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Total testosterone, androgen receptor polymorphism, and depressive symptoms in young black and white men: the CARDIA Male Hormone Study

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SUMMARY

Androgen receptor (AR) CAG repeat length (RL) might modify the relationship between endogenous testosterone (T) and depressive symptoms in men on average over age 50 years. We hypothesized that CAG RL modifies the association between T and depressive symptoms in 525 black and 721 white men under age 40 years participating in the CARDIA Male Hormone study. We assessed cross-sectional associations of quartiles of total and bioavailable T and tertiles of CAG RL with depressive symptoms, defined as Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16, in –1996. 1995 The interaction of CAG RL and total T on depressive symptoms was statistically significant for blacks, whites, and both groups combined. In the combined analysis, the odds ratios (OR) (95% confidence intervals (CI)) across the quartiles of total T were 1.00, 0.17 (95% CI: 0.07–0.43), 0.31 (95% CI: 0.14–0.70), and 0.49 (95% CI: 0.22–1.09) for the shortest RL group. The interaction of CAG RL and bioavailable T on depressive symptoms was statistically significant for black men only, and nonsignificant in a combined analysis. For black men in the shortest RL group, the ORs for the quartiles of bioavailable T were 1.00, 0.41 (95% CI: 0.16–1.05), 0.10 (95% CI: 0.03–0.38), and 0.35 (95% CI: 0.14–0.90). In other CAG groups, there were no relationships of total or

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

CONTRIBUTORS
All authors have contributed to critical revision of the manuscript for important intellectual content, the analysis and interpretation of the data, and have given final approval of this manuscript. Below we have provided a breakdown of individual contributions: Project concept and design and principal investigator: Gapstur
Study concept and design: Gapstur, Colangelo, Sharp, Scholtens, Chiu
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bioavailable T with depressive symptoms. CAG RL might modify the association between endogenous total and bioavailable T and depressive symptoms in younger black men. Clinical trials assessing the effects of T replacement therapy on depressive symptoms in hypogonadal men should consider including CAG RL in their design and/or analysis.

Keywords

testosterone; androgen receptor gene; depression; CAG repeat; sex hormones; polymorphism

INTRODUCTION

Throughout the world, the prevalence of depression is lower in men than women (Kessler, 2003). This has led to a hypothesis that sex hormones might be associated with risk of depression. In men, testosterone (T) is the most important plasma androgen (Kaufman and Vermeulen, 2005). Whether T participates in the pathophysiology of depressive illness is unclear (Sternbach, 1998; Seidman and Walsh, 1999; Seidman, 2003; Carnahan and Perry, 2004): clinical and epidemiologic studies examining associations of T with depressive illness have shown positive, inverse, or null associations (Barrett-Connor et al., 1999; Booth et al., 1999; Shores et al., 2005; Perry et al., 2001; Seidman et al., 2001b). Although some of the variability across studies can be attributed to small sample sizes, different methods of diagnostic evaluation, and heterogeneity in depressive symptoms (Seidman, 2003), some also might be due to genetic factors, such as genetic variability in the androgen receptor gene (AR) (Seidman et al., 2001a).

The regulation of androgen action is mediated by the androgen receptor (AR), a member of the nuclear steroid receptors. The AR is located on the X chromosome at Xq11-12 and encompasses eight exons. The aminoterminal transactivating domain is encoded by exon 1 and contains a highly polymorphic CAG trinucleotide repeat sequence which results in a variable number of glutamines (Brown et al., 1989). The number of repeat lengths (RL) in this sequence ranges from 8 to 31 in normal men (Edwards et al., 1992). Racial variation in CAG RL has been reported (Edwards et al., 1992), with black men having shorter mean repeat lengths than white men. In vitro, transactivation activity of the AR has been found to be inversely correlated with CAG RL (Chamberlain et al., 1994). Seidman et al. reported that CAG RL may modulate the relationship between endogenous T and depressive symptoms in a study of older, predominantly white men (Seidman et al., 2001a). That is, while neither CAG RL nor total T were associated with depressive symptoms as main effects, depressive symptoms were significantly inversely associated with total T in men with a shorter CAG RL (range 8–20), but not in men with moderate (range 21–23) or longer (range 24–40) CAG RLs.

