Aims: Prediabetes and diabetes are associated with increased insulin resistance and decreased insulin production, dyslipidemia, and increased cardiovascular disease (CVD) risk. Our goals were to assess lipoprotein subfractions using novel assays in such subjects.

Methods: Fasting normal, prediabetic, and diabetic Taiwanese men and women (n=2,049) had their serum glucose, glycosylated hemoglobin, insulin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), HDL3-C, apolipoprotein E-HDL-C, direct low-density lipoprotein cholesterol (LDL-C), small dense LDL-C (sdLDL-C), LDL-TG, and remnant lipoprotein cholesterol (RLP-C) levels measured using novel assays. HDL2-C, LDL-C, and large-buoyant LDL-C (lbLDL-C) were calculated.

Results: Prediabetic male and female subjects had significantly higher levels of TG, RLP-C, sdLDL-C, the sdLDL-C/LDL-C ratio, and LDL-TG than normal subjects, and statin treatment abolished this effect in men, but not in women. Diabetic male and female subjects had significantly higher TG and sdLDL-C/LDL-C ratios, and significantly lower levels of HDL-C, HDL2-C, HDL3-C, and apoE HDL-C than normal subjects, as did prediabetic women. Median direct LDL-C levels were >100 mg/dL in all groups, even in those receiving statin therapy. Calculated LDL-C significantly underestimated direct LDL-C by >10% in diabetic subjects.

Conclusions: Our data indicate that prediabetic subjects were more likely to have significantly elevated RLP-C, sdLDL-C, and LDL-TG, while diabetic subjects were more likely to have significantly decreased HDL-C, HDL2-C, HDL3-C, and apoE HDL-C than normal subjects, and calculated LDL-C significantly underestimated their direct LDL-C. In our view, direct LDL-C and sdLDL-C should be measured and optimized in both diabetic and prediabetic subjects to reduce CVD risk.

Key words: Low-density lipoprotein triglyceride, Small dense low-density lipoprotein cholesterol, Type 2 diabetes mellitus, Prediabetes, Lipid-lowering medication

Introduction

Diabetes mellitus is a major risk factor for cardiovascular disease (CVD), and is associated with dyslipidemia characterized by increased serum levels of triacylglycerides (TG), remnant lipoprotein cholesterol (RLP-C), and small dense low-density lipoproteins (sdLDL), and decreased levels of high-density lipoprotein cholesterol (HDL-C). Subjects with prediabetes are also at increased CVD risk, and often have dyslipidemia.
Significant CVD risk factors in patients with diabetes include hypertension, smoking, increased levels of serum glucose and LDL-C, and decreased levels of HDL-C\(^6\). Lowering LDL-C levels with statin therapy has been associated with significant reductions in CVD events in patients with diabetes\(^2-13\).

In the United States, it has been recommended that all patients with established CVD and diabetes over the age of 40 years with LDL-C levels $>70$ mg/dL, an LDL-C value $≥190$ mg/dL, or a ten-year CVD risk $≥7.5\%$ be placed on statin therapy in addition to lifestyle modification in order to achieve a significant LDL-C reduction\(^12-14\). More recently, it has been suggested that in addition to statins, the use of ezetimibe, and/or proprotein convertase subtilisin kexin 9 inhibitors can be considered to reduce LDL-C levels to $<70$ mg/dL in CVD patients and $<100$ mg/dL in high-risk patients including patients with diabetes\(^15,16\). In the United States, there are no recommendations with regard to TG targets\(^12-16\). In Taiwan, current recommendations with regard to LDL-C targets of therapy are the same as in the United States, but it was also recommended that TG levels be lowered to $<150$ mg/dL\(^17,18\). In Japan, it was recommended that CVD patients have their LDL-C values lowered to $<100$ mg/dL, and $<120$ mg/dL for diabetics, and for both groups to get TG levels lowered to $<150$ mg/dL\(^19\). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, it was documented that diabetic subjects on statin therapy did not get additional benefit from the addition of fenofibrate therapy, unless their TG levels were $>204$ mg/dL and their HDL-C levels were $<35$ mg/dL. This latter group got a 28% risk reduction when fenofibrate was added to statin therapy as compared to placebo therapy\(^20\).

It has long been known that hypertriglyceridemia is associated with decreased HDL-C values, as well as increased levels of sdLDL-C\(^21-23\). This latter parameter can now be readily measured with an automated assay\(^24\). In addition, it has been reported that elevated levels of RLP-C, sdLDL-C, and LDL-TG, and decreased levels of HDL-C and its subfractions have been associated with increased CVD risk\(^21-33\). However, these new assays have not been applied to a large diabetic and prediabetic population, especially in an Asian population.

Another goal of this investigation was to examine relationships between lipoprotein subfractions and measures of glucose homeostasis, including insulin, and measures of insulin resistance and production in normal, prediabetic, and diabetic subjects in a large Asian population.

### Methods

Our study population consisted of 2,049 men and women living in Yi-lan County in northern Taiwan. Residents of this province are native to the island of Taiwan and are not recent immigrants from mainland China or other parts of Asia. All subjects agreed to participate in this study using a standard study protocol and informed consent approved by the research committees of Luodong Poh-ai Hospital, Luodong, Taiwan and the School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan. (M2000-2350).

We recruited normal, prediabetic, and diabetic subjects from participants after testing and participation in a standard health examination as previously described\(^34\). Subjects were classified as normal if their fasting serum glucose value was $<100$ mg/dL, as prediabetic if their value was in the $100–125$ mg/dL range, and as diabetic if their value was $>125$ mg/dL using the standard criteria. In order to increase our diabetic subjects, subjects with diabetes were also recruited from a clinic at Luodong Poh-ai Hospital, and were required to have a history of diabetes without any change in treatment including medications for at least 6 months. All diabetic patients received standardized therapies consistent with national Taiwanese, American Diabetes Association and European Association for the Study of Diabetes guidelines. All participants were classified as being obese if their body mass index (BMI) was $≥27$ kg/m\(^2\) (Taiwanese criteria), or in some analyses (see Supplemental Tables) as $≥25$ kg/m\(^2\) (Japanese criteria\(^35,36\)).

Subjects being treated for thyroid disease, or those with laboratory evidence of liver disease (transaminase value $>3$ times the upper limits of normal), or kidney disease (creatinine $>2.0$ mg/dL), or those receiving insulin therapy were excluded from the study. Among the participants, 667 were in the normal group, 345 were in the prediabetic group, and 1,037 were in the diabetic group. In all subjects, a standard history about health status and medication use was obtained, and a physical examination was carried out including measurements of height, weight, and blood pressure. Subjects with a significant history of CVD were excluded from this analysis.

Blood samples were collected from all participants after an overnight fast of 12 hours or more. Serum
glucose was measured using the hexokinase method, glycosylated hemoglobin using a turbidimetric inhibition immunoassay as previously described. Insulin levels were measured by chemiluminescence assay on a Siemens Centaur automated platform (Siemens Healthcare, Germany) with intra- and inter-assay coefficients of variation (CVs) of <5%. Serum creatinine, liver transaminases, TC, TG, HDL-C, LDL-C, apoE, HDL-C, direct LDL-C, sdLDL-C, LDL-TG, and RLP-C were measured by automated standardized enzymatic analysis on a Cobas C501 analyzer (Roche Diagnostics, Germany). The specialized lipid assay kits were provided by the Denka-Seiken Corporation (Tokyo, Japan) as previously described. All specialized lipid assays had within and between run CVs were <6.0%, and in most cases <3.0%. Homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of insulin production (HOMA-β) were calculated from glucose and insulin levels using the following formulas: HOMA-IR = (insulin in µU/mL × glucose in mg/dL) / 405, and HOMA-β = [insulin in µU/mL × (glucose in mg/dL - 63)] %, and HOMA-IR = [glucose in mg/dL × (insulin in µU/mL)/405]. lbLDL-C were calculated by subtracting sdLDL-C from direct LDL-C. LDL-C, HDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

