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ORIGINAL RESEARCH

Adiposity and Muscle Strength in Men With Prostate Cancer and Cardiovascular Outcomes

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ABSTRACT

BACKGROUND There are limited data on the physical effects of androgen deprivation therapy (ADT) for prostate cancer (PC), and on the relationships of such measures of adiposity and strength to cardiovascular outcomes.

OBJECTIVES The primary objective of this study was to evaluate the relationships of measures of adiposity and strength to cardiovascular outcomes (cardiovascular death, myocardial infarction, stroke, heart failure, arterial revascularization, peripheral arterial disease, and venous thromboembolism) in patients with PC. A secondary objective was to characterize the relationships between ADT use and 12-month changes in these physical measures.

METHODS This international, prospective cohort study included 3,967 patients with PC diagnosed in the prior 12 months or being treated with ADT for the first time. Median follow-up duration was 2.3 years.

RESULTS Participants' mean age was 68.5 years, and 1,731 (43.6%) were exposed to ADT. ADT was associated with a 1.6% increase in weight, a 2.2% increase in waist circumference, a 1.6% increase in hip circumference, a 0.1% increase in waist-to-hip ratio, a 27.4% reduction in handgrip strength, and a 0.1% decrease in gait speed. High waist circumference and low handgrip strength were associated with adverse cardiovascular outcomes. Adjusting for age, education, race, tobacco and alcohol use, physical activity, cardiovascular disease, glomerular filtration rate, and ADT use, waist circumference above the highest quartile (110 cm) and handgrip strength below the lowest quartile (29.5 kg) were associated with higher likelihoods of a future cardiovascular event, with respective HRs of 1.40 (95% CI: 1.03-1.90; $P = 0.029$) and 1.59 (95% CI: 1.14-2.22; $P = 0.006$).

CONCLUSIONS ADT was associated with increased adiposity and reduced strength over 12-month follow-up. High waist circumference and low baseline strength were associated with future adverse cardiovascular outcomes. (JACC CardioOncol. 2024;6:761-771) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ADT = androgen deprivation therapy

CVD = cardiovascular disease

GFR = glomerular filtration rate

PC = prostate cancer

TUGT = timed get-up-and-go test

Androgen deprivation therapy (ADT) is a fundamental treatment for advanced prostate cancer (PC). However, ADT has been shown to increase body weight and fat mass.[1] Obesity is a major risk factor for hypertension, diabetes, and cardiovascular disease (CVD), which are common in men with PC[2] and are important causes of morbidity and mortality.[3] In addition, ADT reduces muscle strength,[4] which is also a risk factor for CVD and mortality.[5]

There are important limitations to the existing data on the physical effects of ADT. Research demonstrating changes in physical measurements in ADT recipients consists of studies with modest sample sizes without adjustment for covariates.[4,6,7] These limitations leave uncertainty as to: 1) the extent to which changes in physical measurements are due to ADT vs the natural history of body composition and muscle strength in patients with PC; and 2) the generalizability of the findings. Evaluating changes in physical measurements in a large cohort of ADT recipients, accounting for important confounding factors and for the natural history of these physical measurements, is crucial to understanding the adverse effects of ADT. In addition, there are scant data on the prognostic importance of these physical measurements in individuals with PC.

The primary objective of this analysis was to evaluate changes in physical measures (body weight, waist and hip circumference, waist-to-hip ratio, handgrip strength, strength-to-weight ratio, and gait speed) in a large, well-characterized cohort of patients with PC stratified according to ADT exposure. The secondary objectives were: 1) to assess whether the relationships between ADT use and changes in these physical measurements is influenced by factors that are known to affect adiposity and muscle strength, including age, education level, tobacco and alcohol use, and physical activity level; and 2) to describe the relationships between these physical measures and subsequent adverse clinical outcomes.

METHODS

This study is an analysis of the RADICAL PC (Role of Androgen Deprivation Therapy in Cardiovascular Disease—A Longitudinal PC; NCT03127631) study.[2] RADICAL PC is an ongoing prospective cohort study that has been approved by the relevant Institutional Review Boards at participating sites and is conducted according to the principles of the Declaration of Helsinki. Inclusion criteria are PC with one of the following: 1) diagnosis within the prior 12 months; 2) treatment with ADT for the first time within the past 6 months; and 3) a plan to initiate ADT within the

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next month. The only exclusion criterion is age <45 years. To enhance the generalizability of the study, sites were encouraged to screen consecutive patients for eligibility. All participants provide written informed consent, after which baseline characteristics and physical measurements are documented. Participants are then followed at least annually to identify outcome events and repeat physical measurements. The present analysis includes 3,967 participants from 7 countries (Canada, the United States, Brazil, Australia, Israel, Colombia, and Chile) who had weight measured at baseline.

