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# Association of apolipoprotein C3 with insulin resistance and coronary artery calcium in patients with type 1 diabetes

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## Abstract

**Background:** Apolipoprotein C3 (APOC3) is a risk factor for incident coronary artery disease in people with type 1 diabetes (T1D). The pathways that link elevated APOC3 levels to an increased risk of incident CVD in people with T1D are not understood.

**Objective:** To explore potential mechanisms, we investigated the association of APOC3 with insulin resistance and coronary artery calcium (CAC).

**Methods:** In a random sub-cohort of subjects with T1D from Coronary Artery Calcification in Type 1 Diabetes (CACTI) (n=134), serum APOC3, HDL-associated APOC3, and retinol binding protein 4 (RBP4; a potential marker of insulin resistance) were measured by targeted mass spectrometry. We used linear regression to evaluate associations of serum APOC3 and HDL-APOC3 with APOB, non-HDL cholesterol, serum- and HDL-associated RBP4, estimated insulin sensitivity (eIS), and logistic regression to evaluate association with presence of CAC, adjusted for age, sex, and diabetes duration.

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Author Contributions

T.B. and B.S. performed experiments and data analysis. J.S-B. and K.E.B. conceived the study. T.B. wrote the manuscript. K.E.B., J.S-B., J.W.H., and R.H.E. reviewed/edited the manuscript. J.S-B. is the guarantor of this work and, as such, had full access to all the study's data and takes responsibility for data integrity and accurate analysis.



Conflict of Interest

The authors have no conflicts of interest to disclose.

**Results:** Serum APOC3 correlated positively with APOB and non-HDL cholesterol and was associated with increased odds of CAC (OR: 1.68, $p$=0.024). eIS was not associated with serum- or HDL-RBP4 but was negatively associated with serum APOC3 in males (ß estimate: −0.318, $p$=0.0040) and decreased odds of CAC (OR: 0.434, $p$=0.0023).

**Conclusions:** Serum APOC3 associates with increased insulin resistance and CAC in T1D.

### Keywords

apolipoproteins; diabetes; epidemiology; insulin resistance; HDL

## Introduction

Cardiovascular disease (CVD) is a major contributor to mortality in type 1 diabetes (T1D)[1,2]. Although dyslipidemia increases the risk of CVD[3], patients with T1D usually have normal lipid profiles. Therefore, it is critical to identify factors associated with CVD development in this form of diabetes.

Apolipoprotein C3 (APOC3) is associated with triglyceride-rich lipoproteins (TRLs; VLDL, chylomicrons and their remnant lipoproteins), LDL, and HDL. Importantly, APOC3 is exchangeable between lipoproteins. During lipolysis of TRLs, APOC3 is transferred to HDL. However, APOC3 is not uniformly distributed among different HDL populations[4]. APOC3 inhibits lipoprotein lipase, slowing the hydrolysis of triglycerides in TRLs and the conversion of VLDL to LDL in plasma[5–8]. It also prevents hepatic clearance of TRLs through LDL family receptors[9–12]. We recently demonstrated that total serum APOC3 levels —but not HDL-associated APOC3—predict incident coronary artery disease (CAD) in a cohort of T1D patients in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study[13]. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, both total serum APOC3 and HDL-associated APOC3 nominally associated with incident CVD in subjects with T1D[14]. In both studies, APOC3 associated with CVD risk in subjects with T1D and normal or near-normal plasma triglyceride levels. Other studies have demonstrated that APOC3 associated with HDL predicts CVD risk in subjects without T1D[15]. Importantly, inhibiting APOC3 by an antisense oligonucleotide reduced triglyceride levels and prevented atherosclerosis in a mouse model of T1D[13]. The APOC3 antisense therapeutic volanesorsen has likewise been shown to lower triglyceride levels in human cohorts[16,17]. These studies point to APOC3 as an important CVD risk factor and mediator in T1D. The reason APOC3 predicts CVD risk in subjects with T1D is unknown.

It is well established that insulin resistance increases the risk of CVD in T1D[18–20]. Although patients with T1D often have normal lipoprotein profiles, decreased insulin sensitivity during adolescence and adulthood associates with higher triglyceride levels and a more atherogenic lipoprotein profile[21]. A prospective study of 603 patients with T1D involved in the Pittsburgh Epidemiology of Diabetes Complications Study found that insulin resistance (but not glycemia) was positively associated with risk of CAD events[22]. However, there are many unanswered questions about the interplay among apolipoproteins, insulin sensitivity,

and CVD risk in T1D. A goal of this study was to investigate the links among APOC3, insulin resistance and coronary artery calcium (CAC) in T1D.