Table 1. Characteristics of all male subjects (*n = 1030*)

| Variable                                   | NGT | PreDM | DM  | P value |
|--------------------------------------------|-----|-------|-----|---------|
|                                            | n = 277 | n = 200 | n = 553 |         |
| Age, year                                  | 55.8 (20.3) | 60.6 (18.6) | 61.5 (14.6) | 0.002 |
| BMI, kg/m²                                  | 24.2 (4.2) | 25.3 (3.9) | 26.1 (4.8) | 0.001 |
| Obesity Prevalence                         | 50 (18.1%)** | 53 (26.5%)** | 217 (39.2%)** | 0.001 |
| Systolic BP, mmHg                           | 123.0 (16.8) | 128.0 (21.0) | 130.0 (14.0) | 0.004 |
| Diastolic BP, mmHg                          | 75.0 (13.8) | 76.0 (16.0) | 70.0 (10.0) | 0.022 |
| Fasting Glucose, mg/dL                     | 93.0 (8.0) | 105.0 (9.0) | 133.0 (40.0) | 0.000 |
| HbA1c, %                                   | 5.5 (0.4) | 5.8 (0.4) | 6.9 (1.3) | 0.000 |
| Insulin                                    | 8.0 (1.5) | 10.6 (21.2) | 10.7 (10.4) | 0.000 |
| HOMA-IR                                    | 1.8 (1.7) | 2.8 (2.2) | 3.5 (3.6) | 0.000 |
| HOMA-β                                     | 100.4 (90.4) | 86.5 (58.7) | 58.9 (65.8) | 0.018 |

Lipids and Lipoproteins

| Total cholesterol, mg/dL                   | 192.0 (55.0) | 189.5 (43.3) | 171.0 (39.2) | 0.507 |
| Triglycerides, mg/dL                      | 103.0 (75.0) | 120.0 (87.0) | 118.0 (94.0) | 0.002 |
| RLP-C, mg/dL                               | 6.3 (7.3) | 8.7 (10.7) | 6.3 (9.1) | 0.001 |
| LDL-C, mg/dL                               | 113.3 (46.7) | 111.8 (43.7) | 106.4 (32.7) | 0.880 |
| calculated LDL-C, mg/dL                   | 115.2 (51.1) | 109.4 (43.8) | 93.2 (35.7) | 0.176 |
| sdLDL-C, mg/dL                             | 29.5 (22.2) | 34.5 (25.0) | 32.7 (20.4) | 0.018 |
| sdLDL-C/LDL-C ratio                        | 0.260 (0.111) | 0.305 (0.150) | 0.299 (0.153) | 0.000 |
| lbLDL-C, mg/dL                             | 80.1 (34.1) | 78.0 (33.8) | 73.2 (27.0) | 0.094 |
| LDL-TG, mg/dL                              | 22.2 (11.0) | 23.3 (10.1) | 19.4 (7.7) | 0.006 |
| Non-HDL-C, mg/dL                           | 140.7 (54.8) | 138.7 (41.6) | 122.7 (38.1) | 0.945 |
| HDL-C, mg/dL                               | 51.3 (17.2) | 50.3 (16.1) | 46.0 (13.5) | 0.460 |
| HDL2-C, mg/dL                              | 26.9 (13.3) | 27.0 (10.0) | 25.1 (8.1) | 0.447 |
| HDL3-C, mg/dL                              | 22.8 (5.1) | 22.8 (5.2) | 20.5 (5.2) | 0.784 |
| ApoE-HDL, mg/dL                            | 4.6 (2.2) | 4.7 (2.0) | 3.9 (1.7) | 0.879 |

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

Data are presented as the median values with inter-quartile ranges since many variables were not normally distributed. All statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY). Mann–Whitney U testing was used to assess the sta-
tistical significance of differences for assessed variables between groups. Pearson’s correlation coefficients were used for assessing the significance of correlations between variables. A P value of <0.05 was considered statistically significant.

Results

Data on all male (n=1,030) and female (n=1,019) participants are shown in Tables 1 and 2, respectively. Since this study focused on lipoprotein subfractions, data on male (n=605) and female (n=622) subjects off lipid-lowering medications are shown in Table 3 and 4, respectively, while data on men (n=347) and women (n=339) on statin therapy are shown in Tables 5 and 6, respectively. In addition, we tabulated relative percentage differences between normal, prediabetic, and diabetic male and female subjects for all lipoprotein subfractions in all subjects, those off statins, and in those on statin therapy in Figs.1, 2, and 3, respectively. In addition, we have analyzed the effects of obesity classified as ≥27 kg/m² using the Taiwanese criteria in normal prediabetic and diabetic subgroups for men in Table 7, and for women in Table 8. Comparisons of normal, prediabetic, and diabetic men and women with and without obesity classified as ≥25 kg/m² using Japanese criteria are shown in Supplemental Tables 1 and 2. Comparison of variables between participants with and without statin use are shown in Supplemental Table 3–5 (normal group in Supplemental Table 3, prediabetic group in Supplemental Table 4, and DM group in Supplemental Table 5).

Table 2. Characteristics of all female subjects (n=1019)*

| Variable                  | NGT n=390 | PreDM n=145 | DM n=484 | NGT vs PreDM | PreDM vs DM | DM vs NGT |
|---------------------------|-----------|-------------|----------|--------------|-------------|-----------|
| Age, year                 | 51.7 (16.4) | 61.5 (18.8) | 63.7 (12.3) | 0.000       | 0.018       | 0.000     |
| BMI, kg/m²                | 22.8 (4.0)  | 23.8 (4.6)  | 25.5 (5.0)  | 0.001       | 0.000       | 0.000     |
| Obesity Prevalence        | 36 (9.2%)  | 31 (21.4%)  | 172 (35.5%) | 0.001       | 0.000       | 0.000     |
| Systolic BP, mmHg         | 118.0 (19.0) | 123.0 (16.0) | 130.0 (14.0) | 0.003       | 0.000       | 0.000     |
| Diastolic BP, mmHg        | 69.0 (14.0) | 71.0 (14.3) | 70.0 (10.0) | 0.028       | 0.076       | 0.000     |
| Fasting Glucose, mg/dL    | 90.0 (9.0)  | 105.0 (11.0) | 132.0 (41.0) | 0.000       | 0.000       | 0.000     |
| HbA1c, %                  | 5.5 (0.4)   | 5.9 (0.5)   | 7.0 (1.4)   | 0.000       | 0.000       | 0.000     |
| Insulin,                  | 8.3 (5.8)   | 12.7 (8.3)  | 13.2 (10.1) | 0.000       | 0.251       | 0.000     |
| HOMA-IR                   | 1.8 (1.3)   | 3.3 (2.4)   | 4.3 (4.0)   | 0.000       | 0.000       | 0.000     |
| HOMA-β                    | 113.1 (76.4) | 97.7 (67.8) | 66.1 (68.0) | 0.004       | 0.000       | 0.000     |