The Coronary Artery Risk Development in (Young) Adults (CARDIA) Male Hormone Study (CMHS) is a population based, longitudinal study of young black and white men with data collected on total and bioavailable T, CAG RL, and depressive symptoms at an examination time (year 10) when the cohort was aged 28 to 40 years. Thus, the CMHS provides an opportunity to assess whether T or CAG RL are associated with depressive symptoms and, based on previous research (Seidman et al., 2001a), to test the hypothesis that an interaction of T with CAG RL on the outcome of depressive symptoms can also be observed in a younger, bi-ethnic cohort of men. Racial variation in distributions of T (Ellis and Nyborg, 1992), CAG RLs (Edwards et al., 1992), and prevalence of depressive disorders have been reported (Skarupski et al., 2005; Dunlop et al., 2003). Therefore, we also explored whether the differences in CAG RL distributions and in T levels between black and white men might partially explain a higher prevalence of depressive symptoms in black men in CARDIA.

METHOD

Study Population

The CARDIA study is a multicenter, longitudinal study of lifestyle and the evolution of cardiovascular disease risk factors in 5115 young black and white men and women aged 18 to 30 years at the baseline examination (1985–86) recruited from Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Five follow-up examinations were completed in 1987–88 (year 2), 1990–91 (year 5), 1992–93 (year 7), 1995–96 (year 10), and 2000–01 (year 15). A detailed description of the design, recruitment, and methods of the CARDIA study has been published previously (Friedman et al., 1988).

The numbers of black men and white men who completed the baseline CARDIA examination were 1157 and 1171, respectively. The CMHS was designed to compare eight-year changes in serum hormone levels between 624 black male and 796 white male CARDIA participants who had serum samples available from both the year 2 and the year 10 examinations; year 7 serum samples were also used when available. From this cohort of 1420 men, we excluded from the analysis: men who did not have DNA available ($N = 95$), who did not provide consent to use DNA ($N = 19$), who were missing data either on total or bioavailable T, the measure of depressive symptoms, or because their CAG RL could not be determined ($N = 15$), and who were missing pertinent covariate data ($N = 22$). Finally, 23 men who were taking anti-depressant medication were excluded from the analyses because anti-depressants could potentially alter T levels (Bell et al., 2006) in addition to their established mood altering effects. Thus, the final analytic sample consisted of 525 black men and 721 white men. The CMHS has been approved by the Institutional Review Board at Northwestern University. Informed consent was obtained from each participant at each examination.

Data Collection

Height and weight were measured with the participant wearing light clothing with no shoes, and body mass index (BMI) was computed as weight (kg) divided by height squared (m^2). Age, race, years of education, income, marital and employment status, number of cigarettes smoked per day, and use of anti-depressant medication were self-reported. Alcohol intake (ml/d) was computed from the self-reported frequency of beer, wine, and liquor consumed per week (Dyer et al., 1990). A physical activity score was obtained from the CARDIA Physical Activity History, a modified version of the Minnesota Leisure Time Physical Activity Questionnaire (Jacobs Jr. et al., 1989).

Depressive symptoms were measured at the year 10 examination using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), which has a maximum score of 60. Participants are asked to indicate how often they experienced each symptom in the past week (0, rarely or none of the time; 1, some of the time; 2, much of the time; 3, most or all of the time). For this study, we classified participants as having a high level of depressive symptoms if they scored 16 or higher on the CES-D, a standard cutoff used in epidemiologic studies (Radloff, 1977). The factor structure of the CES-D has been validated in Caucasian populations (Weissman et al., 1977; Herzog et al., 1990) and replicated in low socioeconomic status blacks (Nguyen et al., 2004).

Hormone Measurement

At each CARDIA examination, blood was collected by venipuncture between 0730 and 1200 h from over 95% of the CMHS participants. Aliquots of serum were stored at −70° C. Total testosterone was measured by radioimmunoassay using Immulite (Diagnostic Products Corporation, Los Angeles, CA). Assay variability was monitored by including 10% quality control (QC) serum samples in each analytic batch. The within- and between-batch coefficients

of variation were 10% and 13% for total testosterone. Sex hormone binding globulin was measured by chemiluminescent enzyme immunometric assay using Immulite, and using the total testosterone and SHBG concentrations, the concentration of bioavailable testosterone was calculated according to the method of Södergard et al. (Södergard et al., 1982). Because there were no associations between time of blood draw and hormone levels in the study (Gapstur et al., 2002), time of blood draw was not considered further.

