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Serum Adiponectin, C-peptide and Leptin and Risk of Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial

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Abstract

Background—Recent epidemiologic studies have identified obesity as a risk factor for benign prostatic hyperplasia (BPH). We examined whether adiponectin, leptin and C-peptide were associated with incident, symptomatic BPH and whether these factors mediate the relationship between obesity and BPH risk.

Methods—Data are from Prostate Cancer Prevention Trial placebo arm participants who were free of BPH at baseline. Incident BPH (n=698) was defined as treatment, two International Prostate Symptom Score (IPSS) values >14, or an increase of ≥5 in IPSS from baseline documented on at least two occasions plus at least one score ≥12. Controls (n=709) were selected from men reporting no BPH treatment or IPSS >7 during the seven-year trial. Baseline serum was analyzed for adiponectin, C-peptide, and leptin concentrations.

Results—Neither C-peptide nor leptin was associated with BPH risk. The odds ratio [95% CI] contrasting highest to lowest quartiles of adiponectin was 0.65[0.47, 0.87] $p_{\text{trend}}=0.004$. Findings differed between levels of physical activity: there was a strong inverse association between adiponectin and BPH among moderately/very active men OR=0.43[0.29, 0.63], and no association among sedentary/minimally active men OR=0.92[0.65, 1.30] $p_{\text{interaction}}=0.005$. Adiponectin concentrations explained only a moderate amount of the relationship between obesity and BPH risk.

Conclusions—High adiponectin concentrations were associated with reduced risk of incident, symptomatic BPH. This association was limited to moderately/very active men; suggesting the relationship between obesity and BPH involves a complex interaction between factors affecting

glucose uptake and insulin sensitivity. However, adiponectin is likely not the only mechanism through which obesity affects BPH risk.

Keywords

Benign prostatic hyperplasia; Lower urinary tract symptoms; Obesity; Insulin Resistance

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common medical conditions in middle-aged and older males, affecting 40 to 50 percent of men by age 50 and up to 80 percent of men by age 70[1,2]. Despite the high prevalence of BPH, its pathogenesis remains unclear, and few modifiable risk factors have been established. Recent epidemiologic studies have identified obesity as a risk factor for BPH[3–5]. The largest of these studies, from the Prostate Cancer Prevention Trial (PCPT)[3] and the Health Professionals Follow-up Study cohorts, both found that obesity, in particular abdominal obesity, was associated with a 16–43% significant increase in risk of symptomatic BPH[4].

Relatively little is known about the mechanisms that underlie the association of obesity and BPH risk. Obesity is characterized by enlarged depots of adipose tissue, which are metabolically active and secrete numerous hormones and proteins that influence local adipocyte biology as well as distant organ systems[6]. Obesity is associated with higher serum insulin[7] and leptin[8], and lower adiponectin[9]; thus, it is reasonable to hypothesize that obesity-related abnormalities in the circulating concentrations of these factors may play a role in the pathogenesis of BPH.

Here we give results of a nested case-control study examining risk of incident, symptomatic BPH among placebo-arm participants in the PCPT. This report examines whether concentrations of two adipokines, adiponectin and leptin, and C-peptide, a measure of insulin secretion, affect the risk of symptomatic BPH. We also evaluated whether these factors mediate the relationship between obesity and risk of BPH.

METHODS

Data are from the PCPT, a randomized, placebo-controlled trial testing whether finasteride, a 5 α -reductase inhibitor, could reduce the 7-year period prevalence of prostate cancer. Details regarding study design and participant characteristics have been described previously[10]. Briefly, 18,880 men age 55 years and older with a normal digital rectal exam, prostate-specific antigen level of 3 ng/ml or below, no history of prostate cancer or other clinically significant coexisting conditions, and no severe BPH symptoms (International Prostate Symptom Score (IPSS) of 20 or higher), were randomized to receive finasteride (5 mg/day) or placebo.

Participants for this nested case-control study were drawn from the 9,457 men randomized to the placebo arm of the PCPT. Analyses are restricted to the placebo arm because finasteride both prevents and treats BPH[10]. Exclusion criteria included men who, at baseline, had medical or surgical treatment for BPH (n=701), a self-reported history of BPH (n=1,904), or an IPSS >7 (n=1,820). In addition, men using steroid hormones at any time (n=61) were excluded, leaving 4,971 men eligible for this study.