Lipids and Lipoproteins

| Variable                  | NGT n=390 | PreDM n=145 | DM n=484 | NGT vs PreDM | PreDM vs DM | DM vs NGT |
|---------------------------|-----------|-------------|----------|--------------|-------------|-----------|
| Total cholesterol, mg/dL  | 197.0 (48.8) | 194.0 (42.0) | 175.0 (36.3) | 0.254       | 0.000       | 0.000     |
| Triglycerides, mg/dL      | 86.5 (58.8)  | 116.0 (94.0) | 119.0 (82.3) | 0.000       | 0.983       | 0.000     |
| RLP-C, mg/dL              | 5.3 (4.7)   | 7.9 (9.8)   | 6.2 (7.6)  | 0.000       | 0.000       | 0.000     |
| LDL-C, mg/dL              | 117.0 (39.6) | 114.3 (42.7) | 106.6 (35.5) | 0.448       | 0.007       | 0.000     |
| calculated LDL-C, mg/dL   | 116.7 (42.9) | 112.3 (42.1) | 95.1 (34.7)  | 0.098       | 0.000       | 0.000     |
| sdLDL-C, mg/dL            | 27.3 (17.1)  | 33.5 (21.4)  | 31.5 (19.6) | 0.000       | 0.165       | 0.000     |
| sdLDL-C/LDL-C ratio       | 0.231 (0.085) | 0.287 (0.127) | 0.290 (0.129) | 0.000       | 0.813       | 0.000     |
| lbLDL-C, mg/dL            | 87.9 (28.0)  | 80.6 (29.3)  | 74.5 (26.5) | 0.001       | 0.002       | 0.857     |
| LDL-TG, mg/dL             | 21.2 (10.0)  | 25.2 (10.5)  | 20.9 (8.3)  | 0.000       | 0.000       | 0.000     |
| Non-HDL-C, mg/dL          | 134.4 (48.1) | 139.3 (41.7) | 121.6 (36.3) | 0.335       | 0.000       | 0.000     |
| HDL-C, mg/dL              | 59.2 (18.4)  | 52.2 (17.9)  | 52.5 (15.8) | 0.000       | 0.962       | 0.000     |
| HDL3-C, mg/dL             | 34.0 (14.7)  | 28.9 (11.8)  | 29.4 (11.0) | 0.000       | 0.171       | 0.000     |
| HDL2-C, mg/dL             | 25.0 (4.7)   | 23.9 (5.4)   | 22.8 (5.6)  | 0.018       | 0.001       | 0.000     |
| ApoE-HDL, mg/dL           | 5.7 (2.3)    | 5.0 (2.0)    | 4.7 (1.9)   | 0.000       | 0.020       | 0.000     |

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participants (percentage of obese participants) (BMI ≥27 kg/m²).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, non HDL cholesterol;
Table 3. Characteristics of male subjects not on lipid medications (n=605)*

| Variable                  | NGT n=207 | PreDM n=117 | DM n=281 | P value       |
|---------------------------|-----------|-------------|----------|---------------|
| Age, year                 |           |             |          |               |
| BMI, kg/m²                | 52.2 (18.3)| 54.5 (18.5) | 61.9 (13.4)| 0.017         |
| Obesity Prevalence        | 23.9 (4.1)| 25.3 (4.0) | 25.4 (4.7) | 0.000         |
| Systolic BP, mmHg         | 122.0 (15.8)| 130.0 (22.0)| 130.0 (14.0)| 0.001         |
| Diastolic BP, mmHg        | 74.0 (13.0)| 77.0 (17.0) | 76.0 (10.0) | 0.006         |
| Fasting Glucose, mg/dL    | 92.0 (7.5) | 105.0 (10.0)| 134.0 (35.0)| 0.000         |
| HbA1c, %                  | 5.5 (0.4) | 5.8 (0.5) | 6.9 (1.1) | 0.000         |
| Insulin                   | 7.9 (7.4) | 10.6 (8.9) | 10.5 (10.7) | 0.000         |
| HOMA-IR                   | 1.8 (1.6) | 2.7 (2.3) | 3.3 (3.7) | 0.000         |
| HOMA-β                    | 99.5 (96.2)| 85.1 (63.5)| 55.2 (61.7) | 0.008         |
| **Lipids and Lipoproteins** |          |             |          |               |
| Total cholesterol, mg/dL  | 196.1 (50.5)| 192.0 (32.0)| 171.0 (33.0)| 0.388         |
| Triglycerides, mg/dL      | 103.0 (79.5)| 133.0 (99.0)| 116.0 (91.0)| 0.006         |
| RLP-C, mg/dL              | 6.3 (8.2) | 10.1 (11.6) | 5.6 (8.0) | 0.001         |
| LDL-C, mg/dL              | 116.7 (44.8)| 115.5 (40.9)| 107.2 (30.1)| 0.686         |
| calculated LDL-C, mg/dL   | 117.7 (47.3)| 113.5 (39.9)| 94.1 (31.0) | 0.103         |
| sdLDL-C, mg/dL            | 30.7 (22.9)| 34.9 (26.1) | 31.8 (18.8) | 0.075         |
| sdLDL-C/LDL-C ratio       | 0.256 (0.118)| 0.310 (0.164)| 0.288 (0.139)| 0.004         |
| lbLDL-C, mg/dL            | 84.9 (33.0)| 79.7 (32.5) | 74.6 (25.2) | 0.115         |
| LDL-TG, mg/dL             | 22.1 (11.3)| 23.4 (10.9) | 18.1 (6.6) | 0.026         |
| Non HDL-C, mg/dL          | 142.9 (52.2)| 141.6 (33.2)| 122.8 (30.9)| 0.815         |
| HDL-C, mg/dL              | 51.6 (18.1)| 51.4 (18.0) | 46.0 (13.6) | 0.551         |
| HDL≥C, mg/dL              | 27.6 (13.0)| 26.3 (12.4) | 25.2 (8.3) | 0.448         |
| HDL≤C, mg/dL              | 23.0 (5.8) | 22.9 (5.5) | 20.5 (5.1) | 0.899         |
| ApoE-HDL, mg/dL           | 4.6 (2.1) | 4.8 (2.1) | 3.7 (1.5) | 0.857         |

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

Correlations between variables for all subjects, men and women are shown in Supplemental Tables 6, 7, and 8.

For all subjects and for those not receiving or receiving statin therapy, the median BMI, obesity prevalence, systolic blood pressure, serum glucose, HbA1c, serum insulin, and calculated insulin resistance (HOMAIR) were all significantly higher in prediabetic and diabetic subjects than in normal subjects. In contrast, median calculated insulin production (HOMAβ) values were significantly lower in prediabetic and diabetic subjects than in normal, especially in those with diabetes (see Tables 1-6). Interestingly, serum insulin levels were not significantly different between prediabetic and diabetic subjects in all categories, but there were significantly higher HOMAIR values and significantly lower HOMAβ values in diabetic subjects than in normal subjects.

In all male prediabetic subjects, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects (see Table 1). In male prediabetics not on statin therapy, TG, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects (see Table 3). In male prediabetics on statin therapy, all these significant differences were abolished (see Table 5). In all female prediabetic subjects, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects, while lbLDL-C, HDL-C, HDL2-C, and apoE-HDL-C were all significantly lower than in normals (see Table 2). In female prediabetic subjects off statin...
therapy, TG, RLP-C, sLDL-C, sLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normals, while HDL-C, HDL2-C, and apoE-HDL-C were all significantly lower than in normal subjects (see Table 4). In female prediabetic subjects on statin therapy, TG, RLP-C, and sLDL-C/LDL-C ratio values were all significantly higher than in normal, while HDL-C, HDL2-C, and apoE-HDL-C were all significantly lower than in normal (see Table 4). In male diabetic subjects, TG, sLDL-C/LDL-C ratio, and LDL-TG values were all significantly higher than in normal subjects, while direct LDL-C, calculated LDL-C, non-HDL-C, HDL-C, HDL2-C, HDL3-C, and apoE-HDL-C were all significantly lower than in normal subjects (see Table 1). In diabetic men not on statin therapy, with very similar differences being observed in diabetic men not on statin therapy versus normal subjects (see Table 5). In all female diabetics, TG, RLP-C, sLDL-C, and sLDL-C/LDL-C ratio values were all significantly higher than in normal subjects, while lbLDL-C, HDL-C, and apoE-HDL-C were all significantly lower than in normal subjects. In all female diabetics off statin therapy, TG, sLDL-C, and sLDL-C/LDL-C ratio values were all significantly higher than in normal subjects, while direct LDL-C, calculated LDL-C, lbLDL-C, non-HDL-C, HDL-C, HDL2-C, HDL3-C, and apoE-HDL-C were all significantly lower than in normal subjects. Interestingly, median direct LDL-C values in male and female diabetic subjects in all three categories ranged from 104.1–108.4 mg/dL, whereas for calculated LDL-C, these values ranged from 90.7–99.0 mg/dl, with an average