Genetic Analyses

DNA was isolated from whole blood samples collected at the year 5 examination. For each study subject, the fragment of the AR containing the polymorphic CAG repeat was amplified using the following primers: Sense-5′TCC′AGA′ATC′TGT′TCC′-AGA′GCG′TGC3′; Antisense-5′FAM-Label-GCT′GTG′AAG′GTT′GCT′GTT′CCT′CAT3′. PCR was performed in a 96-well format using 5 ng of DNA in a 15 μL reaction containing 50 mM KCl, 10 mM Tris (pH 8.3), 150 μM of each dinucleotide, 1.5 mM $MgCl_2$, 5% DMSO, 0.1 pmol of each primer, and 0.6 Units Taq polymerase (Promega, Madison, WI).

After amplification by PCR, 1 μl from each amplification product was diluted in a buffer containing 2.5 ml formamide, 0.5 ml blue dextran (50mM EDTA, 50 mg/ml blue dextran). The samples were analyzed in a denaturating 6% gel (0.4 mm) and submitted to electrophoresis at 800V/40 mA/28W in a DNA sequencer (ABI 377, Applied Biosystems, Foster City, CA). To identify the different alleles, the length of the reaction products was compared to a sample with a known number of CAG repeats based on direct sequence analysis. Moreover, a TAMRA-labeled size standard was included as a marker in every lane.

Quality control was performed by randomly selecting 5% of the participants DNA samples for re-analysis. For the CAG repeat analyses, only one sample did not show consistent agreement (<1%).

Statistical Analysis

Total and bioavailable T were normally distributed and, therefore, left untransformed. Initial analysis of total and bioavailable T as continuous variables with inclusion of higher degree terms in regression models indicated relationships with depressive symptoms were nonlinear. Furthermore, one study described an association between T and depression that was inverse for T levels <590 ng/dl, and null for T levels >590 ng/dl (Booth et al., 1999). Therefore, total and bioavailable T were categorized into quartiles. So that black and white men could be compared across similar categories, CAG RL was categorized into tertiles with the races pooled. Race-specific univariate logistic regression was used to assess the association of total and bioavailable T and CAG RL with depressive symptoms. Subsequent multivariate analyses added age followed by several potential confounders: BMI, cigarettes, alcohol intake, and total physical activity. Socioeconomic risk factors for depression were also considered, but they did not confound the associations, so were not included. For each ethnic group a formal test for interaction between T and CAG RL group with risk of depressive symptoms was done using the likelihood ratio test: Results warranted stratifying analyses by CAG RL group. Finally, we assessed whether observed differences in prevalence of depressive symptoms between black and white men could be partially explained by CAG RL and total T levels. This was done by examining the odds ratio (OR) of having depressive symptoms for blacks compared to whites in models that excluded and included dummy variables representing T quartiles, CAG RL groups, and the interactions of these variables. Attenuation of the OR for race in the model adjusting for the T-CAG RL variables would be evidence that these factors at least partially explain a higher prevalence of depressive symptoms in black men. BMI, cigarette smoking, alcohol consumption, physical activity, and socioeconomic variables were included in the

multivariate analyses because previous studies show that they are confounders of the association between race and depression (Dunlop et al., 2003; Skarupski et al., 2005).

RESULTS

Median, minimum, and maximum CAG RLs were 19, 10, and 31 in black men and 21, 7, and 31 in white men. There were 110 (21%) black men and 91 (13%) white men with clinically significant depressive symptoms. Mean (SD) total and bioavailable T in black men were 5.80 (1.96) ng/ml and 2.97 (1.11) ng/ml, respectively. In white men they were 5.68 (1.77) and 2.80 (0.91) respectively.

For both black and white men, those who had depressive symptoms tended to smoke more, had less education, were more likely to be unemployed and unmarried, and had a lower annual income than those without depressive symptoms (see Table 1).

In quartile analysis, after adjusting for potential confounders, there was an inverse threshold relationship of total and bioavailable T with depressive symptoms in black men (see Table 2), although the associations for bioavailable T were not statistically significant. For white men, the ORs for quartiles of total T were nonsignificant in both age-adjusted and multivariate-adjusted models. For bioavailable T, there was a positive association with the presence of depressive symptoms, which was statistically significant only for the third quartile of bioavailable T. However, there was no trend over the quartiles. In black men only, there was a higher risk of depressive symptoms in the second tertile of CAG RL compared to the first (see Table 2).

