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Association between oxidized LDL, obesity and type 2 diabetes in a population-based cohort, the Health Aging and Body Composition study

Omer T. Njajou[1], **Alka M. Kanaya**[1], **Paul Holvoet**[2], **Stephanie Connelly**[3], **Elsa S. Strotmeyer**[4], **Tamara B. Harris**[5], **Steve R. Cummings**[1], and **Wen-Chi Hsueh**[1] **for the Health ABC Study**

[1]University of California, San Francisco, CA

[2]Katholieke Universiteit Leuven, Belgium

[3]University of Tennessee at Memphis, TN

[4]University of Pittsburgh, PA

[5]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda MD

Abstract

Aims/hypothesis—Accumulating evidence suggests a cross-sectional association between oxidative stress and type 2 diabetes (T2D). Systemic oxidative stress, as measured by oxidized LDL (oxLDL), has been correlated with visceral fat. We examined the relationship between oxLDL, and T2D- and obesity-related traits in a bi-racial sample of 2,985 subjects at baseline and after 7 years of follow-up.

Methods—We examined six T2D-related traits (T2D status, HbA1c, fasting glucose, insulin, adiponectin and HOMA-IR) as well as six obesity-related traits (obesity status, BMI, leptin, % body fat, visceral and subcutaneous fat mass) using logistic and linear regression models.

Results—In all subjects at baseline, oxLDL was positively associated with T2D (OR=1.3,95% CI:1.1–1.5), fasting glucose (β=0.03±0.006), HbA1c (β=0.02±0.004), fasting insulin (β=0.12±0.02), HOMA-IR (β=0.13±0.02) and negatively with adiponectin (β=−0.16±0.03), (all $p<0.001$). The strength and magnitude of these associations did not differ much between blacks and whites. In both blacks and whites, oxLDL was also associated with obesity (OR=1.3, 95% CI: 1.1–1.4) and 3 of its related traits (β=0.60±0.14 for BMI, β=0.74±0.17 for % body fat, β=0.29±0.06 for visceral fat;

all $p<0.001$). Furthermore, of 4 traits measured after 7 years of follow-up (fasting glucose, HbA1c, BMI and % fat), their relationship with oxLDL were similar to baseline observations. No significant association was found between oxLDL and incident T2D. Interestingly, oxLDL was significantly associated with % change in T2D- and obesity-related traits in whites but not in blacks.

Conclusion/interpretation—Our data suggest that systemic oxidative stress may be a novel risk factor for T2D and obesity.

Corresponding author: Wen-Chi Hsueh, M.P.H., Ph.D., Department of Medicine, School of Medicine, University of California, San Francisco, 513 Parnassus Ave, HSE 672C, San Francisco, CA, 94143-1640 USA, Tel: (415) 992-5376, Fax: (415) 476-5355, wen-chi.hsueh@ucsf.edu.

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Keywords

oxLDL; diabetes; oxidation; obesity

INTRODUCTION

There is increasing interest in the role of oxidative stress in common metabolic disorders such as type 2 diabetes (T2D) and obesity in recent years. Some studies have shown that oxidative stress and inflammatory processes play an important role in the development of vascular pathologies [1–3], T2D [2] and the metabolic syndrome which is characterized by insulin resistance, central obesity, hypertension and dyslipidemia [4]. For instance, the levels of a commonly used marker for oxidative stress, plasma oxidized LDL (oxLDL), were shown to be elevated in individuals with the metabolic syndrome compared to those without [5–8]. OxLDL level, not LDL-cholesterol, was also found to be predictive of incident T2D [9]. This suggests that the oxidative modification of LDL may be a marker of metabolic changes preceding or accompanying the onset of T2D [9]. Furthermore, oxidative stress is also associated with some risk factors of these clinical diseases. OxLDL has been positively associated with obesity and inflammation [10, 11], and among individuals with elevated abdominal fat, the effect of oxidative stress was even greater on cardiovascular disease (CVD) risk [12, 13].