| Variable                  | NGT n = 324 | PreDM n = 90 | DM n = 208 | P value          |
|---------------------------|-------------|--------------|------------|-----------------|
| Age, year                 | 49.3 (12.9) | 54.7 (19.2)  | 63.6 (11.9) |                |
| BMI, kg/m²                 | 22.5 (4.0)  | 24.1 (5.2)   | 24.8 (4.8)  |                |
| Obesity Prevalence        | 25 (7.7)%   | 23 (25.6)%   | 57 (27.4)% |                |
| Systolic BP, mmHg         | 117.0 (19.0)| 120.0 (17.0) | 130.0 (19.5)|                |
| Diastolic BP, mmHg        | 68.0 (14.0) | 70.5 (11.8)  | 70.0 (10.0) |                |
| Fasting Glucose, mg/dL    | 89.5 (8.0)  | 105.0 (11.0) | 132.0 (39.5)|                |
| HbA1c, %                  | 5.4 (0.4)   | 5.8 (0.7)    | 7.0 (1.2)   |                |
| Insulin                   | 7.9 (5.6)   | 11.9 (8.2)   | 12.0 (9.4)  |                |
| HOMA-IR                   | 1.8 (1.3)   | 3.2 (2.2)    | 4.0 (3.6)   |                |
| HOMA-β                    | 110.7 (76.0)| 95.7 (64.5)  | 60.9 (60.0) |                |
| Lipids and Lipoproteins   |             |              |            |                 |
| Total cholesterol, mg/dL  | 198.0 (47.3)| 194.5 (38.5)| 178.0 (31.1)| 0.678           |
| Triglycerides, mg/dL      | 81.0 (57.5) | 106.5 (82.8)| 118.0 (75.0)| 0.000           |
| RLP-C, mg/dL              | 4.8 (4.2)   | 7.0 (8.4)    | 5.3 (6.1)   | 0.000           |
| LDL-C, mg/dL              | 117.7 (39.2)| 118.1 (39.5)| 108.4 (29.7)| 0.934           |
| calculated LDL-C, mg/dL   | 117.4 (41.1)| 113.5 (36.2)| 99.0 (28.1) | 0.521           |
| sdLDL-C, mg/dL            | 26.5 (16.8) | 32.5 (22.5)  | 29.4 (19.9) | 0.001           |
| sdLDL-C/LDL-C ratio       | 0.226 (0.081)| 0.272 (0.103)| 0.272 (0.124)| 0.000           |
| lbLDL-C, mg/dL            | 89.8 (27.4) | 84.4 (22.7)  | 76.4 (24.1) | 0.115           |
| LDL-TG, mg/dL             | 20.1 (9.9)  | 23.3 (10.6)  | 19.3 (7.9)  | 0.000           |
| Non HDL-C, mg/dL          | 133.4 (48.1)| 139.7 (38.8)| 124.4 (33.5)| 0.216           |
| HDL-C, mg/dL              | 59.9 (18.8) | 53.6 (16.7)  | 50.3 (17.2) | 0.000           |
| HDL2-C, mg/dL             | 34.7 (16.1) | 29.8 (13.7)  | 28.4 (11.8) | 0.000           |
| HDL3-C, mg/dL             | 25.1 (4.7)  | 23.9 (5.4)   | 22.2 (5.2)  | 0.186           |
| ApoE-HDL, mg/dL           | 5.7 (2.3)   | 5.2 (2.3)    | 4.4 (2.0)   | 0.001           |

* Data are expressed as median (interquartile range).
** Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

Table 4. Characteristics of female subjects not on lipid medications (n = 622)*
underestimation of 11.5% (p<0.001).

For all groups, we have tabulated relative percent differences between normal, prediabetic, and diabetic male and female subjects for all lipid and lipoprotein subfractions (see Figs.1, 2, and 3). A number of different patterns emerged. One pattern is that prediabetic subjects had the greatest increases in RLP-C, sdLDL-C, and LDL-TG values, especially in female subjects, as compared with normal subjects. Another pattern that emerged is that diabetic subjects had the greatest decreases in HDL-C and its subfractions as compared with normal, especially in men. In women, significant decreases in HDL-C and its subfractions were observed in prediabetic subjects as compared with normal; however, this was not the case for prediabetic men. A final pattern that emerged was that calculated LDL-C significantly underestimated direct LDL-C values in diabetic male and female subjects, with less discrepancy observed in normal and prediabetic subjects.

We examined the effects of obesity classified as having a BMI > 27 kg/m² versus being non-obese in normal, prediabetic, and diabetic men and women. The data are shown in Tables 7 and 8. In normal men, being obese resulted in significantly higher systolic blood pressure, insulin, HOMAIr, HOMAβ, TG, sdLDL-C, sdLDL-C/LDL-C ratio, non-HDL-C, and LDL-TG values, and significantly lower HDL-C, HDL2-C, and apoE-HDL-C as compared with non-obese normal subjects (see Table 7). In normal women, being obese resulted in the same differences except that TG and non-HDL-C levels were not significantly higher, but HDL3-C was significantly lower as compared with

Table 5. Characteristics of male subjects on statins (n = 347)*

| Variable                  | NGT n = 62 | PreDM n = 79 | DM n = 206 | NGT vs PreDM | PreDM vs DM | DM vs NGT | P value |
|---------------------------|------------|--------------|------------|--------------|-------------|-----------|---------|
| Age, year                 |            |              |            |              |             |           |         |
| BMI, kg/m²                | 66.0 (16.2)| 66.0 (12.7)  | 62.4 (15.2)| 0.911        | 0.030       | 0.089     |         |
| Obesity Prevalence        | 24.7 (3.4) | 25.0 (4.1)   | 26.6 (4.9) | 0.923        | 0.000       | 0.001     |         |
| Systolic BP, mmHg         | 130.0 (15.3)| 127.0 (12.0)| 130.0 (10.0)| 0.630        | 0.797       | 0.694     |         |
| Diastolic BP, mmHg        | 75.0 (10.8)| 75.0 (11.0)  | 70.0 (10.0)| 0.742        | 0.878       | 0.447     |         |
| Fasting Glucose, mg/dL    | 94.0 (7.0) | 106.0 (8.6)  | 132.0 (39.8)| 0.000        | 0.000       | 0.000     |         |
| Insulin, μg/dL            | 5.6 (0.3)  | 5.9 (0.4)    | 6.8 (1.4)  | 0.000        | 0.000       | 0.000     |         |
| HOMA-IR                   | 1.9 (1.5)  | 3.0 (2.1)    | 3.5 (3.0)  | 0.000        | 0.081       | 0.000     |         |
| HOMA-β                    | 104.0 (68.5)| 90.4 (51.9)| 60.0 (56.7)| 0.669        | 0.000       | 0.000     |         |
| Lipids and Lipoproteins   |            |              |            |              |             |           |         |
| Total cholesterol, mg/dL  | 175.5 (57.2)| 184.0 (56.0)| 168.0 (50.8)| 0.437        | 0.006       | 0.141     |         |
| Triglycerides, mg/dL      | 100.5 (47.3)| 111.0 (69.0)| 118.0 (88.3)| 0.119        | 0.478       | 0.014     |         |
| RLP-C, mg/dL              | 5.7 (5.6)  | 7.4 (8.3)    | 7.3 (9.4)  | 0.066        | 0.779       | 0.096     |         |
| LDL-C, mg/dL              | 102.1 (46.0)| 106.7 (48.8)| 104.7 (40.9)| 0.540        | 0.881       | 0.451     |         |
| calculated LDL-C, mg/dL   | 100.6 (51.9)| 102.4 (46.3)| 92.0 (41.7) | 0.628        | 0.002       | 0.029     |         |
| sdLDL-C, mg/dL            | 27.5 (15.0)| 33.4 (22.4)  | 33.2 (21.0) | 0.070        | 0.847       | 0.016     |         |
| sdLDL-C/LDL-C ratio       | 0.265 (0.070)| 0.288 (0.121)| 0.304 (0.140)| 0.054        | 0.486       | 0.003     |         |
| lbLDL-C, mg/dL            | 76.0 (32.7)| 73.8 (31.0)  | 72.4 (26.8) | 0.639        | 0.557       | 0.389     |         |
| LDL-TG, mg/dL             | 22.0 (8.2) | 22.9 (8.8)   | 20.0 (8.1) | 0.094        | 0.000       | 0.116     |         |
| Non HDL-C, mg/dL          | 122.9 (51.7)| 131.1 (50.3)| 119.5 (44.6)| 0.260        | 0.013       | 0.404     |         |
| HDL-C, mg/dL              | 49.9 (16.0)| 49.4 (13.8)  | 46.8 (14.1) | 0.651        | 0.187       | 0.046     |         |
| HDL2-C, mg/dL             | 26.4 (12.9)| 27.1 (7.9)   | 25.4 (8.4) | 0.648        | 0.430       | 0.201     |         |
| HDL3-C, mg/dL             | 22.8 (4.2) | 22.5 (5.3)   | 20.9 (5.3) | 0.975        | 0.006       | 0.009     |         |
| ApoE-HDL-C, mg/dL         | 4.5 (2.5)  | 4.6 (1.9)    | 4.1 (1.8)  | 0.884        | 0.011       | 0.009     |         |