To determine whether the association between serum androgen levels and depressive symptoms differed across categories of CAG repeat length, we assessed the interaction of the quartiles of total T or bioavailable T with the tertiles of CAG RL in each race group and in analyses of black and white men combined. The test for interaction between total T and CAG RL group was statistically significant for black men ($p = 0.01$), for white men ($p = 0.05$) (see Table 3), and in a combined analysis ($p = 0.0003$). In general, for the shortest CAG RL group there were statistically significant but nonlinear associations for quartiles of total T with presence of depressive symptoms. In the combined analysis of black and white men, the odds ratios (95% confidence intervals (CI)) across the upper three quartiles of total T were 0.17 (95% CI = 0.07 to 0.43), 0.31 (95% CI = 0.14 to 0.70), and 0.49 (95% CI = 0.22 to 1.09) for the ≤18 RL However, in the 19–21 RL group, the highest quartile was significantly associated with reduced risk for depressive symptoms (OR = 0.38, 95% CI = 0.16 to 0.91) relative to quartile 1, whereas the ORs for quartiles 2 and 3 did not differ from 1.0. In the 22+ RL group, each quartile above the first had nonsignificantly increased risk for depressive symptoms (ORs [95% CI] = 1.89 (0.66 to 5.43), 2.20 (0.79 to 6.11), and 2.05 (0.75 to 5.62), respectively).

For black men only, the test for interaction between bioavailable T and CAG RL was significant ($p = 0.01$). In the shortest RL group, the ORs for all quartiles above the first were less than one with the third and fourth quartiles statistically significant ($p = 0.0008$ and $p = 0.03$, respectively). In the other two CAG RL groups, there were no significant associations between quartiles of bioavailable T and presence of depressive symptoms. In white men, the test for bioavailable T by RL group interaction could not be assessed because there were no cases of depressive symptoms in the highest T quartile of the ≤18 RL group. −21 and 22+ RL In the groups, there were no associations between bioavailable T and depressive symptoms. For black and white men combined, the test for interaction was not significant ($p = 0.41$). Results were generally similar to the findings for total T, although in the ≤18 RL group, ORs and nonsignificant (ORs [95% CI] = 0.69 (0.32 to 1.50), 0.75 (0.35 to 1.61), and 0.56 (0.25 to 1.26), respectively, for quartiles 2 through 4).

Associations of race with depressive symptoms are shown in Table 4. Model 1, which adjusts only for age, indicates a highly significant crude association of black race with depressive symptoms (OR = 1.87, $p < 0.0001$). After adding T-CAG RL dummy variables to the model (see Model 2), the OR for race (OR = 1.94) does not become attenuated, indicating that T together with CAG RL does not explain the association between race and depressive symptoms. On the other hand, after adjustment for lifestyle and socioeconomic variables (see Model 3), the OR is notably attenuated compared to the age-only adjusted model (OR = 1.30 and OR = 1.87, respectively). Finally, adding the T-CAG RL variables does not attenuate the OR further.

DISCUSSION

In this large cohort of black and white men, there were no main effect associations of total or bioavailable T, or CAG RL with depressive symptoms. After stratifying by CAG RL, there was a statistically significant association between total T and bioavailable T and depressive symptoms for black men in the shortest RL group that indicated T levels in the upper three quartiles compared to the lowest quartile were associated with less risk for depressive symptoms. There were no associations for black men in other CAG RL groups. In the analysis pooling black and white men there were also significant associations for total T in the shortest RL group. Finally, T and CAG RL did not explain the difference in the prevalence of depressive symptoms between black and white men.