Although some studies on the relation between oxLDL and T2D have been carried out, the results are neither consistent nor conclusive, due to either the limited sample sizes or the cross-sectional nature of most studies. Very few studies investigated the relation between oxLDL and obesity. Moreover, no study on the relationship between oxLDL, T2D and obesity has been carried out in blacks. The prevalence of T2D and obesity, as well as fat distributions, are known to differ between whites and blacks. Thus the current literature cannot be easily generalized to other populations. The novelty of the current study is three fold. Firstly, we report on the association between oxLDL, obesity and T2D in blacks. Secondly, we report on a more comprehensive array of traits related to T2D and obesity. We examined six T2D-related traits (T2D status, HbA1c, fasting glucose, insulin, adiponectin and HOMA-IR) and six obesity-related traits (obesity status, BMI, leptin, % body fat, visceral and subcutaneous fat mass), where as in the literature, only glucose, insulin, BMI and waist circumference were investigated, in people with cardiovascular diseases or the metabolic syndrome. Lastly, we also look at the relationship between oxLDL measured at baseline and changes between traits values at baseline and after 7 years of follow-up. In the current study, we aim to investigate whether oxLDL predicts T2D- and obesity related traits. Moreover, we also aim to evaluate if oxLDL measured at baseline is associated with prospective changes in these traits.

MATERIALS AND METHODS

Study Participants

The Health, Aging, and Body Composition (Health ABC) Study is a prospective cohort study that aims at studying the relation of age-related changes in health and body composition with incident functional limitations in initially well-functioning elderly adults. At baseline, the cohort included 3,075 persons aged 70 to 79 years; 41.6% were Black and 51.6% were female. Participants were recruited from Medicare listing in Pittsburgh, Pennsylvania, and Memphis, Tennessee between April 1997 and June 1998. Eligibility criteria included: 1) reported ability to walk one quarter mile (0.4 km), climb 10 steps, and perform basic activities of daily living without difficulty; 2) absence of life-threatening illness; and 3) intention to remain in the current geographic area for at least 3 years. All

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participants gave informed written consent; the protocol was approved by the institutional review boards of the clinical sites and the Data Coordinating Center (University of California, San Francisco).

Phenotypic measurements

Diagnosis of T2D was based on self-report diagnosis of T2D by a physician, the use of hypoglycemic medications, or a fasting glucose ≥126 mg/dl (≥7.0 mM), or a 2-hour plasma glucose ≥200 mg/dl (≥11.1 mM) in accordance with the American Diabetes Association criteria [14]. Information on the status of pre-existing T2D, duration since the T2D diagnosis, and use of antidiabetic medications was obtained by an interviewer-administered questionnaire. Plasma levels of fasting glucose, a post-challenge glucose 2 hours after a standard oral glucose tolerance test (for those not using antidiabetic medications) were measured by an automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH). Glycated hemoglobin (HbA1c) was measured by high performance liquid chromatography (Biorad Diamat, Richmond, CA), and fasting insulin (for those not using exogenous insulin) was measured using a micro-particle enzyme immunoassay (Pharmacia, Uppsala, Sweden; Abbott IMx analyzer). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as [fasting insulin (mU/l) × fasting glucose (mmol/l)]/22.5 [15].

Fasting glucose, insulin, and HbA1c were measured at baseline. Incident T2D status was assessed annually while fasting glucose and HbA1c were re-assessed after 5 years of follow-up. A total of 712 (23%) subjects had T2D at baseline and 179 (9%) subjects were identified as incident cases after 7 years of follow-up.

Body weight was measured with a standard balance beam scale to the nearest 0.1 kg. Height was measured barefoot using a Harpenden stadiometer (Holtain, UK) to the nearest 0.1 cm. BMI was calculated as weight divided by height squared (kg/m^2). The status of obesity was defined as having a BMI of ≥30 kg/m^2. A total body DXA scan was performed to measure % total body fat using fan-beam technology (Hologic QDR4500A, software version 8.21; Hologic, Waltham, NY, USA). Abdominal computed tomography (CT) scans were performed to determine abdominal fat masses. Visceral fat tissue was manually distinguished from subcutaneous fat tissue by tracing along the facial plane defining the internal abdominal wall.