PHYSICAL MEASUREMENTS. Participants had the following physical measurements collected at baseline and at 12 months: weight, height, waist circumference (the smallest circumference between the costal margin and the iliac crest using a tape measure), and hip circumference (the largest circumference around the iliac crest). Handgrip strength was measured 3 times in both hands using a dynamometer (model 5030J1, Jamar), and values were averaged. The strength-to-weight ratio was calculated as the ratio of handgrip strength to body weight. Gait speed was evaluated using the timed get-up-and-go test (TUGT), in which participants were instructed to rise from a chair, walk 3 m, return to the chair, and sit down. The time taken to perform this task was measured using a stopwatch.

OTHER VARIABLES COLLECTED. Baseline covariates recorded included ADT use, age, education, ethnicity, tobacco and alcohol use (categorized as current, former, or never), CVD (peripheral arterial disease, coronary artery disease [myocardial infarction, angina, or coronary revascularization], cerebrovascular disease or stroke, heart failure, or atrial fibrillation), and physical activity levels, which were measured using the International Physical Activity Questionnaire and categorized as low, medium, or high, as previously described.[8] PC risk was categorized as low, intermediate, or high,[9] with metastatic disease considered high risk.

FOLLOW-UP. The median follow-up duration was 27 months (Q1-Q3: 14-37 months) after enrollment. Initially, we had planned to undertake physical measurements annually. However, because of restrictions in face-to-face research imposed as a result of the COVID-19 pandemic, the protocol was amended so that physical measurements could be collected every second year during follow-up. The median time between baseline and follow-up physical measurements was 12.4 months (Q1-Q3: 11.9-13.7 months). For simplicity, follow-up physical measurements are referred to as 12-month measurements.

Vital status and new myocardial infarction, stroke, heart failure, arterial revascularization, peripheral arterial disease, and venous thromboembolism were recorded annually. These clinical events were identified from participants (or, if deceased, their contacts) either in person or via phone calls and by review of medical charts. Prespecified outcome event definitions are included in Supplemental Table 1. We considered the occurrence of any of these events, including cardiovascular death, as an adverse cardiovascular event because obesity is an established risk factor for each of these outcomes.

STATISTICAL ANALYSIS. Continuous data are expressed as mean ± SD if normally distributed or as median (Q1-Q3) if skewed, while categorical data are presented as count (percentage). Physical measurements included weight, waist and hip circumference, waist-to-hip ratio, handgrip strength, strength-to-weight ratio, and TUGT. Changes in these measurements stratified by ADT use were evaluated using repeated-measures analysis of variance. The relationship between ADT use at baseline and changes in these physical measurements was evaluated using mixed-effects models in which we assumed a Gaussian distribution of the overall error distribution of the models, a random intercept, and linear coefficients.[10] Fixed effects included visit (baseline or follow-up), treatment group (ADT at baseline vs no ADT), and visit-by-treatment group interaction. To determine whether the change in physical measures differed between those on ADT at baseline or due to commence ADT within the next month (the ADT group) vs not on ADT (the control group), ADT use was modeled as part of an interaction term with study visit. A significant interaction at $P < 0.05$ was suggestive of evidence that the 12-month change in the physical measurement differed between the ADT group and the control group. Model covariates included age, education, ethnicity, tobacco and alcohol use, CVD (recorded as a time-varying covariate), baseline glomerular filtration rate (GFR), and the baseline value of the physical measurement of interest by simultaneous forced entry. As a sensitivity analysis, we generated propensity scores for ADT use for each physical measurement. Covariates contributing to the propensity scores were chosen in keeping with published recommendations to account for participant age, education, ethnicity, employment, prior prostatectomy or radiotherapy, PC risk (which incorporates T stage, prostate-specific antigen concentration at diagnosis, and Gleason score), metastatic disease, tobacco and alcohol use, physical activity, history of CVD, baseline GFR, baseline

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TABLE 1 Baseline Participant Characteristics Stratified by the Use of ADT at Baseline

	No ADT (n = 2,236)	ADT (n = 1,731)	*P* Value
Age, y	67 ± 7	71 ± 8	<0.001
Ethnicity			0.004
Black	139 (6)	122 (7)	
White	1,935 (87)	1,436 (83)	
Other	160 (7)	170 (10)	
Education			<0.001
Primary school	323 (14)	450 (26)	
High school	572 (26)	468 (27)	
More than high school	1,321 (60)	792 (47)	
Employed	952 (43)	504 (29)	<0.001
Gleason grade			<0.001
≤3 + 4	1,456 (66)	388 (24)	
4 + 3	455 (21)	384 (24)	
8	161 (7)	383 (23)	
9 or 10	124 (6)	477 (29)	
PC risk			<0.001
Low/intermediate	1,377 (63)	251 (15)	
High	810 (37)	1,468 (85)	
Metastatic disease	30 (1)	336 (19)	<0.001
Prostatectomy	689 (31)	344 (20)	<0.001
Radiotherapy	341 (15)	782 (45)	<0.001
Alcohol use			<0.001
Never	339 (15)	339 (20)	
Former	257 (12)	323 (19)	
Current	1,636 (73)	1,063 (61)	
Tobacco use			0.032
Never	986 (44)	725 (42)	
Former	1,032 (46)	793 (46)	
Current	215 (10)	210 (12)	
Cardiovascular disease	474 (21)	456 (26)	<0.001
Diabetes	348 (16)	348 (20)	<0.001
Hypertension	1,026 (46)	911 (53)	<0.001
Physical activity			0.004
Low	359 (17)	348 (22)	
Moderate	843 (41)	624 (39)	
High	870 (42)	637 (39)	
GFR, mL/min	78.4 ± 19.8	76.1 ± 20.2	<0.001
Weight, kg	86.2 ± 14.9	85.6 ± 17.3	0.24
Height, m	1.74 ± 0.13	1.73 ± 0.11	0.004
Body mass index, kg/m^2	28.2 ± 4.4	28.3 ± 4.8	0.58
Waist circumference, cm	102.3 ± 12.1	103.7 ± 12.8	<0.001
Hip circumference, cm	103.2 ± 10.1	103.9 ± 11.9	0.049
Waist-to-hip ratio	0.99 ± 0.08	1.00 ± 0.08	0.002
Handgrip strength, kg	38.2 ± 10.8	33.9 ± 10.9	<0.001
Strength-to-weight ratio	0.45 ± 0.14	0.41 ± 0.14	<0.001
TUGT, s	8.6 ± 3.4	10.3 ± 5.2	<0.001