Extensive medical data, including self-report of physician diagnosis of and treatment for BPH were collected at the baseline visit, each clinic visit (6- and 12-month), and at every phone contact (3- and 9-month) between clinic visits. At recruitment (3 months prior to

randomization), randomization and each 12-month clinic visit, participants completed the 7-item IPSS as a self-administered questionnaire. Clinic staff measured height, weight, waist and hip circumference at randomization, and body mass index (BMI) was calculated as weight (kg) divided by height² (m). Age, race/ethnicity, physical activity (type, frequency, duration, pace, and intensity), alcohol consumption (type, frequency and dose) and history of smoking were collected at baseline using self-administered questionnaires. Physical activity was categorized into 4 levels; sedentary (low activity index (calculated as the multiple of frequency, duration and pace indices) and participated in intense activities less than once a week), light (low activity index and participated in intense activities four times a week or less), moderate (moderate or high activity index and participated in intense activities four times a week), and very active (high activity index and participated in intense activities five or more times a week).

Incident BPH was defined either as a report of treatment for or development of significant lower urinary tract symptoms. Treatments included use of α -blockers, finasteride or any surgical intervention (transurethral prostatectomy, balloon dilation or laser prostatectomy). Development of significant symptoms was defined as either (1) two IPSS scores >14 ; or (2) an increase of ≥ 5 in IPSS from baseline documented on at least two occasions plus at least one score ≥ 12 . There were a total of 727 incident BPH cases, which were further categorized into clinical BPH (322 cases defined by medical or surgical treatment and 105 cases defined by two IPSS scores of 15 or higher) and symptomatic progressive BPH (300 cases defined by two IPSS scores at least 5 units higher than baseline plus at least one score ≥ 12). Men who reported transient elevations in IPSS or a physician diagnosis of BPH in the absence of symptoms or treatment were not included as cases.

Controls were drawn from the 1,497 men who, during seven years of observation, had no more than two missing IPSS, no single IPSS >7 , no surgical or medical treatment for BPH, and no report of a diagnosis of BPH. From this sample, we selected all men aged 70 years and over and all non-Caucasian men, in order to maximize statistical power when examining these subgroups. Remaining controls were randomly selected to yield a total control sample ($n=727$) that was frequency matched to the age distribution (in 5 year age groups) of cases. To minimize the influence of diabetes on either the exposure (serum adiponectin, C-peptide or leptin concentrations) or outcome (BPH risk), we further excluded men with a self-reported history of diabetes (diagnosis or treatment) at baseline ($n=6$ cases and $n=2$ controls).

Non-fasting blood samples were drawn at recruitment into a 7 ml EDTA vacutainer tube and shipped overnight to a central storage facility, where they were centrifuged, aliquoted and stored at -70°C until analysis. Serum concentrations of adiponectin, C-peptide, and leptin were quantified using a multiplex sandwich enzyme-linked immunosorbent assay at Pierce Biotechnology Inc., Woburn, MA. Samples were run in a series of dilutions, and plates were imaged using the SearchLight® Black Ice Imaging system, and images were analyzed using SearchLight® Array Analyst software. Serum was not available from 39 men, and analyses were completed using 698 cases and 709 controls.

Descriptive statistics were used to characterize the study sample and distribution of adiponectin, C-peptide, and leptin concentrations in cases and controls. Serum concentrations of analytes were categorized into quartiles based on the distribution in the controls, and unconditional logistic regression was used to calculate relative odds ratios (OR, referred to as risk) and their 95% confidence intervals for risk of BPH. All models were adjusted for age at baseline (continuous), BMI (continuous), race (white, other), and alcohol consumption (continuous). Controlling for other factors associated with BPH risk in this sample, including baseline IPSS[3], waist to hip ratio[3], insulin-like growth factors

(IGF-1, and IGFBP-3)[11], steroid hormones (testosterone, 3- α -diol gulcaronide, testosterone:3- α -diol gulcaronide ratio, and serum hormone binding globulin)[12] and dietary intake (fat, protein, red meat, and vegetable servings)[13], did not affect risk estimates and were not included in the final models. Tests for linear trend across quartiles were performed by using an ordinal variable corresponding to rank from lowest to highest category[14].