Findings for the relation between T and depressive illness, without accounting for AR variability, from other studies are inconsistent. Two studies in men aged 50 years and older (Barrett-Connor et al., 1999; Shores et al., 2005) and one in a sample of Vietnam veterans aged 30 to 48 years (Booth et al, 1999) reported inverse associations between total or bioavailable T and depressive illness (Barrett-Connor et al., 1999; Booth et al., 1999; Shores et al., 2005). In the sample of Vietnam veterans (Booth et al., 1999) the inverse association for total T was restricted to T levels <590 ng/dl. In contrast, another study reported a positive correlation between bioavailable T and scores on the Hamilton Depression Scale in a group of healthy men aged 55 to 75 years (Perry et al., 2001). In the Massachusetts Male Aging Study (MMAS), there was a null association between total T and depressive symptoms measured by the CES-D (Seidman et al., 2001a). In another group of elderly men, mean total T levels were lower in the dysthymia group than in the major depressive disorder group and the nondepressed group, whereas the major depressive disorder group did not differ from the nondepressed group on mean total T levels (Seidman et al., 2002). Similarly, Delhez et al. (Delhez et al., 2003) concluded that andropause might be associated with “minor depressive symptoms” that are not pathological. Randomized clinical trials testing whether exogenous T administered to hypogonadal (Seidman et al., 2001b; Pope et al., 2003; Orengo et al., 2005), eugonadal (Seidman et al., 2005), or HIV-infected (Rabkin et al., 2000; Grinspoon et al., 2000) men improves depressive disorders have had inconsistent results as well, with half of the studies reporting null findings (Seidman et al., 2001b; Orengo et al., 2005; Seidman et al., 2005). In summary, our main effect findings are consistent with those from the aforementioned and other studies showing no clear associations of endogenous or exogenous T with depressive symptoms (Sternbach, 1998; Seidman and Walsh, 1999; Seidman, 2003; Carnahan and Perry, 2004).

At least two studies assessed the interaction between CAG RL and T with risk of depression in men. In the MMAS there was an inverse relation between T and depressive symptoms for men with shorter CAG RLs (8–20 repeats) (Seidman et al., 2001a). This association did not exist in men with moderate or longer CAG RLs. These findings are consistent with the data presented here in a cohort of younger men with higher mean total T levels. T’Sjoen et al. found no association between depression defined by the Geriatric Depression Scale (GDS) and free testosterone levels in men with a short CAG RL (T'Sjoen et al., 2005). However, the sample size of that study was limited to a total of 236 men and 30 cases of GDS-defined depression.

Together with the findings of the MMAS (Seidman et al., 2001a), our findings suggest that men with shorter CAG RLs might be more responsive to T replacement therapy. These findings have important implications for future clinical trials testing the efficacy of T administration for depression.

The biologic mechanism underlying an association of T with depressive symptoms is not established. It has been suggested that low testosterone levels might alter serotonin neurotransmission (Shores et al., 2004; Shores et al., 2005). Animal models support this hypothesis (Sumner and Fink, 1998; Fink et al., 1999; Robichaud and Debonnel, 2005). Furthermore, the differential effect of T on depressive illness across CAG repeat length groups is also unclear. As mentioned previously, transactivation activity of the AR is greater for shorter CAG RLs compared to longer RLs (Chamberlain et al., 1994). Also, CAG RL is positively associated with serum T concentrations (Krithivas et al., 1999). Therefore, it is possible that among men with a short CAG repeat length, transactivation activity of the AR is more strongly affected by higher testosterone levels.

Several studies have documented that black men have shorter mean CAG RLs than white men, and that blacks have higher crude prevalence (i.e., unadjusted for socioeconomic factors) of depressive symptoms (Skarupski et al., 2005) and illness (Dunlop et al., 2003) than do whites. Data from the CMHS allowed us to further examine this racial disparity. In our analysis, the difference in CAG RL distributions between black men and white men together with T levels did not explain the higher prevalence of depressive symptoms in black men. Importantly, modifiable lifestyle and socioeconomic factors appear to attenuate the association between race and depressive symptoms.

Strengths of this study include having a large population-based, bi-ethnic sample and the ability to adjust for potential confounders. Additionally, we were able to exclude men who reported anti-depressant medication usage from our study, preventing misclassification of both hormone and depression status. There are several limitations to this study. One is our reliance on the CES-D to classify depressive symptoms as opposed to using a clinical structured interview for depressive disorders. However, the CES-D has demonstrated high sensitivity for detecting clinically diagnosed depression (Weissman et al., 1977; McDowell I, 1996). Second, we were also limited to a single point in time at which CES-D and hormone data were collected contemporaneously. Whether changes in T lead to changes in risk of depressive symptoms is unclear. Third, there are fewer white men in the shortest CAG RL group, limiting the power to find associations for white men. Fourth, the small volume of serum (approximately 0.5 ml) available for this study precluded the direct measurement of bioavailable testosterone.