*Data are expressed as median (interquartile range).
**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides
normal subjects (see Table 8). In prediabetic men, being obese resulted in the same findings as for normal men, except that no significant differences with regard to HDL-C and its subfractions were noted as compared with non-obese prediabetic men. In prediabetic women, being obese resulted in only significantly higher systolic blood pressure, HbA1c, insulin, HOMA-IR, HOMA-β, but no other parameters, as compared with prediabetic, non-obese women (see Table 8). In diabetic men, being obese resulted in significantly higher insulin, HOMA-R, HOMA-β, TG, RLP-C, sdLDL-C, sdLDL-C/LDL-C ratio, LDL-TG, lbLDL-C, non-HDL-C, and significantly lower levels of HDL-C, HDL2-C, HDL3-C, and apoE-HDL-C, compared with non-obese diabetic men (see Table 7). In contrast, in diabetic women, being obese was only associated with significantly higher levels of insulin and HOMA-β, and significantly lower levels of HDL2-C, as compared with non-obese diabetic women (see Table 8). Surprisingly, in this analysis, the presence of obesity had little effect on fasting glucose levels, possibly because group selections by gender were based on this parameter. Similar effects of obesity using the ≥25 kg/m² criteria were observed in all of the above subgroups (see Supplementary Tables 1 and 2). It should also be noted that, as previously mentioned, the prevalence of obesity was significantly higher in prediabetic and diabetic men and women versus controls as shown in Tables 1 and 2.

We also examined the effects of statin use in normal men and women (see Supplementary Table 3), in prediabetic men and women (see Supplementary Table 4), and in diabetic men and women (see Supplementary Table 5).

### Table 6. Characteristics of female subjects on statins (n = 339)*

| Variable               | NGT n = 60 | PreDM n = 52 | DM n = 227 | P value |
|------------------------|------------|--------------|------------|---------|
|                        |            | PreDM vs DM  | DM vs NGT  |
| Age, year              |            |              |            |         |
| BMI, kg/m²             |            |              |            |         |
| Obesity prevalence     |            |              |            |         |
| Systolic BP, mmHg      |            |              |            |         |
| Diastolic BP, mmHg     |            |              |            |         |
| Fasting Glucose, mg/dL |            |              |            |         |
| HbA1c, %               |            |              |            |         |
| Insulin,               |            |              |            |         |
| HOMA-IR                |            |              |            |         |
| HOMA-β                 |            |              |            |         |

| Lipids and Lipoproteins |              |              |              |         |
|-------------------------|--------------|--------------|--------------|---------|
| Total cholesterol, mg/dL| 193.8 (56.0) | 193.5 (54.5) | 172.0 (41.0) | 0.433   |
| Triglycerides, mg/dL    | 107.6 (68.3) | 131.5 (106.3)| 120.0 (78.0)| 0.003   |
| RLP-C, mg/dL            | 7.4 (5.8)    | 9.5 (14.6)   | 6.8 (8.7)   | 0.012   |
| LDL-C, mg/dL            | 112.5 (40.6) | 110.0 (49.0)| 104.1 (39.6)| 0.733   |
| calculated LDL-C, mg/dL | 111.2 (52.1) | 102.9 (55.1)| 90.7 (35.4)| 0.261   |
| sdLDL-C, mg/dL          | 30.0 (17.2)  | 35.8 (21.4)  | 32.8 (16.9)| 0.077   |
| sdLDL-C/LDL-C ratio     | 0.278 (0.091)| 0.330 (0.136)| 0.301 (0.131)| 0.003   |
| lbLDL-C, mg/dL          | 81.7 (31.4)  | 72.2 (29.5)  | 71.7 (27.8)| 0.067   |
| LDL-TG, mg/dL           | 23.8 (6.1)   | 26.9 (10.1)  | 21.7 (8.6)| 0.105   |
| Non HDL-C, mg/dL        | 135.9 (53.9) | 138.5 (54.9)| 117.3 (36.8)| 0.972   |
| HDL-C, mg/dL            | 58.2 (15.4)  | 51.0 (12.6)  | 54.0 (13.9)| 0.002   |
| HDL2-C, mg/dL           | 32.1 (11.1)  | 26.1 (9.1)   | 30.3 (10.2)| 0.002   |
| HDL3-C, mg/dL           | 24.9 (3.9)   | 22.8 (4.9)   | 23.4 (5.3)| 0.092   |
| ApoE-HDL-C, mg/dL       | 5.8 (2.0)    | 4.9 (1.4)    | 5.0 (1.8)| 0.007   |

Data are expressed as median (interquartile range). **Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides.
statin use was significantly associated with higher age, systolic blood pressure, TG, RLP-C, sdLDL/LDL-C ratio, and LDL-TG as compared with non-users. In diabetic women, statin use was significantly associated with higher BMI, sdLDL/LDL-C ratio, LDL-TG, HDL-C, HDL3-C, and apoE-HDL-C as compared with non-users.

We have also examined correlations between parameters in men and women participating in this study (see Supplementary Tables 6, 7, and 8). We observed very strong correlations between TC, calculated LDL-C, direct LDL-C, sdLDL-C, and LDL-TG, and somewhat weaker correlations between TC and HDL3-C, HDL-C, apoE HDL-C, and RLP-C. The strongest correlations were between TC and HDL-C, and between LDL-C and RLP-C.
Our focus in this study was to carefully examine lipids and lipoprotein subfractions using standard and novel markers in subjects with prediabetes and diabetes as compared with normal subjects in a large Asian population of over 2,000 individuals. In addition, we examined these parameters in both men and women, as well as in those who are off and on lipid-lowering medication. In addition, we related these parameters to markers of glucose homeostasis, namely fasting values of glucose, insulin, HbA1c, and calculated HOMAIR and HOMA\(\beta\). Our data reinforces the concept that both increased insulin resistance and decreased insulin production underlie the pathogene-

positive correlations with TG levels were with RLP-C, LDL-TG, and sdLDL-C, as well as strong inverse correlation with HDL-C and somewhat weaker correlations with HDL3-C and apoE HDL-C. We also noted that insulin and HOMAIR values were significantly correlated with TG values, while HOMA\(\beta\) was modestly correlated with LDL-TG.

