therefore, provides no "protection" for obesity. Alternatively, there is an interaction, but our small sample size precluded us from detecting such an interaction. Ultimately, more research is needed to discern these possibilities.

Our study has some limitations. First, our study relied on self-administered questionnaires. Exercise is typically understood as a healthy behaviour and patients may be inclined to overestimate their physical activity on a medical questionnaire. However, given that exercise is not an established protective factor for prostate cancer, any bias that occurred would likely have been non-differential with regard to prostate cancer diagnosis, likely bringing associations to null. In addition, the exercise survey used is a validated instrument [9, 10]. Moreover, this is likely not the case for most men as 45% reported essentially no exercise and 60% reported less than guideline recommended 2.5 h a week of moderate intensity exercise, or <9 MET hours per week [13].Second, 42% of men participating in this cohort were excluded from the present analysis due to missing questionnaire data, creating potential selection bias. Third, the interaction between exercise and BMI may be confounded by other adiposity measures such as body composition and thus BMI may not well reflect adiposity, especially among the high exercise group. We did not have enough subjects in this group to test this. However, we found in a previous study among the same cohort as in this study, that BMI is highly correlated with body fat percentage and waist circumference, validating it as a measurement of obesity in this context

cohort [7]. Also, we ascertained prostate cancer outcomes based on biopsy outcomes and it is well known that some men are misclassified based on biopsy results. Indeed, we have shown that obesity is a risk factor for upgrading and thus our results may actually underestimate the strength of the association between obesity and high-grade disease [14]. Finally, the current study cohort was composed of Veterans Affairs patients and, therefore, the results may not be generalizable to the entire screening population. However, our study population was strong in diversity and performing an analysis in a cohort where all men underwent prostate biopsy affords an ascertainment of cancer status that is not possible among screening cohorts.

In conclusion, our results suggest that higher BMI is associated with aggressive prostate cancer diagnosis, regardless of exercise. In addition, we found that exercise was not significantly related to prostate cancer diagnosis or grade. If confirmed by further research, these results suggest that exercise does not negate the increased risk of aggressive prostate cancer among obese men.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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