Retinol binding protein 4 (RBP4), a retinol transport protein believed to deliver retinol from the liver to peripheral tissues[23], is a potential biomarker of insulin resistance. Thus, it has been associated with insulin resistance in type 2 diabetes[24,25], in individuals with and without obesity[26,27], and in gestational diabetes[28]. RBP4 has also been suggested as a biomarker of insulin resistance in women with polycystic ovary syndrome[29]. RBP4 may lead to vascular damage related to reduced insulin sensitivity[30]. Insulin treatment in T1D is associated with lower RBP4 synthesis[31]. RBP4 is not associated with APOB containing lipoproteins in humans, but small amounts coelute with HDL after separation by high-resolution size exclusion fast protein liquid chromatography[32]. It is not known whether RBP4 can serve as a marker of insulin resistance in T1D and whether it associates with CVD. We therefore included RBP4 in our analyses.

The current study therefore aimed to test associations among serum- and HDL-associated APOC3, APOB, serum- and HDL-associated RBP4, estimated insulin sensitivity, and CAC in people with T1D.

## Materials and Methods

### Study Design

CACTI is a prospective cohort study of 1,420 participants (656 participants with T1D and 764 without T1D) followed for risk factors of heart disease in those with T1D[33]. Participants recruited into the study were asymptomatic for CAD and did not have a history of coronary artery bypass graft, coronary angioplasty, or unstable angina. Those with T1D were diagnosed before the age of 30, had positive auto-antibodies or had a clinical course consistent with T1D. All participants with T1D were treated with insulin within 1 year of diagnosis. A sub-cohort (n=134) of subjects with T1D was randomly selected from CACTI for this study.

### Laboratory Measurements

Blood was collected after an overnight fast and centrifuged; separated plasma was stored at 4ºC until assayed. Standard enzymatic methods were used to measure total cholesterol and triglyceride levels. HDL cholesterol (HDL-C) was quantified through separating plasma with dextran sulfate. HbA1c was measured through high-performance liquid chromatography, as described previously[34]. Levels of APOB were measured through a Beckman Array Nephelometer (Beckman Coulter Inc., Brea, CA). Non-HDL cholesterol was calculated as total cholesterol minus HDL-C. Adiponectin was measured by a radioimmunoassay (LINCO Research, Inc., St. Charles, MO), as described previously[35]. Estimated insulin sensitivity (eIS) was calculated using a validated prediction equation[36] using the formula eIS = exp(4.06154 − 0.01317 * waist [cm] − 1.09615 * insulin dose [daily units per kg] + 0.02027 * adiponectin [μg/mL] − 0.27168 * triglycerides [mmol/L (−0.00307 for mg/dL)] − 0.00733 * DBP [mm Hg]).

### Serum APOC3 and RBP4 Measurements by Targeted Mass Spectrometry

Serum APOC3 and RBP4 were measured using liquid chromatography-electrospray ionization targeted mass spectrometry with $^{15}$N-labeled APOA1 as the standard. In short, parallel reaction monitoring (PRM) was used to measure and quantify serum APOC3 and RBP4 as described previously[13]. Two selected peptides from each protein[37] was used for the quantitative analysis by PRM. The relative levels of each peptide were calculated by the ratio of the total peak area of all the transitions for each peptide to the total peak area of all the transitions from [$^{15}$N]THLAPYSDELR (the internal standard peptide derived from [$^{15}$N]APOA1). To calculate the relative levels of the peptide, we set the average ratio of the peptide in the sub-cohort of subjects with diabetes to an arbitrary unit of 1. To obtain the relative levels of APOC3 and RBP4, the relative levels of the 2 peptides from the protein were averaged.

### HDL Isolation and the Measurement of HDL-APOC3 and HDL-RBP4

Isolation of HDL was completed through sequential ultracentrifugation using freshly thawed serum, as previously described [38]. Isolated HDL was used to measure HDL-associated APOC3 and RBP4 using liquid chromatography-electrospray ionization targeted tandem mass spectrometry. The isolated HDL was digested as previously reported[37] and targeted PRM analysis was used to measure and quantify HDL-associated APOC3 and RBP4 as described above for serum proteomics and as previously reported[13].