Total circulating levels of adiponectin and leptin were measured in duplicate by radioimmuno- assay (RIA, Linco Research, St. Charles, MO). Plasma C-reactiveproteins (CRP) concentrations were measured in duplicate by ELISA (Calbiochem) and standardized according to WHO First International Reference Standard with a sensitivity of 0.08 μg/ml. BMI and % total body fat were re-assessed after 5 years of follow-up. Plasma levels of oxLDL were measured at the Atherosclerosis and Metabolism Unit of the Katholieke Universiteit Leuven as previously described [16] using a monoclonal antibody (4E6)-based competition ELISA. Briefly, the monoclonal antibody 4E6 is directed against a conformational epitope in the apolipoprotein B-100 moiety of LDL that is generated as a consequence of substitution of at least 60 lysine residues of apolipoprotein B-100 with aldehydes. This number of substituted lysines corresponds to the minimal number of substituted lysines required for scavenger-mediated uptake of oxLDL. Substituting aldehydes can be produced by peroxidation of lipids of LDL, resulting in the generation of oxLDL. We calculated the % change in traits values between baseline and follow-up as: % Δ trait = % (year 7 value − year 1 value)/year 1 value. Race, sex, age and other socio-demographic variables were self-reported during the initial clinic visit. LDL cholesterol levels were calculated from the Friedewald equation [17].

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Statistical analysis

To evaluate the association between oxLDL and quantitative outcomes related to T2D, stepwise linear regression analyses were performed. Age, sex, race, LDL-cholesterol and recruitment site were always included as covariates in the models. Additionally, we adjusted our models for factors known to influence T2D including BMI, educational level, CRP, physical activity and use of antidiabetic medication. In the analysis of adiponectin, we further adjusted for % total body fat. In the analysis of insulin and HOMA-IR, we excluded diabetic participants.

The association between oxLDL and obesity-related traits was examined by fitting multiple linear regression models adjusting for age, sex, recruitment site and race. In addition, we adjusted for factors known to influence adiposity namely, physical activity and smoking habits. Furthermore, in the analysis of subcutaneous and visceral fat masses, we further adjusted for body height and weight while in the analysis of leptin, we adjusted for the percentage of total body fat. Effect modification by sex and race was evaluated by adding interaction terms to the regression models.

Logistic regression analysis was performed to determine the odds ratios (OR) for prevalent T2D at baseline and the Cox proportional hazards model was used to evaluate the association between oxLDL (measured at baseline) and time to occurrence of incident T2D/obesity during the 7 years of follow-up.

Glucose, HbA1C and insulin levels were log transformed while leptin, visceral and subcutaneous fat masses were transformed into their squared-root equivalent to approximate a normal distribution. Co-linearity of the covariates was checked and determined not to effect inclusion in the models. Also, since multiple closely related dependent variables were tested, a multivariate model was fitted in order to take into check the correlation among closely related variables. A p value < 0.05 was considered significant. All analyses were performed using SPSS for Windows version 14 (SPSS, Chicago, IL, USA).

RESULTS

Measurement of oxLDL at baseline was available in 3,037 subjects. After excluding subjects with missing information on 12 important covariates, 2,985 subjects were included in our analysis.

Table 1 shows the baseline characteristics of the Health ABC cohort by race and sex. An equal proportion of blacks and whites, men and women were recruited at each of the two recruitment sites. Men and women were of similar age. OxLDL was significantly higher in black women compared to black men. The prevalence of T2D was significantly higher in white men compared to white women. Obesity was more common in men compared to women in whites whereas in blacks, it was more prevalent in women compared to men. The mean levels of fasting glucose and HbA1c were significantly higher in white men compared to white women. The mean level of fasting insulin was significantly higher in white men than in women but significantly higher in black women compared to men. In whites and blacks, the mean subcutaneous fat, % total body fat, adiponectin and leptin were significantly higher in women compared to men..