Values are mean ± SD or n (%). Cardiovascular disease included peripheral arterial disease, coronary artery disease (myocardial infarction, angina or coronary revascularization), cerebrovascular disease or stroke, heart failure, and atrial fibrillation.

ADT = androgen deprivation therapy; GFR = glomerular filtration rate; PC = prostate cancer; TUGT = timed get-up-and-go test.

diabetes, and hypertension.[11,12] In addition, the propensity scores for handgrip strength and gait speed were adjusted for baseline weight, while the propensity scores for weight, waist circumference, hip circumference, and waist-to-hip ratio were adjusted for handgrip strength. In the sensitivity analysis, mixed-effects models were repeated, adjusting for the propensity score. We also performed sensitivity analyses in which the primary analysis was repeated after excluding participants with baseline metastatic disease.

To evaluate whether age (stratified by the cohort's median value), education level, tobacco or alcohol use, or physical activity level affected the change in physical measures in the ADT group (compared with the control group), these covariates were included in the mixed-effects model as a 3-level interaction term with ADT use and study visit. A significant interaction term at $P < 0.05$ was considered evidence that these covariates modified the association between ADT use and change in the physical measurement (Supplemental Table 2). These subgroups were selected because the subgroups represented modifiable characteristics (other than age, which is such a biologically cardinal variable that we also included it) that could with biologic plausibility affect the relationships between physical measurements and the risk for a cardiovascular event.

We assessed the relationships between baseline physical measures and adverse cardiovascular events during follow-up using Kaplan-Meier curves stratified by quartile of the physical measurement and by spline curves adjusted for age, education, race, tobacco and alcohol use, physical activity level, prior CVD, baseline GFR, and ADT exposure. The equality of Kaplan-Meier curves was evaluated using the log-rank test. We performed Cox proportional hazards models adjusted for age, education, race, tobacco and alcohol use, physical activity, prior CVD, baseline GFR, and ADT use by simultaneous forced entry. Results from the Cox models are presented using HRs with 95% CIs. We evaluated whether there was heterogeneity in the relationships between these baseline physical measurements and incident cardiovascular events in different subgroups by testing the interaction between the physical measurement and each of age (stratified by the cohort's median value), education level, tobacco and alcohol use, and physical activity levels in fully adjusted models. In the Cox models, the proportionality of hazards was evaluated by visual inspection of log-log plots and by testing whether scaled Schoenfeld residuals plotted against follow-up time had a nonzero slope. These tests demonstrated no evidence of violation of the proportional hazards assumption.

As a sensitivity analysis, we repeated time-to-event models using competing risks regression,[13] with noncardiovascular death modeled as the

competing risk. Analyses were performed using Stata version 18 (StataCorp).

RESULTS

BASELINE CHARACTERISTICS. Among 3,967 participants, the mean age was 68.5 ± 8.0 years, and 1,731 (43.6%) were in the ADT group. The median time from PC diagnosis to study enrollment was 4.7 months (Q1-Q3: 2.4-8.2 months). Among participants, 505 (12.7%) had metastatic disease. At baseline, 1,123 individuals had received radiotherapy, of whom 782 (69.6%) had also received ADT. Among participants, 294 (7.4%) were recruited as they were initiating ADT for recurrent disease.

Among participants exposed to ADT, the median duration of ADT exposure was 2.6 months (Q1-Q3: 0.7-4.5 months) at the time of the baseline study visit. From the baseline visit until the most recent follow-up visit, the median duration of ADT exposure was 21 months (Q1-Q3: 14-26 months). Of this ADT-exposed group, 1,448 (83.7%) had been exposed to a gonadotropin-releasing hormone agonist, 175 (10.1%) to degarelix, 824 (47.6%) to bicalutamide, 32 (1.8%) to dutasteride, 60 (3.5%) to abiraterone, 24 (1.4%) to enzalutamide, 23 (1.3%) to apalutamide, 19 (1.1%) to darolutamide, 3 (0.2%) to cyproterone, 2 (0.1%) to estrogen, and 5 (0.3%) to investigational hormonal therapies. In participants exposed to bicalutamide, the median duration of bicalutamide exposure was 30 days (Q1-Q3: 22-31 days). The median durations of exposure to abiraterone, enzalutamide, apalutamide, and darolutamide were, respectively, 22 months (Q1-Q3: 9-63 months), 13 months (Q1-Q3: 8-19 months), 12 months (Q1-Q3: 3-21 months), and 5 months (Q1-Q3: 2-10 months).

