Published in final edited form as:

Metabolism. 2016 March ; 65(3): 92–99. doi:10.1016/j.metabol.2015.10.017.

Associations of Insulin Resistance, Inflammation and Liver Synthetic Function with Very Low Density Lipoprotein: The Cardiovascular Health Study

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Abstract

Introduction—Production of very low density lipoprotein (VLDL) is increased in states of metabolic syndrome, leading to hypertriglyceridemia. However, metabolic syndrome is often associated with non-alcoholic fatty liver disease, which leads to liver fibrosis and inflammation that may decrease VLDL production. In this study, we aim to determine the interactive impact on VLDL profiles from insulin resistance, impairment in liver synthetic function and inflammation.

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Conflict of interest / financial disclosure

Authors declare no conflict of interest pertinent to this study

Writing assistance

No writing assistance involved in preparation of the manuscript

Author contributions

ZGJ, IHB, RHM, LHK, KJM are involved in study design and data analysis; All authors are involved in data interpretation and manuscript preparation.

Methods—We examined cross-sectional associations of insulin sensitivity, inflammation, and liver synthetic function with VLDL particle (VLDL-P) concentration and size among 1,850 older adults in the Cardiovascular Health Study.

Results—Indices for high insulin sensitivity and low liver synthetic function were associated with lower concentrations of VLDL-P. In addition, insulin resistance preferentially increased concentration of large VLDL and was associated with mean VLDL size. Indices for inflammation however demonstrated a nonlinear relationship with both VLDL-P concentration and VLDL size. When mutually adjusted, one standard deviation (SD) increment in Matsuda index and C-reactive protein (CRP) were associated with 4.9 nmol/L (−8.2 – −1.5, $p = 0.005$) and 6.3 nmol/L (−11.0 – −1.6, $p = 0.009$) lower VLDL-P concentration respectively. In contrast, one-SD increment in factor VII, a marker for liver synthetic function, was associated with 16.9 nmol/L (12.6 – 21.2, $p < 0.001$) higher VLDL-P concentration. Furthermore, a one-SD increment in the Matsuda index was associated with 1.1 nm (−2.0 – −0.3, $p = 0.006$) smaller mean VLDL size, whereas CRP and factor VII were not associated with VLDL size.

Conclusion—Insulin sensitivity, inflammation and markers for liver synthetic function differentially impact VLDL-P concentration and VLDL size. These results underscore the complex effects of insulin resistance and its complications on VLDL production.

Keywords

Very low density lipoprotein (VLDL); triglyceride; insulin resistance; metabolic syndrome; liver synthetic function; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH)

Introduction

Hypertriglyceridemia secondary to increased very low density lipoprotein (VLDL) production is a hallmark of metabolic syndrome.[1] Based on lipoprotein subclass profiling via nuclear magnetic resonance, higher concentrations of large VLDL particles (VLDL-P) and larger mean VLDL size are associated with impaired glucose tolerance, insulin resistance and the incidence of type 2 diabetes.[2–6] Insulin resistance drives an increase in VLDL production by the loss of negative regulation on apolipoprotein production, an increase in hepatic lipid load from high circulating free fatty acids, and delayed catabolism of VLDL and chylomicrons in the circulation. [7–9]

However, as a product solely from the liver, the secretion of VLDL is also susceptible to other pathophysiological processes that accompany insulin resistance, including impaired liver synthetic function and inflammation. These processes manifest in non-alcoholic fatty liver disease (NAFLD), which is closely related to metabolic syndrome. NAFLD includes a spectrum of diseases including simple steatosis, steatohepatitis (NASH), an inflammatory state of liver parenchyma, and cirrhosis, the end stage of liver disease with significantly impaired synthetic function. [10–12] Impaired liver synthetic function leads to decreased production of circulating proteins and macromolecules, such as albumin, coagulation factors (factor VII, fibrinogen, etc.) and lipoproteins (VLDL and high density lipoprotein). In fact, both NASH and cirrhosis have been associated with decreased levels of apolipoprotein B,

and lower levels of both VLDL and LDL cholesterol.[13–15] Fujita and coworkers have proposed that dysfunctional VLDL synthesis and release is a key factor in NASH pathogenesis.[15] We have observed a robust inverse association between fasting triglyceride and indices of liver fibrosis in US adults.[16] Others have reported associations between low VLDL particle concentration and advanced liver fibrosis.[17] Thus, insulin resistance and its complications can potentially influence VLDL production in complex and potentially contradictory ways.