In summary, our data suggest that CAG RL might modify the associations of total and bioavailable T with depressive symptoms in younger black men, whereas for white men, the findings are inconclusive. Overall, these results should be confirmed in other studies. In addition, future randomized clinical trials of T replacement therapy for depression in hypogonadal men might consider incorporating CAG RL into the study design as a stratification factor or as an eligibility criterion. It is possible that T administration might be more efficacious among men with a shorter CAG repeat length.

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Table 1

Year 10 (1995–1996) characteristics by race and by presence of depressive symptoms.

	Black men				White men			
	Non depressed (*N* = 415)		Depressed (*N* = 110)		Non depressed (*N* = 630)		Depressed (*N* = 91)	
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
Age (years)	34.4	(3.84)	34.3	(3.31)	35.4	(3.44)	35.9	(2.99)
Body mass index (kg/m^2)	28.2	(5.60)	26.7	(5.56)	26.6	(4.36)	26.6	(4.54)
Cigarettes/d	3.4	(6.44)	5.5	(7.65)	3.1	(7.85)	4.5	(8.94)
Alcohol (ml)	16.0	(26.31)	20.8	(30.88)	15.0	(24.10)	13.8	(19.57)
Physical activity score	465	(326)	392	(307)	417	(275)	401	(281)
Years education	13.9	(2.31)	12.9	(2.11)	15.6	(2.69)	14.7	(2.81)
Unemployed (%)	10		26		4		9	
Marital status:								
Unmarried (%)	28		37		26		32	
Married or in a marriage-like relationship (%)	55		43		65		57	
Widowed, separated, divorced, or other (%)	17		20		9		11	
Annual income:								
Less than $12,000 (%)	7		29		4		9	
$12,000 to $24,999 (%)	20		25		9		19	
$25,000 to $49,999 (%)	40		28		32		32	
$50,000 or more (%)	33		17		56		41	

SD, standard deviation.

Table 2

Age-adjusted and multivariate-adjusted OR of having depressive symptoms (CES-D ≥16) according to categories of total and bioavailable testosterone and CAG repeat length for black and white men in CARDIA Male Hormone Study (1995–1996).

	Black men					White men				
		Age-adjusted		Multivariate-adjusted[a]			Age-adjusted		Multivariate-adjusted[a]	
	Cases/ total *N*	OR	(95% CI)	OR	(95% CI)	Cases/ total *N*	OR	(95% CI)	OR	(95% CI)
Quartiles of total T (ng/ml)										
Q1: ≤4.42	31/128	1.00		1.00		24/183	1.00		1.00	
Q2: 4.43–5.54	22/125	0.67	(0.36–1.23)	0.52	(0.27–0.98)	20/184	0.83	(0.44–1.56)	0.82	(0.43–1.56)
Q3: 5.55–6.72	25/132	0.73	(0.40–1.32)	0.48	(0.25–0.91)	29/183	1.30	(0.72–2.34)	1.27	(0.69–2.33)
Q4: ≥ 6.73	32/140	0.92	(0.52–1.63)	0.56	(0.29–1.06)	18/171	0.81	(0.42–1.55)	0.74	(0.37–1.48)
Quartiles of bioavailable T (ng/ml)										
Q1: ≤ 2.20	31/130	1.00		1.00		16/181	1.00		1.00	
Q2: 2.21–2.74	24/119	0.81	(0.44–1.47)	0.64	(0.34–1.21)	24/192	1.49	(0.77–2.92)	1.47	(0.75–2.89)
Q3: 2.75–3.39	24/120	0.79	(0.43–1.45)	0.60	(0.32–1.13)	32/191	2.16	(1.14–4.10)	2.19	(1.15–4.18)
Q4: ≥ 3.40	31/156	0.78	0(.44–1.38)	0.58	(0.32–1.06)	19/157	1.52	(0.75–3.10)	1.50	(0.73–3.06)
Tertiles of CAG RL										
T1: ≤ 18	46/251	1.00		1.00		17/151	1.00		1.00	
T2: 19–21	45/171	1.59	(1.00–2.54)	1.66	(1.02–2.68)	38/279	1.24	(0.67–2.28)	1.23	(0.67–2.28)
T3: 22+	19/103	1.01	(0.56–1.82)	1.07	(0.59–1.96)	36/291	1.10	(0.60–2.04)	1.11	(0.60–2.06)

[a] Adjusted for age, body mass index, cigarettes/d, alcohol consumption (ml/d), and total physical activity score.