Participants' baseline characteristics stratified by ADT exposure are presented in Table 1. Compared with those not on ADT, baseline waist circumference and waist-to-hip ratio were higher in ADT recipients, weight was similar, baseline handgrip strength and strength-to-weight ratio were lower, and gait speed by TUGT was slower.

CHANGES IN PHYSICAL MEASUREMENTS. Of the 3,967 participants in whom baseline physical measurements were recorded, 2,936 (74%) had at least 1 follow-up measurement. At 12 months, measures of adiposity, including weight, did not change among those not receiving ADT but increased by 1.6% among those receiving ADT (Table 2). Among those not receiving ADT and those receiving ADT, waist circumference increased by 0.6% and 2.2%, respectively. Similar changes were seen with hip circumference. Consequently, there was little change in waist-to-hip ratio in both groups.

TABLE 2 Physical Measurements and Percentage Changes in These Values From Baseline to 12 Months

	Baseline	12 Months	% Change	*P* Value
Weight, kg				
No ADT	86.4 (86.2-86.7)	86.5 (86.3-86.8)	0.0%	0.61
ADT	86.0 (85.6-86.3)	87.4 (86.9-88.0)	+1.6%	<0.001
Waist circumference, cm				
No ADT	102.7 (102.5-102.9)	103.3 (103.0-103.6)	+0.6%	0.003
ADT	103.7 (103.4-104.0)	106.0 (105.5-106.6)	+2.2%	<0.001
Hip circumference, cm				
No ADT	103.5 (103.2-103.7)	104.1 (103.8-104.4)	+0.6%	0.002
ADT	103.9 (103.6-104.1)	105.6 (105.0-106.2)	+1.6%	<0.001
Waist-to-hip ratio				
No ADT	0.993 (0.990-0.996)	0.993 (0.990-0.996)	0.0%	0.87
ADT	0.999 (0.996-1.003)	1.008 (1.000-1.016)	+0.1%	0.07
Handgrip strength, kg				
No ADT	38.1 (37.6-38.7)	31.3 (30.6-31.9)	−17.8%	<0.001
ADT	34.0 (33.4-34.5)	24.7 (23.8-25.7)	−27.4%	<0.001
Strength-to-weight ratio				
No ADT	0.45 (0.44-0.46)	0.38 (0.37-0.39)	−15.6%	<0.001
ADT	0.41 (0.40-0.41)	0.30 (0.29-0.32)	−26.8%	<0.001
Get-up-and-go time, s				
No ADT	8.6 (8.4-8.8)	8.4 (8.2-8.7)	−2.3%	0.27
ADT	10.2 (10-1-10.3)	10.1 (9.9-10.4)	−0.1%	0.56

Values are mean (95% CI) unless otherwise indicated.
ADT = androgen deprivation therapy.

Among those not receiving ADT vs those receiving ADT, measures of strength, including handgrip strength, decreased by 17.8% and 27.4%, respectively, a 54% larger decrease among ADT recipients. Among those not receiving ADT vs those receiving ADT, strength-to-weight ratio decreased by 15.6% and 26.8%, respectively, a 72% larger decrease in the ADT group. Although those in the ADT group had slower gait speed than those not prescribed ADT, there was no difference in gait speed trajectory between the groups.

In the multivariable mixed-effects models, after adjusting for age, education, ethnicity, tobacco and alcohol use, physical activity, CVD, GFR, and the baseline value of the physical measurement of interest, the patterns observed were the same as in the crude analyses (Figure 1). Findings from propensity score-adjusted models and from models excluding those with metastatic disease were similar (Supplemental Figures 1 and 2).

CHARACTERISTICS INFLUENCING THE ASSOCIATION BETWEEN ADT AND CHANGE IN PHYSICAL MEASURES. The relationships between ADT use and change in weight, waist circumference, hip circumference,