Despite these insights, the interactive impact on VLDL production by insulin sensitivity, liver synthetic function and inflammation have not been studied together. For instance, it is unclear how inflammation and liver synthetic function correlate with VLDL profile, as both processes are tightly associated with insulin resistance in the setting of NAFLD. Herein, we aim to define and quantify the relationships between VLDL profiles and these three critical physiologies using data from the Cardiovascular Heart Study (CHS), a population-based cohort of community-dwelling adults aged 65 and older from across the U.S.[18, 19]. We hypothesized that insulin resistance would be associated with higher VLDL concentration, while inflammation and lower synthetic function would be associated with lower concentrations.

Methods

Study participants

CHS is a prospective study of 5,888 participants, age 65 years or older, recruited from Medicare-eligibility lists in four communities in the United States. The original CHS study design and objectives have been reported elsewhere.[18] CHS exclusion criteria included: institutionalization, inability to provide informed consent, intention to move outside the enrollment area within 3 years, wheelchair-bound within the home, hospice care, or current chemotherapy or radiation for cancer at the time of enrollment. Baseline examinations conducted at the time of enrollment included standardized medical history questionnaires, physical examination and laboratory examination. All study participants gave informed consent without the need for proxy at enrollment (1989–1993). No additional consent was obtained for this study as all data necessary for analysis was available, and we obtained institutional board review for analyses of these previously collected data. We included all original CHS participants were included in the study, with exception for those with missing variables necessary for analysis. In addition, we excluded individuals on anti-diabetic medication for the analysis of insulin resistance and those on warfarin for the analysis of factor VII. These situations have been specified in detail below. The study was approved by the institutional review board at each participating center.

Measurement of plasma VLDL profiles

Fasting plasma VLDL profiles were measured at LabCorp (Raleigh, NC; previously known as LipoScience) using NMR spectroscopy and Lipoprofile 3 algorithm.[6, 20] A total of 1,850 plasma specimens from the baseline examination were analyzed to determine the lipoprotein subclass concentrations as part of a nested case-control study.[21] The selection and composition of this subgroup had been described previously.[22] Lipoprotein subclass

concentration was determined based on the amplitude of proton spectra corresponding to the hydrocarbon methyl groups that have been calibrated using lipoprotein standards.[20, 23] Concentrations of VLDL particles (nmol/l) were quantified as: large VLDL (> 60 nm), medium VLDL (42–60 nm), and small VLDL (29–42 nm), with total VLDL-P equal to their sum. As an 8–12 hour fast was required, chylomicrons had insignificant contribution to large VLDL-P. The weighted-average VLDL size was calculated as the particle size of each subclass multiplied by its relative mass percentage as estimated from amplitude of its NMR signal. In this study, we used all participants who had information on NMR spectroscopy (n=1850), and employed sampling weights so that our results reflect the underlying CHS population.

Measurement of exposures

We examined three classes of potential determinants of VLDL metabolism – biomarkers for insulin sensitivity, inflammation and liver synthetic function. We used biochemical measurements on plasma collected at baseline in the study. The laboratory methods and quality assurance in CHS have been described previously.[24] For insulin sensitivity, 1/ HOMA-IR and Matsuda index were derived from fasting glucose, insulin, and a two-hour glucose tolerance test respectively.[25, 26] For liver synthetic function, we used plasma concentrations of albumin, fibrinogen and factor VII (%). CRP and interleukin 6 (IL6) were used as markers for inflammation. Individuals with missing values for variables were excluded from the final analysis, which included 232 for HOMA-IR, 399 for Matsuda index and 75 for IL6.

Measurement of other covariates

Other covariates used in this study included age, gender, ethnicity, alcohol consumption, smoking history, body-mass index (BMI) and the use of lipid lowering medications. Alcohol consumption was categorized as non-drinker, rare drinker (< 1 drink per week), mild drinker (1–7 drinks per week), moderate drinker (7–14 drinks per week), and heavy drinkers (more than 14 drinks per week). Smoking history was categorized into never smoker, former smoker and current smoker. We used singly-imputed missing covariate data as described elsewhere.[27] The use of lipid lowering medications included statin and non-statin medications.