### Coronary Artery Calcium (CAC) Measurements

CAC was measured through an ultrafast Imatron C-150XLP EBCT scanner (Imatron, San Francisco, CA). A 100-ms exposure was used for two sets of high resolution, non-contrast, contiguous 3-mm tomographic images starting near the lower margin of bifurcation of the main pulmonary artery. Calcified coronary arteries were defined as having a minimum density of 130 Hounsfeld units (HU) and a minimum area of three pixels (1.03 mm$^2$). The density score (1 for 130–199, 2 for 200–299, 3 for 300–399, and 4 for >399 Hounsfield units) was multiplied by the area to calculate the calcium score. The total CAC score was calculated in Agatston units by summing scores from left main, left anterior descending, circumflex, and right coronary arteries[39]. CAC was assessed as a binary variable of present or absent. Full methods have been described previously[40].

### Statistical Analysis

SAS version 9.4 (SAS institute, Cary, NC, USA) was used for statistical analyses. Demographics were described for all subjects. Serum APOC3 and HDL-APOC3 were log-transformed. Pearson correlation coefficients were calculated between eIS and APOB, APOC3, non-HDL cholesterol, and RBP4. Next, a linear regression framework was used to assess the association between APOB, APOC3, non-HDL cholesterol, and RBP4 with eIS. We also used a linear regression framework to test the association between non-HDL cholesterol and RBP4 and APOC3. Standardized beta estimates are presented. CAC was tested as a binary variable (presence/absence) in a logistic regression framework. Models were adjusted for age, sex, and diabetes duration. Because triglycerides were utilized in estimation of insulin sensitivity, analyses were not adjusted for triglycerides. Odds ratios

represent the odds of having CAC for each one standard deviation increase in the predictor. An interaction term of the apolipoproteins and sex was tested for each outcome in the fully adjusted model. If the interaction term was significant, results were stratified by sex. PROC GLM was used for linear regression analyses, and PROC LOGISTIC was used for logistic regression analyses. A significance level of $p<0.05$ was used for all analyses.

## Results

Participant characteristics and demographics are described by sex in Table 1. Systolic and diastolic blood pressure and waist circumference were significantly higher in males, whereas eIS, HDL-C and adiponectin were significantly higher in females. Serum APOB and RBP4 were significantly higher in males, but there were no gender differences in levels of non-HDL cholesterol (total cholesterol - HDL-C), LDL-cholesterol, triglycerides, serum APOC3, HDL-associated APOC3, or HDL-associated RBP4 (Table 1). Triglycerides were not significantly different between males and females, and median triglyceride levels were within the normal range in both groups. Of the 134 subjects included in our study, 20 reported HMG-CoA reductase inhibitor dose with a range of 5–40 mg/day and a mode of 20 mg/day (doses were normalized to simvastatin equivalents).

To determine how insulin resistance is related to apolipoproteins and other lipid-related biomarkers, we tested the correlation between eIS, apolipoproteins, non-HDL cholesterol, and RBP4 in an unadjusted model. HDL-APOC3 was not significantly correlated with eIS (Pearson correlation coefficient: −0.16 $p$=0.0734). However, APOB (Pearson correlation coefficient: −0.29, $p$=0.0008), serum APOC3 (Pearson correlation coefficient: −0.21, $p$=0.018), and non-HDL cholesterol (Pearson correlation coefficient: −0.30, $p$=0.0005) all correlated significantly and negatively with eIS. eIS was not significantly correlated with serum RBP4 (Pearson correlation coefficient: −0.0020, $p$=0.9819) or HDL-associated RBP4 (Pearson correlation coefficient: 0.0011, $p$=0.9901).

Next, we tested the association of the biomarkers APOB, APOC3, non-HDL cholesterol, and RBP4 with eIS in a model adjusted for age, sex, and diabetes duration. In these models we tested for interaction terms with sex, and only the interaction for serum APOC3 and sex was significant (Table 2). After adjustments for age, sex, and diabetes duration, APOB, non-HDL cholesterol, and serum APOC3 in males significantly and negatively associated with eIS. Neither HDL-associated APOC3, serum RBP4, nor HDL-associated RBP4 were significantly associated with eIS.