Additional analyses were completed stratified by age, physical activity, alcohol intake, and BMI. To increase the stability across stratified estimates, serum concentrations of adipokines and C-peptide were categorized into tertiles based on the distribution among controls. Formal interaction tests were based on p-values for the interaction term of the adipokine or C-peptide concentration rank (from lowest to highest) times a dummy variable for physical activity (sedentary/light versus moderately/very active), alcohol (<1 versus 1+ drink/day) or BMI (<25 versus ≥ 25). We also considered whether the previously-reported finding of an increased BPH risk in obese men[3] was mediated by adiponectin, C-peptide or leptin by examining the association of obesity with BPH risk both unadjusted and adjusted for these analytes. All p-values were two-sided and considered statistically significant at $p < 0.05$. Statistical analyses were conducted using SAS (version 9.1 Cary, NC).

RESULTS

Distributions of demographic, anthropometric, and health-related variables are given in Table 1. Participants were mostly white, overweight or obese, and nonsmokers. Compared with controls, men with BPH consumed less alcohol and had a higher IPSS at baseline. Table 2 gives mean/median values and 5th and 95th percentile distributions of adipokines and C-peptide in cases and controls. Compared with controls, cases had a lower concentration of adiponectin at baseline (Table 2).

Table 3 gives adjusted odds ratios for risk of BPH associated with serum adiponectin, C-peptide, and leptin concentrations. In models adjusted for matching variables (age, race), BMI and alcohol, men in the highest quartile of serum adiponectin had a 35% lower risk of BPH with a monotonic and statistically significant linear trend ($P_{\text{trend}} = 0.004$). Neither C-peptide nor leptin were associated with risk of BPH. There were no substantial differences in results when BPH outcomes (clinical versus symptomatic progression) were considered separately, when analyses excluded men diagnosed with prostate cancer ($n = 104$ cases and $n = 115$ controls), or by lag time between blood collection and BPH event (1–3 years versus 4–7 years)(data not shown).

Several analyses were completed to explore possible effect modification. Associations between BPH and serum adiponectin, C-peptide, and leptin were similar across subgroups stratified by BMI, and alcohol intake (Table 4). However, for strata characterized by level of physical activity, there was no association of adiponectin with BPH risk among sedentary/minimally active men, and a strong inverse association among men who were moderately/very active ($P_{\text{interaction}} < 0.005$, Table 4).

In previous analyses in this cohort, obesity was associated with a increased risk of BPH[3]; therefore, we completed additional analyses to examine whether adipokines or C-peptide mediate the association between obesity and risk of BPH. Compared to men who are normal weight, overweight and obese men have a 24% (OR=1.24, 95%CI 0.96–1.60) and 36% (OR=1.36, 95%CI 1.00–1.85) increased risk of BPH, respectively ($P_{\text{trend}} = 0.04$). Control for adiponectin reduced the overall association between obesity and BPH risk by 25% to 1.18 (95%CI, 0.91–1.52) for overweight, and by 28% to 1.26 (95%CI, 0.92–1.72) for obese

($P_{\text{trend}}=0.14$). Control for C-peptide and leptin had no effect on the overall association between obesity and BPH risk (data not shown).

DISCUSSION

In this nested case-control study there was an inverse dose response association between serum adiponectin concentration and risk of symptomatic BPH. This association did not differ by BMI, alcohol intake, type of BPH diagnosis or time between blood draw and BPH diagnosis; however, it was modified by physical activity level. There was no association between adiponectin and BPH among men who were sedentary/minimally active, and a strong inverse association among men who were moderately/very active. Neither serum C-peptide nor leptin were associated with BPH risk.