Statistical analysis

We examined the relationship of VLDL parameters and markers of insulin resistance, liver synthetic function and inflammation in multivariate analyses. Five VLDL parameters were examined as outcomes: total VLDL particle concentration (VLDL-P), concentrations of three VLDL subclasses (large, medium and small VLDL-P) and mean VLDL size. For plotting purposes, we graphed adjusted VLDL parameters, calculated from the residuals of regression using covariates including age, gender, ethnicity, alcohol consumption, smoking history, BMI and the use of lipid lowering medications against our primary exposures. We tested three categories of exposures (independent variables), including insulin sensitivity (1/ HOMA-IR and Matsuda index), liver synthetic function (albumin, fibrinogen and factor VII) and inflammation (CRP and IL6). We excluded individuals on anti-diabetic medication (n =

117) in analysis for HOMA-IR and Matsuda index, and those on warfarin (n = 98) for any analysis that involved factor VII.

To determine dose-response relationships with VLDL-P and VLDL size, we used a restricted fractional polynomial approach, comparing models using linear, logarithmic and quadratic transformation of the exposures (independent variables). To compare effects on large, medium and small VLDL-P, the concentration of each subclass was first standardized using its Z-score. Fractional polynomial regressions with two degrees of freedom were then performed to determine the shape of associations with each exposure. All regression models were adjusted for the sampling weight of the individuals that underwent NMR spectroscopy measurements to reflect the entire CHS cohort at baseline. The relationship was then plotted using exposures on the X-axis and covariate-adjusted VLDL measurements on the Y-axis. Sensitivity analyses for associations between albumin and VLDL profiles were calculated by excluding individuals with stage 3 or above chronic kidney disease as defined by estimated glomerular filtration rate between < 60 ml/min/1.73 m².

To determine their independent associations, we generated models that mutually adjusted for Matsuda index, CRP, and factor VII, as well as the same covariates used previously. To compare their relative contributions to each VLDL measurement, we used both actual values and standardized Z-scores for Matsuda index, CRP and factor VII. These three indicators were chosen because of their stronger associations with VLDL profiles as compared to other measures of insulin resistance, inflammation, and liver function. The Z-score was calculated by the ratio of the difference each variable and its mean over the standard deviation of that variable. We reported the regression calculated using the Z-score in the main results as it provides the coefficient corresponding to one standard deviation increase of each of the independent variables, i.e. Matsuda index, CRP and factor VII. Multivariate regression models were generated using linear terms of each biomarker first, along with a squared term for CRP as a sensitivity test, given its non-linear relationship with VLDL profiles. We also added a covariate for self-reported arthritis to probe the impact of rheumatic causes of inflammation.

Data management was conducted with SAS, version 9.2 (SAS Institute, Cary, North Carolina), and all statistical analyses were performed using STATA/IC version 13.0 (Stata Corp, College Station, Texas).

Results

Study participants

The background characteristics of CHS study participants are summarized in Table 1. The cohort had a mean age of 73 years and 42% male, among which 28% had either pre-diabetes or diabetes, and 6% were taking lipid lowering medications.

Relationship between VLDL characteristics and insulin sensitivity

In multivariable models, both 1/HOMA-IR and Matsuda index were inversely associated with total VLDL concentration and VLDL size (Supplemental Figure 1 A, B, left, middle). Decreases in insulin sensitivity measured by lower 1/HOMA-IR or Matsuda index were

associated with larger increases in the concentration of large VLDL particles than those of medium or small VLDL particles, where the VLDL subclass concentrations were standardized on the scale of their standard deviations (Supplemental Figure 1 A, B, right).

Relationship between VLDL characteristics and markers for liver synthetic function

Total VLDL concentration was consistently positively associated with all three markers of liver synthetic function in multivariate analyses (Supplemental Figure 2 A–C, left). The associations between mean VLDL size and liver synthetic function were quite variable, varying from no association in albumin to an inverse relationship in fibrinogen (Supplemental Figure 2 A–C, middle). Among the three VLDL subclasses, albumin and fibrinogen demonstrated strong positive associations with small VLDL particles, whereas factor VII was positively related to all three subclasses of VLDL particles (Supplemental Figure 2 A–C, right). The exclusion of individuals with stage 3 or above chronic kidney disease ($n = 350$), strengthened the associations of albumin with total and small VLDL particle concentrations ($p = 0.02$ for both).