The cross-sectional association between oxLDL, T2D- and obesity-related traits for blacks and whites, as well as for both races combined, at baseline is presented in Table 2. Overall, results for blacks and whites are very similar; therefore, results for both races are described below unless otherwise noted. At baseline, higher oxLDL level was associated with increased odds of having T2D, in particular in whites (OR = 1.2, 95% CI: 0.9 – 1.5, $p < 0.2$

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in blacks and 1.4, 95% CI: 1.1 – 1.6, p <0.003 in whites). OxLDL was also significantly associated with all examined T2D-related quantitative traits ($p < 0.001$). Positive and very significant associations with oxLDL were observed for fasting glucose ($\beta = 0.03 \pm 0.006$), HbA1c ($\beta = 0.02 \pm 0.004$), fasting insulin ($\beta = 0.12 \pm 0.02$) and HOMA-IR ($\beta = 0.13 \pm 0.02$) overall. A negative and significant association was observed between oxLDL and adiponectin (-0.16 ± 0.03), a surrogate measure of insulin sensitivity.

A similar pattern was observed for the cross-sectional association between oxLDL and obesity-related traits. The likelihood of obesity increased significantly with increasing oxLDL levels (OR = 1.3, 95% CI: 1.1 – 1.4, $p < 0.001$). Of 5 obesity-related quantitative traits examined, positive and significant associations were observed between oxLDL and BMI, visceral fat and % total body fat ($\beta = 0.60 \pm 0.14$, 0.29 ± 0.06, and 0.74 ± 0.17, respectively). On the contrary, no significant relationship was observed between oxLDL and subcutaneous fat. Leptin was positively and significantly associated with oxLDL in only whites ($\beta = 0.08 \pm 0.04$, $p = 0.02$) but not in blacks ($\beta = -0.07 \pm 0.04$, $p = 0.1$), p value for interaction between race and oxLDL = 0.02. The magnitude of these associations remained unchanged after adjusting for HDL-cholesterol and triglycerides.

The association between oxLDL measured at baseline and 3 T2D-related traits available after 7 years follow-up is shown in Table 3. There was no significant association between oxLDL at baseline and incident T2D in either race. There was a weak association of oxLDL with fasting glucose and HbA1c in whites ($\beta = 0.02 \pm 0.007$, $p = 0.009$), but not in blacks ($\beta = 0.004 \pm 0.01$, p = NS), p value for interaction between race and oxLDL = 0.5). We further tested for the association between oxLDL measured at baseline and the percentage of changes (Δ) in trait values after 7 years. No significant association between oxLDL at baseline and % Δ fasting glucose was observed in either race, but oxLDL measured at baseline was significantly associated with % Δ HbA1c in whites ($\beta = -1.00 \pm 0.28$, $p < 0.001$, vs. $\beta = 0.06 \pm 0.7$, $p = 0.9$ in blacks), p value for interaction between race and oxLDL = 0.06.

After 7 years of follow up, the association between oxLDL levels measured at baseline was still significantly associated with risk of obesity, BMI and % body fat in both races. Higher oxLDL levels were associated with a significantly increased risk of obesity at follow-up (OR = 1.2, 95% CI: 1.1 – 1.4, $p = 0.003$), higher BMI ($\beta = 0.61 \pm 0.15$, $p < 0.001$) and % total body fat ($\beta = 0.88 \pm 0.18$, $p < 0.001$) measured at follow-up. As observed with baseline data, the magnitude and strength of these associations were stronger in blacks compared to whites. In addition, we also observed that oxLDL was significantly associated with % Δ BMI in whites ($\beta = -0.81 \pm 0.30$, $p = 0.008$) but not in blacks ($\beta = -0.03 \pm 0.4$, $p = 0.9$), p value for interaction between race and oxLDL = 0.1. An association of borderline significance with Δ % total body fat was observed in both races, although slightly stronger in whites ($\beta = -0.75 \pm 0.34$, $p = 0.03$ in whites vs. $\beta = -0.75 \pm 0.34$, $p = 0.09$ in blacks), p value for interaction between race and oxLDL = 0.8.