**Discussion**

In order to prevent CVD in prediabetic and diabetic subjects, not only glycemic control, but control of blood pressure and lipids and their subfractions are also important. Our focus in this study was to carefully examine lipids and lipoprotein subfractions using standard and novel markers in subjects with prediabetes and diabetes as compared with normal subjects in a large Asian population of over 2,000 individuals. In addition, we examined these parameters in both men and women, as well as in those who are off and on lipid-lowering medication. In addition, we related these parameters to markers of glucose homeostasis, namely fasting values of glucose, insulin, HbA1c, and calculated HOMAIR and HOMA\(\beta\). Our data reinforces the concept that both increased insulin resistance and decreased insulin production underlie the pathogene-
sis of prediabetes and the transition to diabetes, and that obesity plays an important role in this process. Recent studies using novel automated assays indicate that elevated levels of sdLDL-C and LDL-TG provide significant information about CVD risk above and beyond standard risk factors, and this may be the case for decreased levels of HDL subfractions and apoE HDL-C as well. However, to our knowledge, such new assays have not been applied to a relatively large population of male and female prediabetic and diabetic subjects.

It has long been known that diabetics have dyslipidemia with elevated TG, RLP-C, sdLDL-C, and decreased HDL-C values as compared to controls. However, these older observations were made with a more manual cumbersome method of measuring RLP-C and gradient gel technology for assessing LDL particle size. In addition, more recently, it has been documented that diabetic subjects on statin therapy get additional benefit from the addition of fenofibrate if they have fasting TG values $\geq 204$ mg/dL and HDL-C values $\geq 35$ mg/dL. It is also known that statins can have beneficial effects not only on calculated LDL-C, but also on TG, RLP-C, direct LDL-C, sdLDL-C, and sdLDL-C. While statins clearly have strikingly beneficial effects on CVD risk reduction in
Table 7. Effects of Obesity Status (Taiwanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Men*

| Variables                        | NGT          | PreDM        | DM            |
|----------------------------------|--------------|--------------|---------------|
|                                 | BMI < 27     | BMI ≥ 27     | BMI < 27      | BMI ≥ 27      | p  |
|                                 | n = 220      | n = 50       | n = 140       | n = 53        |    |
| Age, year                        | 55.7 (20.7)  | 54.6 (19.4)  | 60.9 (17.9)   | 58.3 (20.7)   | 0.338 |
| BMI, kg/m²                       | 23.5 (3.4)   | 29.0 (2.5)   | 24.2 (2.9)    | 28.7 (3.3)    | 0.000 |
| Systolic BP, mmHg                | 122.0 (16.0) | 128.0 (19.8) | 127.0 (19.5)  | 131.0 (25.5)  | 0.004 |
| Fasting Glucose, mg/dL           | 7.0 (5.8)    | 13.6 (9.0)   | 10.0 (5.9)    | 17.1 (14.8)   | 0.017 |
| HbA1c, %                         | 5.5 (0.4)    | 5.6 (0.5)    | 5.8 (0.4)     | 5.8 (0.6)     | 0.140 |
| Insulin                          | 92.0 (8.0)   | 93.0 (7.5)   | 104.0 (8.3)   | 105.0 (13.0)  | 0.222 |
| HOMA-IR                          | 1.6 (1.4)    | 3.1 (2.2)    | 2.6 (1.7)     | 4.6 (4.0)     | 0.000 |
| HOMA-β                           | 89.0 (70.5)  | 183.1 (116.2)| 78.9 (49.1)   | 131.8 (106.6)| 0.000 |
| Lipids and Lipoproteins          |              |              |              |              |    |
| Total cholesterol, mg/dL         | 192.0 (53.5) | 198.1 (65.1)| 188.0 (44.3) | 196.0 (37.0)| 0.262 |
| Triglycerides, mg/dL             | 99.0 (62.3)  | 144.5 (99.5)| 111.5 (78.3) | 147.0 (117.0)| 0.000 |
| RLP-C, mg/dL                     | 6.0 (6.8)    | 10.1 (13.5)  | 7.4 (9.2)     | 11.8 (11.7)   | 0.005 |
| LDL-C, mg/dL                     | 111.4 (43.7) | 116.8 (59.7)| 108.5 (40.4) | 120.5 (46.8) | 0.057 |
| calculated LDL-C, mg/dL          | 115.9 (50.7) | 115.7 (48.0)| 111.0 (44.5) | 115.4 (41.1)| 0.319 |
| sdLDL-C, mg/dL                   | 29.0 (20.5)  | 35.4 (35.0)  | 32.0 (20.7)   | 43.6 (26.3)   | 0.001 |
| sdLDL-C/LDL-C ratio              | 0.256 (0.112)| 0.301 (0.154)| 0.289 (0.128)| 0.327 (0.170)| 0.008 |
| lbLDL-C, mg/dL                   | 80.1 (34.1)  | 78.7 (39.1)  | 78.0 (31.6)   | 79.7 (36.7)   | 0.001 |
| LDL-TG, mg/dL                    | 21.8 (10.3)  | 25.4 (17.6)  | 22.4 (9.5)    | 27.3 (9.8)    | 0.003 |
| Non-HDL-C, mg/dL                 | 139.5 (52.8) | 145.6 (58.9)| 137.0 (42.5) | 151.1 (39.3)| 0.032 |
| HDL-C, mg/dL                     | 51.9 (17.4)  | 44.8 (16.1)  | 49.5 (16.4)   | 51.0 (15.4)   | 0.004 |
| LDL₁-C, mg/dL                    | 27.9 (13.2)  | 24.3 (10.8)  | 26.7 (9.2)    | 28.1 (10.8)   | 0.001 |
| LDL₂-C, mg/dL                    | 23.0 (5.5)   | 22.3 (5.0)   | 22.7 (4.9)    | 22.9 (6.0)    | 0.001 |
| ApoE-HDL, mg/dL                  | 4.7 (2.1)    | 4.2 (2.4)    | 4.7 (2.0)     | 4.7 (2.1)     | 0.000 |

*Obesity criteria based on Taiwanese criteria of < or ≥ 27 kg/m², and all data are expressed as median (interquartile range). The prevalence of obesity was 18.5%, 27.5%, and 40.4% in the NGT, prediabetic, and diabetic groups, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.
### Table 8. Effects of Obesity Status (Taiwanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Women

| Variables               | NGT          | PreDM         | DM            |
|-------------------------|--------------|---------------|---------------|
|                         | BMI < 27     | BMI ≥ 27      | BMI < 27      | BMI ≥ 27      | BMI < 27      | BMI ≥ 27      | P            |
| Age, year               |              |               |               |               |               |               |              |
| BMI, kg/m²              |              |               |               |               |               |               |              |
| Systolic BP, mmHg       |              |               |               |               |               |               |              |
| Diastolic BP, mmHg      |              |               |               |               |               |               |              |
| Fasting Glucose, mg/dL  |              |               |               |               |               |               |              |
| HbA1c, %                |              |               |               |               |               |               |              |
| Insulin,                |              |               |               |               |               |               |              |
| HOMA-IR                 |              |               |               |               |               |               |              |
| HOMA-β                  |              |               |               |               |               |               |              |
| Lipids and Lipoproteins|              |               |               |               |               |               |              |
| Total cholesterol, mg/dL|              |               |               |               |               |               |              |
| Triglycerides, mg/dL    |              |               |               |               |               |               |              |
| RLP-C, mg/dL            |              |               |               |               |               |               |              |
| LDL-C, mg/dL            |              |               |               |               |               |               |              |
| calculated LDL-C, mg/dL |              |               |               |               |               |               |              |
| sdLDL-C, mg/dL          |              |               |               |               |               |               |              |
| sdLDL-C/LDL-C ratio     |              |               |               |               |               |               |              |
| lbLDL-C, mg/dL          |              |               |               |               |               |               |              |
| LDL-TG, mg/dL           |              |               |               |               |               |               |              |
| Non HDL-C, mg/dL        |              |               |               |               |               |               |              |
| HDL-C, mg/dL            |              |               |               |               |               |               |              |
| ApoE-HDL-C, mg/dL       |              |               |               |               |               |               |              |