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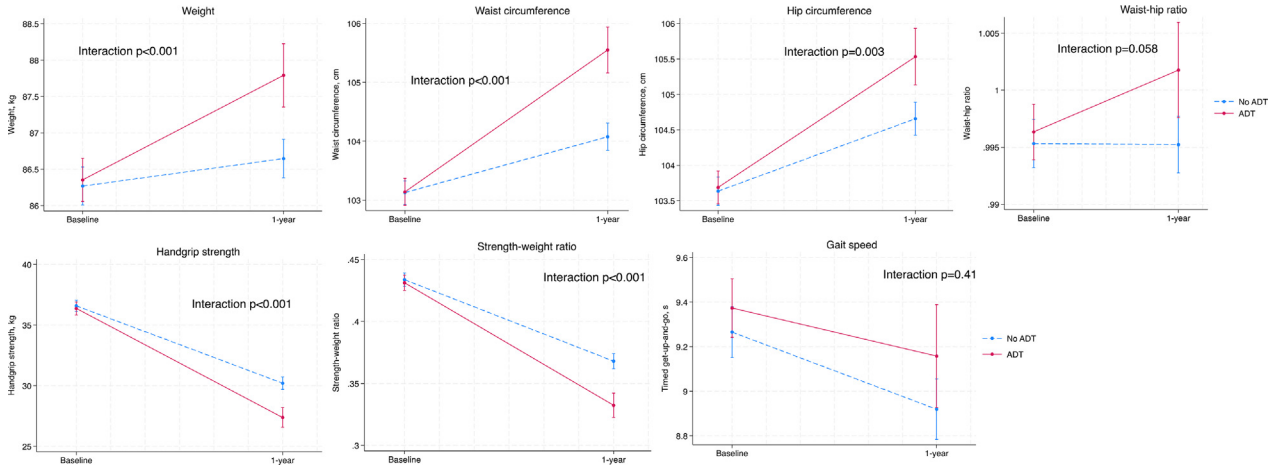
FIGURE 1 Physical Measurements Stratified by ADT Use



Estimates were obtained from linear mixed-effects models adjusted for age, education, ethnicity, alcohol and tobacco use, physical activity levels, cardiovascular disease, and glomerular filtration rate. An interaction *P* value <0.05 suggests that the change in the physical measurement differs between the androgen deprivation therapy (ADT) and no-ADT groups.

waist-to-hip ratio, handgrip strength, strength-to-weight ratio, and gait speed were consistent between older and younger individuals; across education levels; in never, current, and former smokers and drinkers; and across different levels of physical activity (Supplemental Table 2).

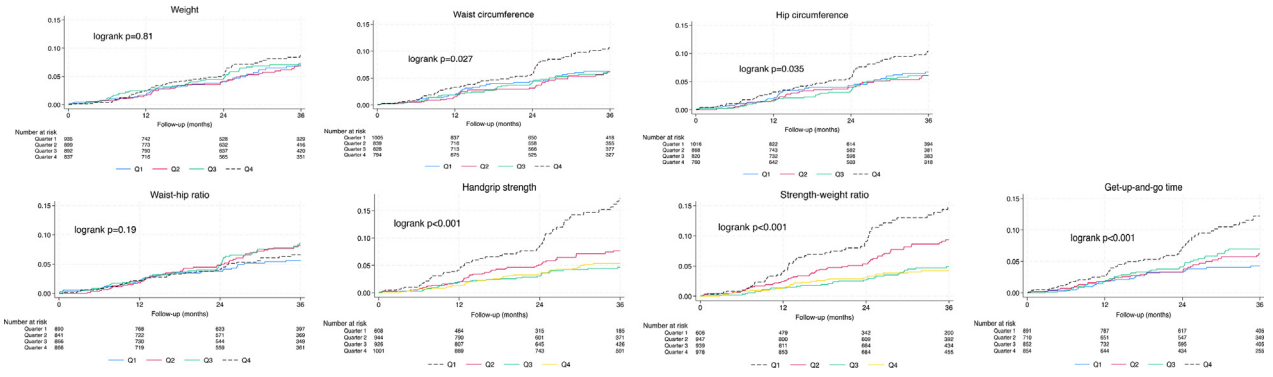
BASELINE PHYSICAL MEASURES AND ADVERSE CARDIOVASCULAR EVENTS. During a median 27 months (Q1-Q3: 14-37 months) of follow-up, 232 individuals (5.8%) experienced new adverse cardiovascular events. There were 69 myocardial infarctions, 39 strokes, 43 new heart failure events, 99 arterial revascularizations, 10 new peripheral arterial disease events, 24 venous thromboembolism events, and 52 cardiovascular deaths. As participants could experience more than 1 of these events, only the time to first event was considered in the time-to-event models. There was no association between baseline weight or waist-to-hip ratio and adverse cardiovascular events (**Figure 2**). However, larger waist or hip circumference, slow gait, low baseline handgrip strength, and low strength-to-weight ratio were associated with a higher risk for subsequent adverse cardiovascular events. The relationships between physical measurements expressed as continuous variables and cardiovascular outcomes are presented in Supplemental Figure 3. These suggest a curvilinear relationship between all physical measurements and cardiovascular events.

The relationship between low strength and adverse cardiovascular outcomes remained independent of the confounders adjusted for (**Table 3**). Compared with those whose handgrip strength was above the lowest quartile (29.5 kg), those whose handgrip strength was in the lowest quartile had a higher risk for an event after adjustment for age, education, race, tobacco and alcohol use, physical activity, prior CVD, baseline GFR, and ADT exposure (HR: 1.59; 95% CI: 1.14-2.22; $P = 0.006$). A handgrip strength value of <35 kg yielded the highest product of sensitivity and specificity for identifying participants who would develop subsequent cardiovascular events.