Relationship between VLDL characteristics and markers for inflammation

We next investigated the associations between VLDL characteristics and markers of inflammation: CRP and IL6. Unlike indices for insulin sensitivity or liver synthetic function, both CRP and IL6 had nonlinear associations with total VLDL particle concentration and VLDL size, approximating an inverse U-shape (Figure 1 A, B, left, middle). This non-linearity was seen in all three VLDL subclasses. IL6 had its strongest association with the concentration of large VLDL particles, whereas no obvious subclass differences were seen with CRP (Figure 1 A, B, right).

Mutual relationships of insulin sensitivity, liver synthetic function and inflammation with VLDL profiles

Lastly, we examined the associations between VLDL profiles and insulin sensitivity, liver synthetic function and inflammation in the same model, while adjusting for age, gender, ethnicity, smoking, alcohol consumption, the use of lipid lowering medications and BMI (Table 2). In multivariate models including standardized Matsuda index, factor VII and CRP, an one-standard-deviation increase in Matsuda index and CRP were associated 4.9 nmol/L (-8.2 to -1.5 , $p = 0.005$) and 6.3 nmol/L (-11.0 to -1.6 , $p = 0.009$) decreases in total VLDL particle concentration respectively; whereas an increase of one-standard-deviation in factor VII was associated with an increase of 16.9 nmol/L (12.6 to 21.2 , $p < 0.001$) in total VLDL particle concentration (Table 3). These relationships were present among all three VLDL subclasses, although Matsuda index generally had a stronger association with large VLDL particles. Consequently, only Matsuda index had a negative association with VLDL size. Interestingly, CRP had simple inverse associations with VLDL total and subclass concentrations when adjusted for insulin sensitivity and liver synthetic function. Among covariates, male gender, BMI and the use of lipid lowering medications had positive associations with VLDL-P, whereas alcohol consumption had negative associations with total VLDL-P concentration and positive association with VLDL size. These results were little changed by adjustment for self-reported arthritis.

Discussion

Although insulin resistance has long been associated with higher VLDL concentration and size, much less is known about the concomitant associations with key consequences of insulin resistance, namely impairment in liver synthetic function and inflammation. In this cross-sectional study of over 1,850 older adults, we aimed to quantify the associations between VLDL profiles and insulin sensitivity, liver synthetic function and inflammation. Indicators for these three processes demonstrated differential but consistent associations with plasma VLDL profiles. Indices of insulin sensitivity were negatively associated with the concentration of total VLDL-P and even more so with large VLDL-P. Markers for liver synthetic function were positively associated with concentrations of all three subclasses of VLDL-P. Inflammatory markers such as CRP and IL6 had non-linear associations with VLDL-P concentration when tested alone, but a negative association when adjusted for insulin sensitivity and liver synthetic function.

Underscoring these observations are the impacts of insulin resistance, inflammation and impaired liver synthetic function on intrahepatic VLDL synthesis. Insulin resistance increases VLDL production by increasing the hepatic load of circulating fatty acids and decreasing the negative regulation on apolipoprotein B production.[9, 28] Furthermore, insulin resistance and hyperglycemia may increase *de novo* lipogenesis, and further exacerbate hepatic lipid load.[29–31] This is in concordance with the association between low insulin sensitivity and increased concentration and size of VLDL particles observed here. VLDL is only produced by the liver, hence directly influenced by impaired liver synthetic function in both total and subclass VLDL particle concentrations. The relationships between inflammatory markers and VLDL profiles were more complicated. We observed a non-linear association, suggesting that at low levels, inflammation increases VLDL-P concentration, whereas at high levels of inflammation, the opposite is seen. Interestingly, after adjustment for insulin sensitivity and liver synthetic function, CRP had strictly negatively association with VLDL-P concentration. Since we do not know the source of inflammation that drives elevated CRP, the mechanism of how inflammation impacts VLDL concentration remains unclear. Nonetheless, it has been shown that NASH is associated with impaired VLDL synthesis and lipid outflow.[15] One may speculate that hepatocellular oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress, all related with inflammation, may contribute to this negative association.[32, 33]