*Obesity criteria based on Taiwan definitions of < or ≥ 27 kg/m², and data are expressed as median (interquartile range). The prevalence of obesity was 6.8%, 22.5%, and 36.4% in the NGT, prediabetic, and diabetic groups, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.
Lipoprotein Subfractions in Prediabetes and Diabetes

In the present study, fasting triglycerides were significantly higher in male and female prediabetic and diabetic subjects as compared with controls in all subjects, as well as in those on and off lipid-lowering medications, except for male prediabetics and female diabetics on lipid-lowering therapy. RLP-C levels were highest in prediabetics, and in this group, lipid-lowering treatment abolished these differences in men, but not in women. It is known that RLP-C may be an especially important CVD risk factor in women, and it is possible that the addition of fibrates or omega-3 fatty acids on top of statin therapy may be very important to minimize CVD risk. With regard to direct LDL-C, calculated LDL-C, and lbLDL-C differences between prediabetics and diabetics versus control subjects were relatively small. An important novel finding in this study was that calculated LDL-C, using the Friedewald formula, significantly underestimated direct LDL-C with the assay used by slightly more than 10%. We therefore recommend the use of direct LDL-C in this population because it is the primary target of lipid-lowering therapy.

It should also be noted that sdLDL has been shown to be the more atherogenic component of LDL. Prediabetic subjects were most likely to have increases in this parameter, as compared with control subjects. However, sdLDL-C differences were greater in female prediabetic and diabetic subjects than in men, and the use of statin therapy in these subjects did not abolish differences in women. These findings indicate that possibly, either more intensive statin therapy or additional treatments such as fibrates or omega-3 fatty acids may be necessary to treat elevated TG-rich lipoproteins and sdLDL-C in prediabetic and diabetic subjects to minimize residual CVD risk.

LDL-TG, a new CVD marker, was highest in the prediabetic subjects, and statin therapy did not minimize these differences. Since a recent study has shown that LDL-TG levels are higher in CHD than in controls, our findings may be one of the reasons why prediabetes is linked to atherosclerosis. However, it was unexpected that LDL-TG levels were lower in this population in diabetic subjects than in normal subjects. We have observed a modest positive correlation between HOMA and LDL-TG, and since diabetics have lower HOMA values, this may account for this difference. Whether this finding is also true in other populations remains to be confirmed. It should be noted that insulin deficiency and decreased HOMA appears to be more common among Asian diabetics than that observed in western Caucasian populations where obesity and insulin resistance may be more common. This may also explain why we see differences in LDL-TG values in this population between prediabetic and diabetic subjects.

In addition, direct LDL-C levels were also lower in diabetic subjects, however, sdLDL-C levels were higher or similar to controls, resulting in sdLDL-C/LDL-C ratios in patients with T2DM that were significantly higher than in any other group. A previous study in a Japanese population has assessed cholesterol and TG in twenty lipoprotein subfractions, and documented that smaller LDL particles carry less TG than larger LDL and VLDL particles. From this viewpoint, it makes sense that LDL-TG levels are lower in diabetics than in controls, since the number of sdLDL particles increases in patients with diabetes. Our overall data indicate that attempts to normalize sdLDL-C and LDL-TG levels in prediabetic and diabetic subjects need to be made to normalize their CVD risk.

Diabetics in our population and female prediabetics had significantly lower levels of HDL-C and HDL subfractions than controls, placing them at increased CVD risk. We have observed significant correlations between HDL-C, HDL3-C, HDL2-C, and apoE-HDL-C, and noted significantly lower values in diabetic men and prediabetic and diabetic women as compared to controls. These differences persisted for all parameters in patients on lipid-lowering treatment, except for HDL2-C. It is still uncertain whether apoE-rich HDL particles are athero-protective. Similarly, there is an ongoing debate as to whether serum HDL3-C is cardioprotective. While serum glucose levels in diabetics are not high enough to be diagnosed as diabetes, overall, their lipid values are similar to those in diabetics. Our findings on the pattern of lipid profiles support the concept that CVD risk in prediabetics may be as high as in those with diabetes.

The strength of this study is the relatively large number of participants in the 3 groups for both genders. Moreover, we examined subjects on and off statin therapy. The data trends were very similar in all groups. In addition, all subjects were on stable therapy for their lipid alterations as well as for diabetes if present for at least 6 months prior to the study. While absolute values of lipid parameters are known to be influenced by lipid medications, the trends and differences observed when normal, prediabetics, and diabetics were compared, was not greatly different. The participants with diabetes were also taking anti-diabetes medications, mostly metformin, but all subjects receiving insulin were excluded. Metformin and other glucose-lowering medication may affect lipid profiles, but do not cause rapid changes since their diabetic conditions were stable and their medications were not changed for at least 6 months. While we only studied a Tai-
wanese population, another limitation of this study, these findings need to be replicated in other populations using these newer lipoprotein assays. It should be noted that our study was cross-sectional, and prospective treatment studies in diabetics or prediabetics need to be performed in order to further assess potential changes in the various lipoprotein fractions measured.

**Conclusion**

In summary, we compared novel lipoprotein parameters in normal, prediabetic and diabetic subjects. Prediabetic subjects were more likely to have elevated TG, RLP-C, sdLDL-C, and LDL-TG, while diabetic subjects were more likely to have decreases in HDL-C and HDL subfractions than normal subjects. These findings indicate that in this large Asian population, prediabetes is associated with greater increases in atherogenic lipoproteins, while diabetes is more likely to be associated with low levels of HDL and its subfractions. These findings suggest that insulin resistance, as seen in prediabetes, plays an important role in modulating changes TG-rich lipoproteins, while both insulin resistance and impaired insulin production, as seen in the diabetic state, may be more important in the regulation of HDL and its subfractions. In our view, both increases in atherogenic lipoproteins and decreases in HDL and its subfractions modulate CVD risk. Weight loss may be the best strategy to improve these abnormalities, and in the case of atherogenic lipoproteins, the combination of statins, fibrates, and omega-3 fatty acids. Moreover, our data indicate that calculated LDL-C significantly underestimated direct LDL-C in subjects with diabetes. In our view, direct LDL-C and sdLDL-C should be measured and optimized in both diabetic and prediabetic subjects to reduce CVD risk.

**Acknowledgements**

The contribution of all participants in this study is gratefully acknowledged and gratefully appreciated. Also, the authors thank Dr. Margaret Diffenderfer for assistance in manuscript preparation.

**Funding**

This study was supported by the research funding of the Lotung Poh-ai Hospital, Lotung, Taiwan. The research project reference AEP2017070059

**Conflict of Interests**

YI is an employee of Denka-Seiken Corporation, MA is supported by a research grant from Denka-Seiken Co., Tokyo, Japan. All other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical Approval**

The research was approved by the ethics committee of the School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan. (Reference number: M2000-2350).