DISCUSSION

This study investigated the relationship between oxLDL, a marker of systemic oxidative stress, T2D- and obesity-related traits in a bi-racial population. Overall, we found that oxLDL was associated with both T2D-related and obesity-related traits in blacks and whites using both cross-sectional and longitudinal data. With reduced sample sizes available at follow up. We observed an association of oxLDL with fasting glucose and HbA1c in whites but not in blacks, whereas significant associations remained between oxLDL and 2 obesity-related traits (BMI and % total body fat) in both blacks and whites. When % change in trait

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values were examined, oxLDL measured at baseline was significantly associated with all 4 available quantitative traits in whites only.

Earlier cross-sectional studies have reported an increase in levels of oxidative stress markers in T2D patients [18–21]. Our findings confirm previously observed cross-sectional relationship, although we did not observe a significant association between oxLDL and incident T2D, likely due to insufficient power (n = 179 for incident T2D cases). Although fasting glucose levels are in high correlation with HBA1c, the measurement of glucose levels is not as stable as that of HbA1c (reflecting glucose levels over a ~3-month period), which may also affect the power for analyses of fasting glucose. Alternatively, another explanation for the association of oxLDL with T2D may be mediated through insulin resistance. This is evidenced in our study by the positive, strong and significant association between oxLDL and measures of insulin resistance (fasting insulin and HOMA-IR measured at baseline), independent of BMI. Meigs et al. [22] have reported an association between oxidative stress and insulin resistance, impaired fasting glucose and the metabolic syndrome based on cross-sectional data of 2,002 non-diabetic subjects of the community-based Framingham Offspring Study. Another observation supportive of this hypothesis is that we observed that higher oxLDL levels were associated with lower levels of adiponectin, a measure of insulin sensitivity. Unfortunately, we do not have measures of insulin resistance at the follow up, thus we are not able to examine the prospective relationship of oxLDL to insulin resistance. This negative association would have been expected since adiponectin levels are lower in obese people [23] and behave more in counter mechanism as an anti-diabetic and anti-inflammatory hormone [24]. Increased lipid peroxidation has been reported in obese people [10, 25–27]. It has also been reported that in obese subjects with the metabolic syndrome and T2D, oxidative stress is increased and the redox state is a potentially useful therapy [28].

A small study (n = 56 men) had previously reported that visceral adipose tissue accumulation was correlated with circulating levels of oxLDL ($r = 0.52$; $P < 0.0001$) [10]. Increased amount of visceral fat is found to be associated with dyslipidemia and with an increase in small dense LDL that are very susceptible to oxidation [29–31]. Our findings based on a much larger sample support these observations and further show that oxLDL was positively and significantly associated with measure of both global and regional adiposity (BMI, % total body fat and visceral fat). The associations with leptin and subcutaneous fat were much weaker. Interestingly, the correlation between leptin and subcutaneous fat was much greater than between leptin and visceral fat (0.65 vs. 0.22). Our observation that oxLDL was associated with visceral fat but not with subcutaneous fat or leptin may be due to the fact that visceral obesity is more strongly associated with dyslipidemia [32–34]. Hypertriglyceridemia has been commonly reported in visceral obesity [30, 35]. It is known that obesity is associated with increased calorie intake and it is also reported that macronutrients cause oxidative stress following glucose and high fat and high calorie meal [36, 37]. This may well be the link between oxidative stress and obesity.