Compared with individuals whose strength-to-weight ratios were above the lowest quartile, participants whose strength-to-weight ratios were in the lowest quartile (ie, <0.35) had an increased risk for future adverse cardiovascular events (adjusted HR: 1.52; 95% CI: 1.10-2.09; $P = 0.011$). After adjustment, the relationships of both gait speed and hip circumference to adverse cardiovascular events were no longer significant.

Participants with waist circumferences above the highest quartile (ie, >110 cm) were at increased risk for adverse cardiovascular outcomes (adjusted HR: 1.40; 95% CI: 1.03-1.90; $P = 0.029$). When both handgrip strength and waist circumference were included in the multivariable model, they independently predicted the occurrence of the cardiovascular

FIGURE 2 **Kaplan-Meier Curves for Incident Adverse Cardiovascular Events Stratified by Quartile of Each Physical Measure**



Cardiovascular events included cardiovascular death, myocardial infarction, stroke, peripheral arterial disease, arterial revascularization, heart failure and venous thromboembolism. *P* values represent the log-rank test for equality of the curves. The y-axes represent the proportion of participants developing cardiovascular events. Q = quartile.

endpoint. Respective HRs for handgrip strength less than the lowest quartile and waist circumference above the highest quartile were 1.55 (95% CI: 1.11-2.17; $P = 0.010$) and 1.37 (95% CI: 1.01-1.87; $P = 0.042$). We performed the likelihood ratio test, which demonstrated that the inclusion of both handgrip strength and waist circumference in the model conferred better fit than either alone ($P < 0.001$).

At the latest follow-up, 180 participants (4.5%) had died without experiencing adverse cardiovascular events during the follow-up period. When this occurrence was modeled as the competing risk in a sensitivity analysis, findings were similar to the primary analysis (**Table 3**).

The relationship between physical measurements and adverse cardiovascular events was consistent across most subgroups (Supplemental Table 2). However, there was no association between waist-to-hip ratio and adverse cardiovascular events among current and never smokers, but there was an inverse relationship between waist-to-hip ratio and adverse cardiovascular events among former smokers (HR: 0.36; 95% CI: 0.20-0.66; *P* for interaction = 0.003).

DISCUSSION

The major findings from this large, international, prospective cohort study of patients with PC are as follows: 1) body weight in patients prescribed ADT increased by an absolute 1.6% over 12 months, and muscle strength as measured using a handgrip dynamometer decreased by an absolute 9.6%; and 2) although high waist circumference was associated with an increase in the risk for future adverse cardiovascular events, low muscle strength as measured by handgrip was at least as strong a cardiovascular risk factor (**Central Illustration**).

THE ASSOCIATION BETWEEN ADT USE AND PHYSICAL MEASUREMENTS. We conducted a structured literature review of prospective studies, excluding cross-sectional and retrospective studies, and identified 37 relevant papers (Supplemental Table 3). Sample sizes varied from 10 to 310. Body weight generally increased by 2% to 3% and waist circumference by 1 to 2 cm. Our findings were consistent with these previously reported estimates. However, most prior studies did not include a control group (which did not receive ADT) or adjust for baseline characteristics. Therefore, these studies were limited in their ability to distinguish changes in adiposity that were due to ADT exposure vs changes in adiposity related to aging or confounding factors such as physical activity levels. No studies were multinational. Our study adds to the existing evidence by describing changes in adiposity in ADT recipients with greater precision and generalizability because of our large sample size and control group. By adjusting for important covariates, we obtained estimates of changes in measurements that accounted for non-ADT factors that could influence adiposity, such as education, tobacco and alcohol use, CVD, and renal dysfunction.

The association between ADT use and impaired muscle strength has also been demonstrated in smaller studies.[14] As with the adiposity measures, our larger and more diverse sample size allows more precise and generalizable estimates of the effects of ADT on muscle strength.

TABLE 3 Cox and Competing Risks Regression for Adverse Cardiovascular Outcomes

		Cox Regression		Competing Risks Regression	
Exposure	Quantile	HR (95% CI)	*P* Value	Subdistribution HR (95% CI)	*P* Value
Weight	Greater than the highest quartile	1.26 (0.91-1.73)	0.16	1.26 (0.91-1.75)	0.17
Waist circumference	Greater than the highest quartile	1.40 (1.03 -1.90)	0.029	1.42 (1.05-1.92)	0.023
Handgrip strength	Less than the lowest quartile	1.59 (1.14-2.22)	0.006	1.52 (1.06-2.13)	0.015
Strength-to-weight ratio	Less than the lowest quartile	1.52 (1.10-2.09)	0.011	1.48 (1.07-2.06)	0.019
Gait speed	Slower than the slowest quartile	1.36 (0.98-1.89)	0.068	1.31 (0.93-1.85)	0.13

The primary outcome is the composite of cardiovascular death, myocardial infarction, stroke, heart failure, arterial revascularization, peripheral arterial disease, or venous thromboembolism. Noncardiovascular death is modeled as the competing risk in the competing risks models. Model covariates included age, education, race, tobacco and alcohol use, physical activity, prior cardiovascular disease, baseline estimated glomerular filtration rate, and androgen deprivation therapy use.