Few epidemiologic studies have investigated the association between adiponectin, C-peptide or leptin and risk of BPH [5,15–18], most were limited by small numbers of BPH cases and use of a cross-sectional study design. Two cross-sectional studies examined the association between leptin concentrations and risk of BPH surgery[5] or clinical BPH[15], and consistent with the findings of this investigation, neither found an association between leptin concentrations and risk of prevalent BPH. No studies have examined the association between C-peptide and risk of BPH; however several have examined the relationship between fasting insulin levels and risk of BPH. The results of these studies, which are inconsistent with our findings, suggest an association between insulin levels and BPH risk. In cross-sectional studies, fasting insulin concentrations were associated with a significantly larger prostate size[16,19], and in case-control studies, elevated fasting insulin concentrations were associated with an increased risk of BPH surgery[5] and symptomatic BPH[16]. Only two small cross-sectional studies have investigated the association between adiponectin and risk of BPH[17,18]; one (n=75) found a non-significant decreased risk of prevalent BPH with increasing adiponectin concentrations [17] and one (n=41) found no association[18].

Adiponectin is a hormone produced exclusively by adipocytes which, unlike most adipokines, is decreased in obesity[9]. Adiponectin plays a role in several physiologic processes, including cell proliferation and apoptosis[20] and metabolism of glucose and fatty acids[21], and there is evidence to support both direct and indirect effects of adiponectin on BPH pathogenesis. Both benign and malignant human prostate tissue express cell surface receptors for adiponectin (AdipoR1 and R2)[22], which are known to activate the AMPK, MAPK and NF- κ signaling pathways[20] involved in the regulation of cell growth, proliferation and apoptosis. *In vitro*, adiponectin inhibits prostate cancer cell growth at physiologic concentrations and suppresses dihydrotestosterone stimulated cell proliferation[23]. Thus, although the effects of adiponectin on normal prostate cells are currently unknown, considerable indirect evidence suggests that it may be anti-proliferative in prostate tissue.

In addition, adiponectin may indirectly affect risk of BPH through its effect on insulin sensitivity. Adiponectin enhances insulin sensitivity by inhibiting both the expression of hepatic gluconeogenic enzymes and endogenous production of glucose[24]. In animal models, adiponectin administration lowers glucose concentrations in normal mice and ameliorates hyperglycemia in ob/ob mice[25]. The insulin-sensitizing effects of adiponectin are also seen in epidemiologic studies, which find associations between low levels of adiponectin and several insulin-related disorders including diabetes mellitus[26], insulin resistance[27], and metabolic syndrome[28]. There is good evidence that insulin resistance promotes the development of BPH. Aberrations in insulin control, including a history of diabetes mellitus[19,29], and high levels of glycosylated hemoglobin[29] and fasting

glucose [19,29] are associated with an enlarged prostate[16,19] and lower urinary tract symptoms(LUTS)[29]. Thus, the evidence is compelling that adiponectin, through increased insulin sensitivity, could reduce BPH risk.

Given our finding of a strong effect for adiponectin on BPH risk and the established effects of adiponectin on insulin sensitivity, the lack of association between C-peptide and BPH in this study was somewhat unexpected. It is possible that an association between C-peptide and BPH does exist, but was not detectable in this study due to increased measurement variance resulting from the use of non-fasting serum. Alternatively, C-peptide is a direct marker of endogenous insulin secretion[30], whereas adiponectin, whose insulin sensitizing effects are independent of insulin levels[25], is a marker of insulin sensitivity[27]. Therefore, insulin sensitivity rather than insulin secretion may be the important factor in development of BPH.

Our finding that the inverse association between adiponectin and BPH is limited to men with higher levels of physical activity is difficult to interpret. One possible interpretation is that physical activity and adiponectin affect BPH risk through complementary mechanisms. Both physical activity and adiponectin improve insulin sensitivity; adiponectin enhances insulin action by suppressing hepatic glucose production[25] and increasing glucose uptake and fatty acid oxidation in muscle[21], whereas physical activity improves insulin sensitivity primarily by inducing the uptake of glucose in skeletal muscle[31]. In addition, physical activity may enhance the activity of adiponectin by increasing circulating adiponectin levels and adiponectin receptor expression in muscle tissue[32]. Perhaps both mechanisms are required in order to see a beneficial effect.