OR, odds ratio, CES-D, Center for Epidemiologic Studies Depression Scale, CARDIA, Coronary Artery Risk Development in Young Adults, CI, confidence interval.

Table 3

Association of testosterone with depressive symptoms (CES-D ≥16) stratified by CAG RL group in black and white men.

CAG RL Group	Quartiles	Black men				White men			
		Cases/total *N*	OR[a]	(95% CI)	$\chi_6^{2\,b}$ (*p* value)	Cases/total *N*	OR[a]	(95% CI)	χ_6^{2b} (*p* value)
	Total Testosterone								
≤18	Q1	17/67	1.00			8/45	1.00		
	Q2	5/61	0.14	(0.04–0.45)		2/48	0.24	(0.04–1.24)	
	Q3	7/61	0.14	(0.05–0.43)		5/34	1.00	(0.27–3.69)	
	Q4	17/62	0.31	(0.11–0.85)		2/24	0.55	(0.10–3.09)	
19–21	Q1	12/46	1.00			12/69	1.00		
	Q2	14/38	1.99	(0.71–5.59)		9/77	0.62	(0.24–1.62)	
	Q3	12/43	1.26	(0.43–3.71)		14/77	0.98	(0.40–2.40)	
	Q4	7/44	0.64	(0.19–2.11)		3/56	0.25	(0.06–0.97)	
22+	Q1	2/15	1.00			4/69	1.00		
	Q2	3/26	0.93	(0.13–6.84)		9/59	2.58	(0.73–9.17)	
	Q3	6/28	1.58	(0.25–10.22)	16.42	10/72	2.50	(0.72–8.70)	12.61
	Q4	8/34	1.74	(0.29–10.57)	(0.01)	13/91	2.09	(0.60–7.27)	(0.05)
	Bioavailable Testosterone								
≤18	Q1	16/66	1.00			3/48	1.00		
	Q2	13/63	0.41	(0.16–1.05)		2/33	0.91	(0.14–6.03)	
	Q3	3/54	0.10	(0.03–0.38)		12/43	3.82[c]	(0.93–15.63)	
	Q4	14/68	0.35	(0.14–0.90)		0/27			
19–21	Q1	13/43	1.00			8/69	1.00		
	Q2	9/37	0.89	(0.31–2.54)		14/85	1.52	(0.59–3.92)	
	Q3	12/39	1.07	(0.39–2.90)		9/68	1.18	(0.42–3.34)	
	Q4	11/52	0.70	(0.25–1.93)		7/57	1.15	(0.38–3.49)	
22+	Q1	2/21	1.00			5/64	1.00		
	Q2	2/19	0.80	(0.10–6.80)		8/74	1.33	(0.41–4.37)	
	Q3	9/27	4.01	(0.71–22.78)	15.83	11/80	1.81	(0.58–5.64)	NA
	Q4	6/36	1.67	(0.29–9.64)	(0.01)	12/73	2.16	(0.69–6.77)	(NA)

[a] Adjusted for age, body mass index, cigarettes/d, alcohol consumption (ml/d), and total physical activity score.

[b] Test statistic and p value are for the interaction between T quartiles and CAG RL groups.

[c] Quartiles 3 and 4 combined in analysis.

CES-D, Center for Epidemiologic Studies Depression Scale, OR, odds ratio, CI, confidence interval.

Table 4

Association of race (black vs. white) with depressive symptoms.

	Factors adjusted for:	OR	(95% CI)	Wald χ^2	*p* value
Model 1	Age	1.87	(1.37, 2.54)	15.87	<0.0001
Model 2	Age, T-CAG RL[a]	1.94	(1.40, 2.69)	15.82	<0.0001
Model 3	Age, body mass index, cigarettes/d, alcohol consumption (ml/d), total physical activity score, marital status, income, years of education, and employment status	1.30	(0.92, 1.83)	2.19	0.14
Model 4	Model 3 factors plus T- CAG RL[a]	1.37	(0.96, 1.97)	2.93	0.09

[a]Dummy variables for T quartiles, CAG RL groups, and interactions of these variables.

OR, odds ratio, CI, confidence interval.