A systematic review identified studies examining the relationship between ADT use and body composition in longitudinal studies.[15] In total, there were 573 participants from 16 studies, although change in weight was reported in only 289 individuals. The mean increase in body mass index was 2.2% (95% CI: 1.2%-3.1%). Lean mass decreased by 2.8% (95% CI: 2.0%-3.6%). Our findings are broadly consistent in a substantially larger cohort.

PHYSICAL MEASUREMENTS AND FUTURE CARDIOVASCULAR EVENTS. Our review of the literature found scant evidence to describe the relationship between anthropometric measurements and cardiovascular outcomes in patients with PC. One study of a cohort of 178 Japanese men with metastatic PC treated with ADT reported psoas muscle volume measured radiologically at baseline.[16] During a median follow-up period of 32 months, psoas muscle volume indexed to height was associated with survival. In a retrospective study of 282 patients with castration-resistant PC, subcutaneous fat, as measured using computed tomography, was associated with better cancer-specific survival.[17] None of the other studies identified reported the association between anthropometric measures and cardiovascular outcomes, although cardiovascular events are an important consequence of obesity in the general population.[18,19] Therefore, our study is the first to describe the relationships among adiposity, muscle strength, and adverse cardiovascular events in this population. We found that lower muscle strength was associated with a higher risk for adverse cardiovascular outcomes. This observation is consistent with our previous research on the prognostic importance of muscle strength,[5] which is also an important marker of physical frailty.[20,21] Our findings in the present study may be particularly relevant to patients with PC because of the effects of ADT on muscle strength and adiposity. Further research is needed to evaluate whether ADT-related changes in muscle strength and adiposity additionally predispose to adverse cardiovascular outcomes. Also, in patients with more advanced PC, cachexia may be an important complication. Our findings suggest that patients with sarcopenia and cachexia related to PC might be at increased risk for cardiovascular events, which would worsen their overall outlook.

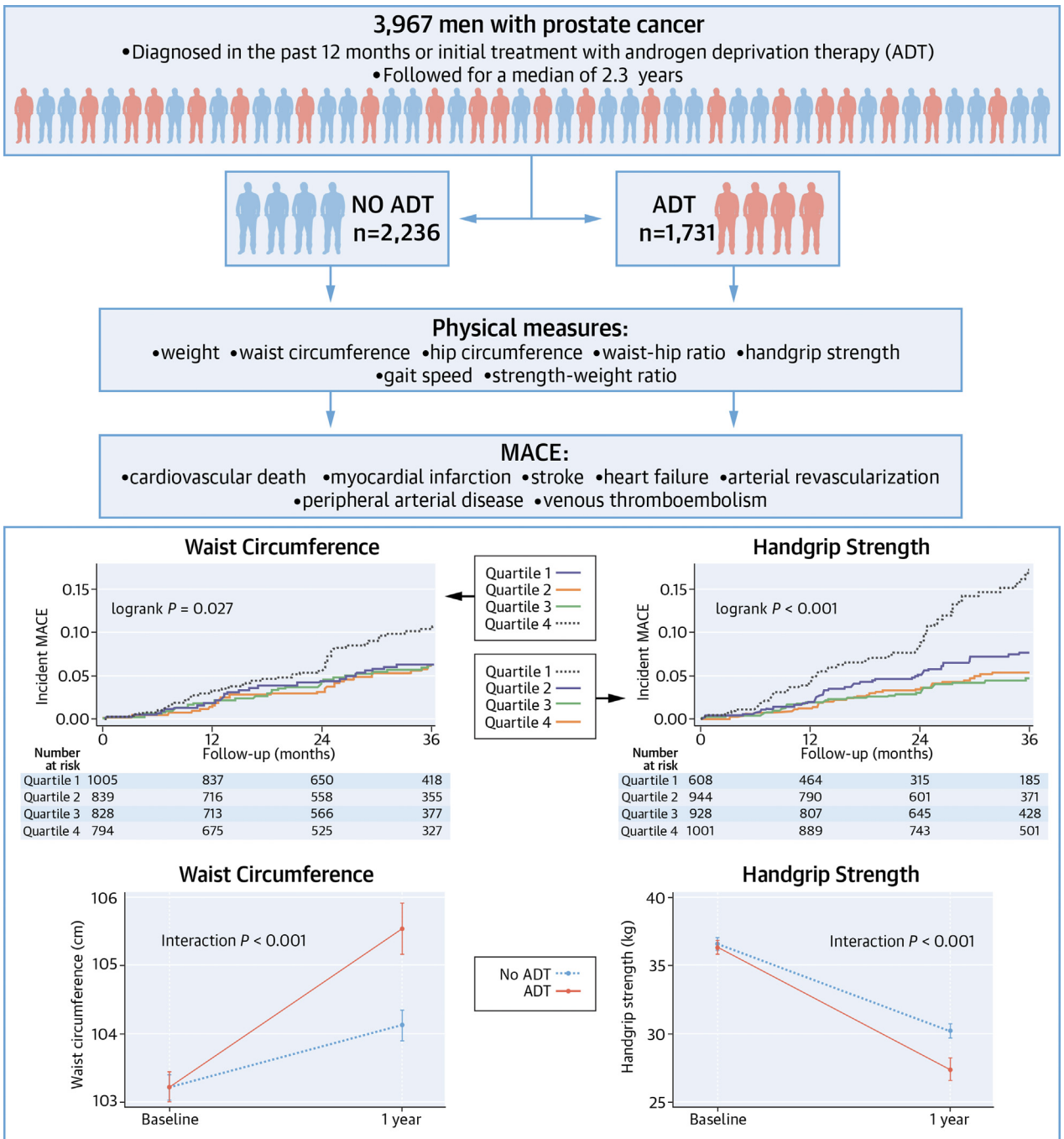
Several mechanisms may explain the relationship between low muscle strength and adverse cardiovascular outcomes. Chronic low-grade inflammation, which is an established cause of cardiovascular events, may have adverse effects on muscle.[22] Low muscle strength in childhood is associated with a higher burden of cardiometabolic risk factors.[23] Therefore, in our study, to the extent that low muscle strength may reflect lifelong lower muscle strength, it may be associated with lifelong exposure to cardiometabolic risk factors, which is increasingly being recognized as an important determinant of adverse cardiovascular outcomes.