The major advantages of our study are, first, its population-based design, second, its large sample size (n = 3,037) and third, the prospective nature of the study, which make it possible to verify cross-sectional observations using longitudinally collected data. On the other hand, there are few limitations to this study. OxLDL was measured only at baseline, we were not able to examine whether changes in oxLDL levels may affect the risk for T2D and obesity. Also we did not have repeated measures of insulin and adipocytokines at follow-up to verify the observed cross-sectional associations. Furthermore, as oxLDL is measuring mainly one aspect of oxidative stress (lipid oxidation), it will also be important to examine the effects of markers measuring different aspects of oxidative stress (e.g. DNA and protein oxidation on T2D and obesity.

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In summary, we observed that oxLDL was associated with T2D related traits and also with obesity- related traits based on both cross-sectional and prospective data. The magnitude of the association with obesity related traits at baseline and follow-up was much greater in blacks compared to whites. More interestingly, we found out that oxLDL was significantly associated with % change in T2D and obesity related traits in whites but not in blacks. Why this association was significant in whites but not in blacks is difficult to interpret and warrants further investigations. Our findings suggest the need for more investigations of oxidative stress in the etiology of T2D and its implication in T2D prevention and treatments.

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Table 1

Characteristics of the Health ABC cohort by race and sex at baseline

Traits (mean ± SD or number, %)	Whites		Blacks	
	Male (933)	Female (844)	Male (543)	Female (717)
Recruitment site				
Pittsburgh (PA)	475 (51%)	453 (54%)	269 (50%)	331 (46%)
Memphis (TN)	458 (49%)	391 (46%)	274 (50%)	386 (54%)
Type 2 diabetes (n, %)	216 (23%)	123 (15%)*	174 (32%)	199 (28%)
Obesity (n, %)	180 (19.3%)	143 (16.9%)*	138 (25.4%)	317 (44.2%)*
Age, years	73.9 ± 2.9	73.6 ± 2.8	73.5 ± 2.8	73.4 ± 3.0
Oxidized LDL, mg/dl	1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.7	1.4 ± 0.8*
Glucose, mg/dl	107 ± 33	95 ± 21*	111 ± 42	109 ± 41
HbA1c, %	6.21 ± 0.9	6.02 ± 0.7*	6.81 ± 1.1	6.66 ± 0.3*
Insulin, μIU/ml	8.4 ± 5.7	7.5 ± 5.1*	8.2 ± 5.5	9.7 ± 5.9*
HOMA-IR, mU · mmol/l^2	40.8 ± 39.6	32.6 ± 27.2*	38.9 ± 30.0	45.0 ± 39.8*
Adiponectin, μg/ml	10.3 ± 5.7	15.5 ± 7.2*	8.0 ± 5.3	10.7 ± 6.7*
BMI, kg/m^2	27.0 ± 3.7	26.0 ± 4.5	27.2 ± 4.4	29.7 ± 5.9*
Total percent fat, %	28.7 ± 4.8	39.0 ± 5.6*	26.8 ± 5.3	40.0 ± 6.1*
Leptin, ng/ml	7.6 ± 6.3	16.1 ± 10.5*	8.0 ± 6.4	21.3 ± 11.8*
Visceral fat, cm^2	170 ± 71	132 ± 63*	130 ± 67	130 ± 59
Subcutaneous fat, cm^2	229 ± 84	308 ± 109*	237 ± 100	372 ± 138*