We then assessed the outcome of CAC with apolipoproteins, non-HDL cholesterol, and RBP4 adjusted for age, sex, and diabetes duration. None of the results differed by sex, as tested through an interaction term. Serum APOC3, APOB, and non-HDL cholesterol significantly and positively associated with CAC (Table 3). HDL-APOC3 and serum- and HDL-RBP4 were not significantly associated with the presence of CAC. We also assessed the association of APOC3 with APOB and non-HDL cholesterol after adjustments for age, sex, and diabetes duration. APOB and non-HDL cholesterol significantly and positively associated with serum APOC3. However, they did not associate with HDL-associated APOC3 (Table 4). Both serum- and HDL-associated RBP4 were significantly associated

with HDL-associated APOC3 (p<0.0001) and serum APOC3 (p<0.0001) (Table 4). Finally, we tested the association between eIS and CAC after adjustments for age, sex, and diabetes duration. None of the results for CAC differed by sex, as tested through an interaction term. Reduced eIS was significantly associated with increased odds of having CAC (OR: 0.434, $p$=0.0023).

## Discussion

Our data indicate that serum APOC3 is negatively associated with insulin sensitivity and positively associated with APOB and non-HDL cholesterol in participants with T1D. Furthermore, serum APOC3 positively associated with CAC. These results are consistent with our recent studies showing that serum APOC3 predicts CAD events in a cohort of T1D CACTI subjects, independently of age, sex, diabetes duration, blood glucose control measured as HbA1c, blood pressure, smoking, and LDL- and HDL-cholesterol, but not independently of triglycerides[13]. They are also consistent with the findings that relative insulin deficiency or insulin resistance, rather than hyperglycemia, is the cause of increased APOC3 levels in diabetic mice[13].

Our study also revealed that the negative association of serum APOC3 and insulin sensitivity in a model adjusted for age and diabetes duration was statistically significant in males and not in females. It is therefore possible that APOC3 is more closely associated with insulin resistance in males with T1D than in females with T1D, perhaps because males were significantly more insulin resistant than females in this study. The reason for the increased APOC3 in females with T1D and increased CVD risk will need further investigation.

Neither serum RBP4 nor HDL-associated RBP4 was associated with eIS or the presence of CAC in this study. There is evidence that RBP4 may not be a marker of insulin resistance in all populations[41]. For example, Broch et al. demonstrated that serum RBP4 was associated with insulin secretion, but not insulin sensitivity[26]. In Mexican Americans, RBP4 was not associated with insulin resistance as measured by oral glucose tolerance test and euglycemic insulin clamp[42]. Additionally, Korek et al. found that in obese and non-obese subjects, RBP4 was not associated with insulin resistance measured as HOMA-IR, but was associated with triglycerides[43]. Similarly, RBP4 has been associated with triglycerides and renal function in patients with chronic kidney disease, but RBP4 was not associated with insulin resistance after adjusting for kidney function[44]. We found that serum RBP4 and HDL-RBP4 were significantly associated with both serum APOC3 and HDL-associated APOC3. The association between RBP4 and triglycerides may be related to its association with APOC3. The fact that RBP4 is mainly associated with HDL, and not with APOB-lipoproteins[32] suggest that the relationship between APOC3 and RBP4 is not due to a direct physical association.

Others have studied the relationship between apolipoproteins and insulin resistance. For example, in children and adolescents with type 2 diabetes, lipoproteins containing APOB and APOC3 associated with increased insulin resistance[45]. Importantly, it may be insulin resistance—and not glucose levels—that is at the root of this relationship in T1D[13,37]. Although our study does not establish temporality between apolipoprotein levels and insulin

resistance, we hypothesize that insulin resistance leads to increased APOC3, as supported by murine models[13].

Our study shows that eIS is negatively associated with CAC. It is known that insulin resistance in T1D is associated with an increased risk of CVD[19] and that poor glycemic control is associated with increased mortality and cardiovascular events[46,47]. Other studies are consistent with the interpretation that patients with T1D who gain weight exhibit an increased risk of total CVD events over time that may be attributed to obesity-related CVD risk factors, such as insulin resistance[20]. Lipoproteins and plasma lipids are known to mediate a significant CVD risk in T1D[48]. In our study, serum APOC3 was negatively associated with insulin sensitivity and positively associated with CAC. The relationship between HDL-associated APOC3 and insulin sensitivity and CAC was not statistically significant, but the associations were trending in the same direction as that of serum APOC3. In another recent study of T1D subjects in the DCCT-EDIC cohort, both total APOC3 and HDL-associated APOC3 (measured as heparin-soluble APOC3) predicted CVD events when the model was adjusted for age, mean HbA1c, triglycerides, and LDL-C. In that study, APOC3 associated with LDL and VLDL (heparin-insoluble APOC3) did not predict CVD events[14]. The relative role for APOC3 in lipoproteins containing APOB (such as LDL, TRLs and their remnants) versus that for APOC3 in HDL thus needs further study. APOC3 readily redistributes between non-HDL lipoprotein particles and HDL during TRL hydrolysis, and HDL is believed to act as a reservoir for APOC3. Further studies are also needed to elucidate whether APOC3 directly affects vascular cells or whether its effects on lipoprotein metabolism mediate the cellular changes.