The relevance of these relationship may manifest in NAFLD, a common disease that influences up to one third of the US population, and likely common in the cohort that we studied.[19] The progression of NAFLD is driven by inflammation and loss of liver synthetic function, manifested in NASH and liver fibrosis. This raises the possibility that VLDL profiles could be used in the diagnosis and risk stratification of NAFLD. For instance, although an increase in VLDL concentration often occurs with insulin resistance, a decline in VLDL concentration could result from improvement in insulin sensitivity or worsening disease characterized by increased inflammation and decline in liver synthetic function. In particular, our results suggest that the combination of large mean VLDL particle size and low VLDL-P concentration suggest a high level of insulin resistance with impaired liver function, a state characteristic for disease progression in NASH. This insight has been

suggested by an accumulating body of evidences. Fujita *et al.* have reported decreased hepatic VLDL synthesis and outflow among individuals with histologically diagnosed NASH.[15] In the Multi-Ethnic Study of Atherosclerosis (MESA), intrahepatic lipid burden measured by liver/spleen attenuation ratio on CT was positively associated with VLDL-P concentration and size.[34] Wree and coworkers showed that serum level of triglyceride, a surrogate marker for VLDL, is associated with NAFLD activity score among obese patients undergoing bariatric surgery.[35] In a recent study by Siddiqui *et al.*, patients with cirrhosis were found to have lower triglyceride levels, apolipoprotein B, VLDL-P concentration and VLDL size.[36]

The strength of this study lies in this large well-defined CHS cohort that provides the information and statistical power for multivariate analyses adjusting for factors known to impact VLDL metabolism, such as obesity, medication, smoking and alcohol consumption. Clearly, the result presented in this study should be interpreted with caution given its cross-sectional design. The biomarkers, although highly suggestive of their physiological relevance, are imperfect, and limited by ones available in the CHS study. Some biomarkers, such as CRP and fibrinogen, are by nature influenced by more than one pathological process. The relationship of our observations with NAFLD remains speculative and hypothesis generating as the CHS cohort lacks direct liver-related measurements. Many currently standard-of-care medications for the treatment of diabetes and hyperlipidemia were not captured in the CHS cohort, limiting the generalizability of this study. These hypotheses need to be tested in patients with well-characterized NAFLD, where liver biopsy may be available.

The physiological relationships with VLDL profiles may guide future studies to understand the impact of metabolic liver disease on lipoprotein metabolism. In particular, the relationship between VLDL profiles and NAFLD disease characteristics measured by serum markers, such as cytokeratin 18, as well as steatohepatitis and liver fibrosis measured on liver biopsy. These physiological relationships also raised the possibility that VLDL profiles may serve as a predictive marker for staging of both steatohepatitis and liver fibrosis.

In summary, in older multiethnic adults, markers for liver synthetic function were positively associated with VLDL concentration, whereas indicators for inflammation and insulin sensitivity were negatively correlated with VLDL concentration. These insights shall shed light on lipoprotein metabolism in metabolic syndrome and NAFLD, and may eventually enable the judicious use of VLDL in clinical diagnostics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and R01HL094555 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was

provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

Abbreviations

ALT	aminotransferase
BMI	body mass index
CHS	Cardiovascular Health Study
CRP	C-reactive protein
IL6	interleukin 6
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NMR	nuclear magnetic resonance
VLDL	very low density lipoprotein
VLDL-P	VLDL particles

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A. C-reactive protein (n = 1848) **B. Interleukin 6 (n = 1774)** **Figure 1. Relationship between markers for inflammation and VLDL characteristics**

The association curves between total VLDL particle concentration, VLDL size and CRP (A1, A2), IL6 (B1, B2) were determined using linear regression. The relationship between the concentrations of VLDL subclasses and CRP (A3), IL6 (B3) were calculated using fractional polynomial regression, where large (red), medium (blue) and small VLDL (green) concentrations were standardized using the Z-score as described in methods.. All five VLDL measurements were adjusted for age, gender, ethnicity, BMI, alcohol, smoking history and the use of lipid lowering medications. The number of observations, P values and 95% CI (dashed line) for each model were shown as indicated.