In this PCPT subsample we observed an association between overall obesity(BMI) and BPH risk, as was found in the larger PCPT study of obesity and BPH[3]. However, when examining whether the association between obesity and BPH risk was mediated by adiponectin, adjustment for adiponectin resulted in only a modest attenuation of the overall risk estimate, indicating that adiponectin is not the only mechanism through which obesity affects BPH risk.

This study has several strengths. It is a prospective analysis in which men with a history of BPH or BPH symptoms were excluded at the time of the baseline blood draw. We had extensive data on covariates and could control for many factors associated with BPH risk. Of special note is baseline IPSS, which was strongly associated with incidental BPH[3]; however, control for baseline IPSS had no appreciable effect on the association of adiponectin and BPH risk (OR for Q4 vs. Q1=0.67, 95%CI 0.48, 0.93). This study uses a rigorous definition of BPH that captures all current medical treatments as well as LUTS, which were collected annually using a standardized and well validated self-administered questionnaire. This is in contrast to most previous studies which relied on prostate size, which correlates poorly with symptoms[33], or BPH surgery alone as an endpoint, which may be biased because this definition cannot separate factors associated with surgical treatment (e.g. health insurance, age, co-morbidities) from those that predict severe BPH.

There are several limitations to this study. First, our definition of BPH by LUTS can not distinguish between LUTS due to BPH and LUTS due to other urologic, neurologic or bladder conditions[34]. We used the age-specific prevalences of 'other conditions' associated with LUTS within the Olmstead County cohort (13.5%)[35] to estimate a prevalence of these conditions (6.5%) in the PCPT study population (lower because the PCPT excludes men with a history of prostate surgery). This level of non-specificity is unlikely to explain our study results. Second, in order to maximize the contrast between groups we deliberately selected a control group with a definitive absence of symptoms

associated with BPH. Thus, men who developed mild to moderate symptoms were excluded from this study. It is unclear whether the development of mild/moderate symptoms is indicative of an intermediate form of symptomatic BPH, though the inclusion of these men would likely have attenuated our results. Third, a single measurement of leptin may be susceptible to short-term variations; thus the results from our study may have been biased resulting in an under-estimation of the true relationship between serum leptin concentrations and BPH risk. Fourth, bloods were non-fasting and drawn at all times during the day, which probably increased variability in adipokine and C-peptide concentrations. However, we have no reason to believe that the distribution of time since last meal or time of blood draw differed markedly between cases and controls; therefore, this error is unlikely to introduce differential bias and would only attenuate the associations with BPH.

In conclusion, we found that higher adiponectin concentrations were associated with a reduced risk of symptomatic BPH; however, only among men who were moderately/very active. This suggests that the relationship between obesity and BPH risk involves a complex interaction between factors that affect glucose uptake and insulin sensitivity. Adiponectin explained only a moderate proportion of the association between obesity and BPH risk, and thus it is not the only mechanism through which obesity affects risk of BPH. It is possible that several other obesity-related metabolic abnormalities, including alterations in steroid hormone levels, and chronic, low-level inflammation could also contribute to the development of BPH. Future studies will be needed to confirm our finding and assess the role of other potential mediating pathways.

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Table 1

Demographic and lifestyle characteristics of the study population^a

	Benign Prostatic Hyperplasia (BPH)			
	Cases (N=698) ^b		Controls (N=709) ^b	
	n	(%)	n	(%)
Age				
55–59	209	(30.0)	213	(30.1)
60–64	197	(28.2)	198	(27.9)
65–69	187	(26.8)	186	(26.2)
70+	105	(15.0)	112	(15.8)
Race/Ethnicity				
White	647	(92.7)	657	(92.7)
Other	51	(7.3)	52	(7.3)
Waist to hip ratio				
<0.95	261	(37.4)	306	(43.2)
0.95–0.99	220	(31.5)	229	(32.3)
1.00–1.04	125	(17.9)	113	(15.9)
1.05+	18	(2.6)	21	(3.0)
Body Mass Index (kg/m ²)				
Normal (<25)	164	(23.5)	200	(28.2)
Overweight (25–29.9)	362	(51.9)	360	(50.8)
Obese (≥30)	161	(23.1)	146	(20.6)
Alcohol Consumption (grams/day)				
<0.25	198	(28.4)	155	(21.9)
0.25 – 1.74	92	(13.2)	128	(18.0)
1.75 –12.9	241	(34.5)	238	(33.6)
13 –26.9	100	(14.3)	109	(15.4)
≥ 27	66	(9.5)	79	(11.1)
Physical activity				
Sedentary	112	(16.1)	102	(14.4)
				0.30