How might non-HDL cholesterol lipoproteins containing APOC3 and APOB promote atherosclerosis in the setting of T1D? Increased APOB and non-HDL cholesterol predicted cardiovascular risk in children with T1D[49], and in the CACTI study, APOB and non-HDL cholesterol were complementary predictors of CVD risk[50]. Another small study demonstrated that patients with T1D had higher fasting levels of APOB48 than controls, indicating the accumulation of chylomicron remnants[51]. Mouse studies support the concept that remnant lipoproteins containing APOB, APOC3, and APOE accumulate in the artery wall during diabetes[13]. Our study provides further evidence that serum APOC3 associates with increased risk of cardiovascular events in T1D. Impaired insulin signaling in T1D may lead to a more atherogenic lipid profile, increasing the risk of cardiovascular events. Alternatively, APOC3 might worsen insulin sensitivity, as observed in a small study of subjects with type 2 diabetes treated with the APOC3 antisense therapeutic volanesorsen[52].

Limitations of this study include the small sample size. Thus, sub-group sex interaction analyses may be under-powered. The lack of statistical significance does not preclude the possibility that a statistically significant association could be found in a larger dataset.

## Conclusions

Our results are consistent with the proposal that increased APOC3 in T1D associates with insulin resistance, APOB, and non-HDL cholesterol. RBP4 is not a marker of insulin

resistance in T1D but is significantly associated with levels of APOC3. Moreover, serum APOC3, APOB, and non-HDL cholesterol associate with increased odds of having CAC.

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## Data availability statement

Data will be shared upon request (contact: Teresa Buckner, teresa.buckner@cuanschutz.edu)

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## Highlights

- Insulin resistance associates with coronary artery calcium (CAC) in type 1 diabetes
- APOC3 associates with increased insulin resistance in adults with type 1 diabetes
- APOC3 associates with the presence of CAC in the same subjects

**Table 1:**

Patient Variables by Sex

| Variable | Male (n=63) | Female (n=71) | p-value |
|---|---|---|---|
| Age (years)* | 37.4±9.1 | 36.7±8.9 | 0.64 |
| T1D Duration (years)* | 22.8±8.4 | 23.8±7.9 | 0.49 |
| Race (NHW)† | 65 (98.5%) | 75 (94.9%) | 0.24 |
| Current Smokers† | 9 (13.9%) | 8 (10.1%) | 0.49 |
| Ever Smokers† | 12 (18.5%) | 21 (26.6%) | 0.25 |
| Hypertension† | 38 (57.6%) | 34 (43.0%) | 0.081 |
| **Average Systolic BP (mm Hg)*** | **123.9±16.1** | **113.9±13.7** | **<0.0001** |
| **Average Diastolic BP (mm Hg)*** | **81.2±8.8** | **74.8±8.3** | **<0.0001** |
| CAC (present)† | 28 (42.2%) | 26 (32.9%) | 0.24 |
| On lipid-lowering medications† | 15 (22.7%) | 11 (13.9%) | 0.17 |
| On HMG-CoA reductase inhibitors† | 14 (21.2%) | 10 (12.7%) | 0.17 |
| On anti-hypertensive medications† | 30 (45.5%) | 30 (37.9%) | 0.36 |
| BMI (kg/m$^2$)* | 27.0±4.1 | 25.7±4.6 | 0.056 |
| **Average Waist Circumference (cm)*** | **91.4±10.4** | **81.3±12.1** | **<0.0001** |
| HbA1C (%)‡ | 7.5 (6.9, 8.2) | 7.5 (6.9, 8.4) | 0.64 |
| Insulin Dose (units/day/kg body wt)* | 0.69±0.24 | 0.62±0.32 | 0.14 |
| **Adiponectin (μg/mL)*** | **12.8±7.5** | **17.3±8.5** | **0.0010** |
| **eIS (mg/kg/min)‡** | **4.7 (3.2, 6.4)** | **7.3 (5.4, 9.8)** | **<0.0001** |
| Plasma Lipid Panel: | | | |
| Total cholesterol (mg/dL)* | 169.4±37.4 | 171.4±30.4 | 0.72 |
| LDL cholesterol (mg/dL)* | 100.4±31.3 | 93.3±25.1 | 0.13 |
| **HDL cholesterol (mg/dL)*** | **48.3±12.5** | **60.6±16.4** | **<0.0001** |
| Triglycerides (mg/dL)‡ | 85 (59, 112) | 70 (55, 99) | 0.19 |
| **APOB (mg/dL)*** | **94.0±27.3** | **83.9±19.1** | **0.010** |
| HDL APOC3 (AU)‡§ | 0.89 (0.60, 1.17) | 0.95 (0.68, 1.33) | 0.46 |
| Serum APOC3 (AU)‡§ | 0.88 (63, 1.19) | 0.99 (0.75, 1.17) | 0.54 |
| Non-HDL cholesterol (mg/dL)* | 119.4±34.9 | 110.8±27.9 | 0.10 |
| **Serum RBP4 (AU)*§** | **1.17±0.48** | **0.88±0.41** | **0.0001** |
| HDL RBP4 (AU)*§ | 1.06±0.58 | 0.99±0.49 | 0.40 |