*Men vs. women, p<0.001

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Table 2

Association between oxidized LDL and T2D- and obesity-related traits at baseline

	Blacks		Whites		Overall	
Trait	**β ± S.E.**	**P**	**β ± S.E.**	**P**	**β ± S.E.**	**P**
Type 2 diabetes[#]	*1.2 (0.9 – 1.5)*	*0.2*	*1.4 (1.1 – 1.6)*	*0.003*	*1.3 (1.1 – 1.5)*	*0.001*
Fasting glucose[*]	0.02 ± 0.01	0.03	0.03 ± 0.007	<0.001	0.03 ± 0.006	<0.001
HbA1c[*]	0.02 ± 0.007	0.02	0.02 ± 0.004	<0.001	0.02 ± 0.004	<0.001
Fasting Insulin[*]	0.11 ± 0.03	<0.001	0.13 ± 0.02	<0.001	0.12 ± 0.02	<0.001
HOMA-IR[*]	0.13 ± 0.03	<0.001	0.17 ± 0.02	<0.001	0.13 ± 0.02	<0.001
Adiponectin[†]	−0.11 ± 0.04	0.004	−0.17 ± 0.03	<0.001	−0.16 ± 0.03	<0.001
Obesity[#]	*1.3 (1.1 – 1.5)*	*0.007*	*1.3 (1.1 – 1.5)*	*0.007*	*1.3 (1.1 – 1.4)*	*<0.001*
BMI	0.60 ± 0.24	0.01	0.49 ± 0.17	0.003	0.60 ± 0.14	<0.001
% total body fat	0.85 ± 0.27	0.002	0.56 ± 0.21	0.009	0.74 ± 0.17	<0.001
Leptin[†]	−0.07 ± 0.04	0.1	0.08 ± 0.04	0.02	0.02 ± 0.03	0.5
Visceral fat[†]	0.21 ± 0.09	0.03	0.35 ± 0.08	<0.001	0.29 ± 0.06	<0.001
Subcutaneous fat[†]	0.17 ± 0.09	0.06	0.008 ± 0.08	0.9	0.08 ± 0.06	0.2

[#]For type 2 diabetes and obesity, values are odds ratios with 95% confidence interval.

[*]Values were Log transformed.

[†]Values were transformed into their squared-root equivalent.

Model: diabetes related trait = age + sex + race + site + BMI + education + CRP + physical activity + LDL + oxLDL + T2D Rx.

Adiposity related trait = age + sex + race + site + smoking + physical activity + LDL + oxLDL.

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Table 3

Association between oxidized LDL at baseline and T2D- and obesity-related traits after 7 years of follow-up

	Blacks		Whites		Overall	
Traits	**β ± S.E.**	**P**	**β ± S.E.**	**P**	**β ± S.E.**	**P**
Incident type 2 diabetes[#]	*1.2 (0.9 – 1.6)*	*0.3*	*1.0 (0.7 – 1.3)*	*0.7*	*1.1 (0.9 – 1.4)*	*0.3*
Fasting glucose[*]	0.004 ± 0.01	0.8	0.02 ± 0.007	0.009	0.08 ± 0.05	0.1
% Δ Fasting glucose	−1.4 ± 1.6	0.4	−1.3 ± 0.7	0.07	−1.25 ± 0.60	0.04
HbA1c[*]	0.02 ± 0.008	0.06	0.01 ± 0.004	0.003	0.01 ± 0.003	<0.001
% Δ in HbA1c	0.06 ± 0.7	0.9	−1.0 ± 0.28	<0.001	−0.64 ± 0.30	0.03
Obesity[#]	*1.2 (1.0 – 1.5)*	*0.03*	*1.2 (1.0 – 1.4)*	*0.07*	*1.2 (1.1 – 1.4)*	*0.003*
BMI	0.83 ± 0.26	0.001	0.41 ± 0.17	0.01	0.61 ± 0.15	<0.001
% Δ in BMI	−0.03 ± 0.4	0.9	−0.81 ± 0.30	0.008	−0.51 ± 0.24	0.03
% Total body fat	1.06 ± 0.29	<0.001	0.72 ± 0.21	0.001	0.88 ± 0.18	<0.001
% Δ Total body fat	−0.86 ± 0.51	0.09	−0.75 ± 0.34	0.03	−0.82 ± 0.29	0.004

[#]For type 2 diabetes and obesity, values are odds ratios with 95% confidence interval.

[*]Values were Log transformed.

Model: diabetes related trait = age + sex + race + site + BMI + education + CRP + physical activity + LDL + oxLDL + T2D Rx.

Adiposity related trait = age + sex + race + site + smoking + physical activity + LDL + oxLDL.