Benign Prostatic Hyperplasia (BPH)					<i>p</i> ^c
Cases (N=698) ^b		Controls (N=709) ^b			
	n	(%)	n	(%)	
Light activity	312	(44.7)	297	(41.9)	
Moderate activity	199	(28.5)	234	(33.0)	
Very active	72	(10.3)	74	(10.4)	
Smoking status					
Yes (current)	52	(7.5)	41	(5.8)	
No (former/never)	645	(92.4)	668	(94.2)	
Baseline IPSS					
1–3	309	(44.3)	552	(77.9)	
4–5	281	(40.3)	140	(19.8)	
6–7	108	(15.5)	17	(2.4)	

^aExcludes 23 cases and 16 controls with missing adipokine and c-peptide data, and 6 cases and 2 controls with a history of diabetes at baseline.

^bNumbers may not add up to the total number of cases/controls and percentages may not add up to 100 due to missing data.

^c*P* from chi-square test

Table 2

Serum concentration of adipokines and C-peptide for cases and controls

	Cases (N=698)	Controls (N=709)	P
Adiponectin (ug/ml)			
Geometric mean (95%CI)	4.86 (3.63, 6.49)	5.42 (4.06, 7.24)	<0.01
Median	4.84	5.41	<0.01 ^a
5 th –95 th percentiles	0.64 – 25.60	0.80 – 26.14	
C-peptide (ng/ml)			
Geometric mean (95%CI)	1.30 (0.95, 1.79)	1.31 (0.92, 1.70)	0.82
Median	1.35	1.33	0.96 ^a
5 th –95 th percentiles	0.18 – 7.28	0.19 – 5.67	
Leptin (ng/ml)			
Geometric mean (95%CI)	4.72 (3.42, 6.55)	4.56 (3.25, 6.55)	0.41
Median	4.59	4.74	0.41 ^a
5 th –95 th percentiles	0.76 – 34.27	0.62 – 49.46	

^aWilcoxon rank-sum test

Table 3

Association of adipokines and C-peptide on BPH risk

	No. cases/controls	Adjusted ¹		Fully Adjusted ²	
		OR	(95% CI)	OR	(95% CI)
Adiponectin (ug/ml)					
Q1	222/176	1.00		1.00	
Q2	177/178	0.78	(0.59,1.04)	0.80	(0.60,1.07)
Q3	161/177	0.71	(0.53,0.96)	0.75	(0.56,1.01)
Q4	138/178	0.60	(0.45,0.82)	0.65	(0.47,0.87)
<i>P</i> for trend			0.0008		0.004
C-peptide (ng/ml)					
Q1	191/177	1.00		1.00	
Q2	151/177	0.79	(0.58,1.06)	0.74	(0.55,1.00)
Q3	185/177	0.96	(0.72,1.29)	0.90	(0.67,1.22)
Q4	171/178	0.89	(0.66,1.19)	0.80	(0.59,1.08)
<i>P</i> for trend			0.72		0.31
Leptin (ng/ml)					
Q1	141/177	1.00		1.00	
Q2	223/177	1.59	(1.18,2.14)	1.48	(1.09,2.01)
Q3	146/177	1.03	(0.76,1.41)	0.91	(0.66,1.27)
Q4	188/178	1.33	(0.98,1.79)	1.05	(0.73,1.50)
<i>P</i> for trend			0.47		0.48

Quartile cutpoints: C-peptide: 0.87, 1.33, 2.09; Leptin: 2.68, 4.74, 7.39; Adiponectin: 3.78, 5.41, 7.71

¹ Adjusted for matching covariates only (age at baseline and race)² Adjusted for matching covariates, and body mass index(linear), and alcohol intake (grams/day)