Table 1

Background characteristics of study participants

Demographics		Laboratory Values	
Age	72.8 ± 5.6	Lipid panel	
Male	43%	Triglyceride, mg/dL	140 ± 77
Ethnicity		Total cholesterol, mg/dL	213 ± 39
Caucasian	83%	HDL-C, mg/dL	54 ± 16
African American	16%	LDL-C, mg/dL	180 ± 43
Others	1%	VLDL measurements	
Smoking History		VLDL-P, nmol/L	82.9 ± 73.6
Never	47%	Large VLDL, nmol/L	4.3 ± 6.3
Former	41%	Medium VLDL, nmol/L	31.0 ± 40.3
Current	12%	Small VLDL, nmol/L	47.6 ± 39.5
Alcohol History		VLDL size, nm	51.6 ± 14.2
Never	50%	Calc VLDL triglyceride, mg/dL	101 ± 105
< 1 drink per week	23%	hs-CRP, mg/L	3.7 ± 6.3
1–7 drinks per week	15%	Interleukin-6, ng/L	2.2 ± 1.9
8–14 drinks per week	6%	Platelet count, ×10 ³ /μl	250 ± 75
> 14 drinks per week	6%	Albumin, g/dL	4.0 ± 0.3
Num. of daily medications	2.3 ± 2.2	Factor VII, % ¹	123 ± 30
Lipid lowering medication	6%	Fibrinogen, mg/dL	324 ± 67
BMI	26.7 ± 4.7	Insulin resistance index	
Overweight	40.3%	Matsuda index	3.5 ± 2.2
Obese	17.9%	HOMA-IR	5.4 ± 13.6
History of diabetes			
None	72%		
Pre-diabetes	12%		
Diabetes	16%		

¹ Only 66 subjects had factor VII level less than lower limits of normal (70%), among which 23 subjects were taking warfarin

Table 2
Adjusted regression coefficient for VLDL profiles from Matsuda index, CRP and Factor VII

	Matsuda index		CRP (mg/L)		Factor VII (%)	
	Coef. (95% CI)	P value	Coef. (95% CI)	P value	Coef. (95% CI)	P value
Total VLDL-P, nmol/L	-2.1 (-3.6 – -0.5)	0.008	-1.2 (-2.0 – -0.4)	0.004	0.6 (0.5 – 0.8)	<0.001
Large VLDL, nmol/L	-0.5 (-0.6 – -0.4)	<0.001	-0.07 (-0.14 – 0.001)	0.05	0.04 (0.03 – 0.06)	<0.001
Medium VLDL, nmol/L	-1.1 (-2.0 – -0.4)	0.005	-0.6 (-1.0 – -0.1)	0.01	0.3 (0.2 – 0.4)	<0.001
Small VLDL, nmol/L	-0.4 (-1.4 – 0.5)	0.4	-0.5 (-1.0 – -0.05)	0.03	0.3 (0.2 – 0.4)	<0.001
VLDL size, nm	-0.6 (-0.9 – -0.2)	0.006	-0.07 (-0.2 – 0.08)	0.4	-0.02 (-0.05–0.007)	0.1

¹ Regression models calculated using three primary exposures (Matsuda index, CRP, factor VII), and covariates including age, gender, ethnicity, BMI, alcohol, smoking history and the use of lipid lowering medications.

Table 3
Adjusted regression coefficients for VLDL profiles from standardized Matsuda index, CRP and factor VII

	Matsuda index (SD)		CRP (SD)		Factor VII (SD)	
	Coef. (95% CI)	P value	Coef. (95% CI)	P value	Coef. (95% CI)	P value
Total VLDL-P, nmol/L	-4.6 (-7.9 – -1.2)	0.007	-6.1 (-10.8 – -1.4)	0.01	17.0 (12.7 – 21.3)	<0.001
Large VLDL, nmol/L	-1.1 (-1.4 – -0.8)	<0.001	-0.4 (-0.7 – -0.08)	0.02	1.3 (0.9 – 1.7)	<0.001
Medium VLDL, nmol/L	-2.5 (-4.2 – -0.8)	0.005	-2.8 (-5.6 – -0.03)	0.05	7.7 (5.3 – 10.1)	<0.001
Small VLDL, nmol/L	-1.0 (-3.0 – 1.0)	0.3	-2.9 (-5.4 – -0.3)	0.03	8.0 (5.7 – 10.2)	<0.001
VLDL size, nm	-1.2 (-2.0 – -0.3)	0.006	-0.5 (-1.2 – -0.2)	0.2	-0.5 (-1.4 – 0.4)	0.3

¹ Regression models calculated using the Z-scores of three primary exposures (Matsuda index, CRP, factor VII) in units of standard deviation (SD), and covariates including age, gender, ethnicity, BMI, alcohol, smoking history and the use of lipid lowering medications.