Numbers presented as mean±SD(*), median (25$^{th}$, 75$^{th}$ percentile)‡ or number (%)†

§AU, arbitrary unit (measured as fold changes with mean set to 1)

Significant differences are indicated by bold font

**Table 2:**

Association of apolipoproteins, non-HDL cholesterol, and RBP4 with eIS (mg/kg/min)

| Predictor | | ß estimate | p-value |
|---|---|---|---|
| **APOB (mg/dL)** | | **−0.342** | **<0.0001** |
| HDL APOC3 (AU)[§*] | | −0.122 | 0.13 |
| Serum APOC3 (AU)[§] | Overall | −0.131 | 0.0906 |
| | **Male** | **−0.318** | **0.0040** |
| | Female | 0.049 | 0.65 |
| **Non-HDL cholesterol (mg/dL)** | | **−0.320** | **<0.0001** |
| Serum RBP4 (AU)[§] | | −0.014 | 0.86 |
| HDL RBP4 (AU)[§] | | −0.023 | 0.78 |

All models adjusted for age, sex, and diabetes duration

Significant differences are indicated by bold font

[§]AU, arbitrary unit (measured as fold changes with mean set to 1)

[*]Overall F test p-value was 0.08

**Table 3:**

Association of apolipoproteins and non-HDL cholesterol with CAC

| Predictor | SD | Odds Ratio (95% CI) | p-value |
|---|---|---|---|
| **APOB (mg/dL)** | **23.60** | **1.602 (1.052, 2.439)** | **0.028** |
| HDL APOC3 (AU)[§] | 0.612 | 1.514 (0.972, 2.357) | 0.070 |
| **Serum APOC3 (AU)[§]** | **0.621** | **1.681 (1.070, 2.640)** | **0.024** |
| **Non-HDL cholesterol (mg/dL)** | **31.47** | **1.550 (1.014, 2.370)** | **0.043** |
| Serum RBP4 (AU)[§] | 0.463 | 1.390 (0.568, 3.401) | 0.47 |
| HDL RBP4 (AU)[§] | 0.531 | 1.239 (0.553, 2.778) | 0.60 |

All models adjusted for age, sex, and diabetes duration

Significant differences are indicated by bold font

[§]AU, arbitrary unit (measured as fold changes with mean set to 1)

**Table 4:**

Association of APOB and non-HDL cholesterol with APOC3

| **HDL APOC3 (AU)**[§] | | |
|---|---|---|
| **Predictor** | **ß estimate** | **p-value** |
| APOB (mg/dL) | 0.135 | 0.10 |
| Non-HDL cholesterol (mg/dL) | 0.131 | 0.12 |
| **Serum RBP4 (AU)**[§] | **0.556** | **<0.0001** |
| **HDL RBP4 (AU)**[§] | **0.752** | **<0.0001** |
| **Serum APOC3 (AU)**[§] | | |
| **Predictor** | **ß estimate** | **p-value** |
| **APOB (mg/dL)** | **0.282** | **0.0006** |
| **Non-HDL cholesterol (mg/dL)** | **0.288** | **0.0005** |
| **Serum RBP4 (AU)**[§] | **0.630** | **<0.0001** |
| **HDL RBP4 (AU)**[§] | **0.391** | **<0.0001** |

All models adjusted for age, sex, and diabetes duration

Significant differences are indicated by bold font

[§]AU, arbitrary unit (measured as fold changes with mean set to 1)