Table 4

Association of adipokines and C-peptide with BPH risk, stratified by physical activity, alcohol consumption and BMI.¹

		No. cases/controls	OR (95% CI) ²	No. cases/controls	OR (95% CI) ²
		Sedentary/Minimally Active		Moderately/Very Active	
Adiponectin (ug/ml)	T1	173/141	1.00	117/95	1.03 (0.72, 1.46)
	T2	120/142	0.71 (0.51, 0.99)	90/93	0.81 (0.56, 1.16)
	T3	124/114	0.92 (0.65, 1.30)	60/119	0.43 (0.29, 0.63)
		$P_{\text{interaction}}=0.005$			
C-peptide (ng/ml)	T1	134/119	1.00	101/116	0.79 (0.55, 1.13)
	T2	125/127	0.84 (0.59, 1.20)	80/107	0.63 (0.43, 0.92)
	T3	158/151	0.85 (0.60, 1.20)	86/84	0.85 (0.58, 1.27)
		$P_{\text{interaction}}=0.24$			
Leptin (ng/ml)	T1	115/122	1.00	89/111	0.86 (0.59, 1.26)
	T2	149/129	1.15 (0.81, 1.63)	111/105	1.05 (0.72, 1.53)
	T3	153/146	0.93 (0.63, 1.35)	67/91	0.65 (0.42, 1.00)
		$P_{\text{interaction}}=0.57$			
		<1 drink/day ³		1+ drink/day ³	
Adiponectin (ug/ml)	T1	170/153	1.00	67/83	1.16 (0.71, 1.89)
	T2	154/177	0.81 (0.61, 1.09)	51/58	0.64 (0.38, 1.10)
	T3	197/188	0.69 (0.51, 0.93)	47/47	0.65 (0.39, 1.10)
		$P_{\text{interaction}}=0.53$			
C-peptide (ng/ml)	T1	223/184	1.00	68/52	0.83 (0.51, 1.35)
	T2	164/169	0.75 (0.55, 1.03)	47/66	0.86 (0.51, 1.44)
	T3	134/165	0.88 (0.65, 1.19)	50/70	0.97 (0.54, 1.72)
		$P_{\text{interaction}}=0.39$			
Leptin (ng/ml)	T1	162/168	1.00	42/67	0.73 (0.43, 1.24)
	T2	193/167	1.10 (0.81, 1.50)	69/67	1.13 (0.68, 1.88)
	T3	166/183	0.77 (0.54, 1.08)	54/54	0.98 (0.57, 1.70)
		$P_{\text{interaction}}=0.07$			

		No. cases/controls	OR (95% CI) ²	No. cases/controls	OR (95% CI) ²
		Sedentary/Minimally Active		Moderately/Very Active	
		BMI < 25		BMI ≥ 25	
Adiponectin (ug/ml)	T1	44/51	1.00	247/185	1.42 (0.87, 2.32)
	T2	59/68	1.00 (0.58, 1.70)	152/167	0.98 (0.59, 1.61)
	T3	61/81	0.90 (0.53, 1.52)	123/154	0.86 (0.52, 1.43)
		P _{interaction} =0.37			
C-peptide (ng/ml)	T1	78/81	1.00	159/155	0.97 (0.64, 1.48)
	T2	49/70	0.71 (0.43, 1.14)	156/165	0.86 (0.56, 1.33)
	T3	37/49	0.75 (0.44, 1.28)	207/186	1.00 (0.64, 1.55)
		P _{interaction} =0.23			
Leptin (ng/ml)	T1	98/125	1.00	109/110	1.16 (0.77, 1.74)
	T2	54/53	1.32 (0.83, 2.10)	208/181	1.30 (0.88, 1.91)
	T3	15/22	0.87 (0.43, 1.78)	205/215	0.98 (0.63, 1.53)
		P _{interaction} =0.42			

¹ Adjusted for age, race, body mass index(linear), and alcohol intake (grams/day)

² Joint effects models, in which the odds ratios for interactions are reported using a single reference group

³ 1 drink per day is equivalent to 13 grams of alcohol per day