Our observation that higher handgrip strength, when analyzed as a continuous exposure (Supplemental Figure 3), may also be associated with a higher risk of cardiovascular events in this population is surprising. A biologically plausible explanation attributable to the covariates studied is not readily apparent. We cannot exclude a role for residual confounding (eg, by genetic factors).

Although our study demonstrates a higher risk for cardiovascular events with high waist circumference, the relationship between measures of adiposity and outcomes is complex because low body weight is strongly associated with increased mortality, and the optimal level of body fat in patients with PC is not known.

STUDY LIMITATIONS. The major limitation of our study is the possibility of unmeasured confounding. However, the only way to avoid confounding is to randomize patients to ADT vs placebo; such a randomized trial is considered unethical, as ADT is the

CENTRAL ILLUSTRATION **Adverse Cardiovascular Events, Adiposity, and Muscle Strength and Their Relationships With ADT**



- Waist circumference >110 cm and handgrip strength <30 kg are associated with increased MACE in patients with prostate cancer.
- ADT use is associated with accelerated increase in waist circumference and loss of handgrip strength.

Leong DP, et al. JACC CardioOncol. 2024;6(5):761–771.

Baseline waist circumference >110 cm and handgrip strength <30 kg were associated with an increased risk for adverse cardiovascular events. Androgen deprivation therapy (ADT) use was associated with accelerated increase in waist circumference and loss of handgrip strength. MACE = major adverse cardiovascular events.

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backbone PC therapy for advanced disease. Therefore, carefully performed, prospective observational research is the only feasible way to evaluate the potential adverse effects of ADT. Also, in our study, we measured and adjusted for more confounding factors than is possible in studies using administrative data.

Another limitation is that most participants were White. In future research, greater racial diversity would be desirable. Also, longer follow-up would be valuable to understand whether the changes in physical measurements observed are chronic and to better characterize the relationships between these changes and individual clinical outcomes. At present, insufficient cardiovascular events have occurred after 12-month physical measurements to allow robust inferences as to whether changes in these measurements predisposes to adverse clinical events. Participants and study personnel were not blinded to ADT use, so we cannot exclude the possibility that the performance of physical tests might be influenced by knowledge of its use. PC risk was categorized using an approach not intended for patients with metastatic disease, which we adapted to enable the inclusion of all participants in this analysis. Screening logs were not required, and thus the numbers of eligible patients and reasons for nonparticipation were not collected, so the generalizability of study findings may be limited.

Follow-up physical measurements were not obtained in all participants, which may have influenced the reliability and precision of our estimates. Also, differential mortality rates between the ADT and no-ADT groups before a repeat physical measurement could be obtained may have biased these measurements. However, in the case of handgrip strength, higher mortality and frailty rates in the ADT group compared with the no-ADT group would be expected to bias these findings toward the null because of greater loss of frail participants in the ADT group.

CONCLUSIONS

High waist circumference and low muscle strength are associated with an increased risk for adverse cardiovascular outcomes in patients with PC and are associated with ADT use.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ADT for PC is associated with increases in markers of adiposity and decreases in indexes of muscle strength. Baseline muscle strength and high waist circumference were associated with future adverse cardiovascular events.

TRANSLATIONAL OUTLOOK: Future research should seek to determine whether increasing muscle strength in patients with PC can reduce the risk for adverse cardiovascular outcomes.

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KEY WORDS adiposity, androgen deprivation therapy, cardiovascular, muscle strength, obesity, prostate cancer

APPENDIX For supplemental figures, tables, and references as well as, a list of RADICAL PC investigators, please see the online version of this paper.