**Contributorship**

HH and MA designed and conducted the study. HH, PH, and MHC recruited study subjects and collected data. HH, EK, and MA, analyzed the data. HH, MA, and EJS wrote the first version of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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### Supplemental Table 1. Effects of Obesity Status (Japanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Men *

| Variables | NGT | | | | PreDM | | | | DM | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|           | BMI < 25 | BMI ≥ 25 | n = 162 | n = 108 | p | BMI < 25 | BMI ≥ 25 | n = 94 | n = 99 | p | BMI < 25 | BMI ≥ 25 | n = 206 | n = 331 | p |
| Age, year | 56.1 (21.0) | 54.0 (20.7) | 0.334 | | | 61.5 (19.3) | 59.6 (18.0) | 0.457 | | | 63.8 (15.9) | 60.4 (14.2) | 0.000 |
| BMI, kg/m² | 22.6 (2.6) | 26.7 (3.1) | 0.000 | | | 23.2 (2.4) | 27.2 (3.1) | 0.000 | | | 23.1 (2.1) | 28.0 (3.7) | 0.000 |
| Systolic BP, mmHg | 121.0 (17.0) | 124.0 (16.0) | 0.009 | | | 123.0 (20.0) | 130.0 (23.8) | 0.000 | | | 130.0 (11.0) | 130.0 (14.0) | 0.836 |
| Diastolic BP, mmHg | 71.0 (15.0) | 77.0 (12.0) | 0.002 | | | 74.0 (14.0) | 80.0 (13.8) | 0.002 | | | 70.0 (10.0) | 70.0 (10.0) | 0.375 |
| Fasting Glucose, mg/dL | 5.5 (0.4) | 5.5 (0.4) | 0.215 | | | 5.8 (0.4) | 5.8 (0.5) | 0.671 | | | 6.8 (1.2) | 7.1 (1.3) | 0.078 |
| Insulin, | 6.3 (4.9) | 11.9 (8.9) | 0.000 | | | 8.8 (4.3) | 13.0 (10.5) | 0.000 | | | 7.5 (6.0) | 13.3 (11.0) | 0.000 |
| HOMA-IR | 1.4 (1.1) | 2.6 (2.1) | 0.000 | | | 2.3 (1.4) | 3.5 (3.0) | 0.000 | | | 2.6 (2.1) | 4.4 (4.1) | 0.000 |
| HOMA-β | 82.9 (61.0) | 150.2 (111.6) | 0.000 | | | 76.3 (39.0) | 110.8 (81.4) | 0.000 | | | 40.5 (44.5) | 69.1 (66.4) | 0.000 |

| Lipids and Lipoproteins | | | | | | | | | | | |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Total cholesterol, mg/dL | 193.0 (53.0) | 190.5 (58.3) | 0.828 | | | 189.5 (45.3) | 190.0 (41.0) | 0.255 | | | 171.0 (37.8) | 171.0 (42.0) | 0.968 |
| Triglycerides, mg/dL | 94.0 (54.5) | 125.0 (90.3) | 0.000 | | | 108.0 (76.0) | 142.0 (94.5) | 0.004 | | | 102.0 (75.8) | 128.0 (94.5) | 0.000 |
| RLP-C, mg/dL | 5.7 (6.0) | 8.3 (11.9) | 0.593 | | | 7.1 (8.5) | 10.1 (10.6) | 0.018 | | | 5.0 (6.3) | 7.9 (10.0) | 0.002 |
| LDL-C, mg/dL | 111.4 (43.2) | 113.8 (51.5) | 0.480 | | | 107.3 (42.7) | 118.3 (47.4) | 0.031 | | | 106.8 (32.0) | 106.6 (33.4) | 0.448 |
| Calculated LDL-C, mg/dL | 118.6 (50.1) | 109.9 (46.5) | 0.691 | | | 113.6 (43.4) | 111.5 (42.5) | 0.543 | | | 94.3 (30.6) | 94.1 (36.1) | 0.910 |
| sLDL-C, mg/dL | 28.3 (18.8) | 33.5 (29.1) | 0.001 | | | 29.6 (19.8) | 39.5 (24.1) | 0.000 | | | 29.2 (18.7) | 35.4 (21.9) | 0.000 |
| sLDL-C/LDL-C ratio | 0.247 (0.104) | 0.289 (0.144) | 0.000 | | | 0.272 (0.136) | 0.317 (0.170) | 0.003 | | | 0.267 (0.111) | 0.320 (0.172) | 0.000 |
| lbLDL-C, mg/dL | 81.9 (35.5) | 77.8 (34.1) | 0.170 | | | 78.1 (28.6) | 79.5 (37.1) | 0.631 | | | 75.5 (25.4) | 72.1 (28.0) | 0.028 |
| LDL-TG, mg/dL | 20.8 (10.3) | 24.2 (11.4) | 0.000 | | | 21.8 (8.1) | 25.4 (10.1) | 0.000 | | | 18.3 (7.6) | 20.1 (7.8) | 0.012 |
| Non-HDL-C, mg/dL | 140.9 (53.8) | 139.7 (58.9) | 0.268 | | | 139.0 (42.3) | 139.0 (45.8) | 0.108 | | | 119.5 (33.9) | 125.1 (37.4) | 0.052 |
| HDL-C, mg/dL | 53.0 (19.1) | 47.1 (16.7) | 0.000 | | | 49.9 (18.0) | 50.1 (14.2) | 0.320 | | | 50.1 (15.0) | 44.6 (11.5) | 0.000 |
| HDL₁-C, mg/dL | 29.1 (13.6) | 24.4 (9.7) | 0.000 | | | 26.8 (11.1) | 27.1 (9.6) | 0.475 | | | 27.4 (10.3) | 24.0 (7.1) | 0.000 |
| HDL₂-C, mg/dL | 23.3 (5.6) | 22.3 (5.4) | 0.172 | | | 22.8 (5.3) | 22.5 (5.4) | 0.190 | | | 21.1 (4.9) | 20.3 (5.1) | 0.012 |
| ApoE-HDL-C, mg/dL | 4.8 (2.3) | 4.3 (2.2) | 0.001 | | | 4.7 (2.2) | 4.7 (1.9) | 0.515 | | | 4.2 (1.8) | 3.7 (1.5) | 0.000 |

*Obesity criteria based on Japanese criteria of < or ≥ 25 kg/m², and all data are expressed as median (interquartile range). The prevalence of obesity was 40.0%, 51.3%, and 61.6% in the NGT, prediabetic, and diabetic groups, respectively. Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.
## Supplemental Table 2. Effects of Obesity Status (Japanese Criteria) on Biochemical Variables in Normal, Prediabetic, and Diabetic Women

| Variables                      | Normal          | PreDM           | Diabetic        |
|--------------------------------|-----------------|-----------------|-----------------|
|                                | BMI < 25       | BMI ≥ 25       | BMI < 25       | BMI ≥ 25       | P    |
|                                | n = 291        | n = 90         | n = 88         | n = 50         | P    |
| Age, year                      | 50.5 (16.7)    | 53.9 (19.8)    | 58.1 (18.2)    | 66.7 (17.2)    | 0.009 |
| BMI, kg/m²                     | 21.8 (2.9)     | 26.6 (2.2)     | 22.3 (2.6)     | 28.0 (3.8)     | 0.000 |
| Systolic BP, mmHg              | 116.5 (20.0)   | 121.0 (13.0)   | 122.0 (20.0)   | 125.0 (16.0)   | 0.002 |
| Diastolic BP, mmHg             | 68.0 (14.0)    | 73.0 (12.5)    | 70.0 (12.3)    | 72.0 (15.5)    | 0.000 |
| Fasting Glucose, mg/dL         | 89.0 (8.0)     | 92.0 (8.0)     | 105.0 (11.3)   | 105.0 (10.8)   | 0.356 |
| HbA1c, %                       | 5.4 (0.5)      | 5.6 (0.4)      | 5.9 (0.6)      | 6.0 (0.6)      | 0.001 |
| Insulin                        | 7.5 (5.5)      | 10.7 (5.6)     | 11.1 (7.4)     | 14.8 (10.3)    | 0.002 |
| HOMA-IR                        | 1.6 (1.3)      | 2.3 (1.2)      | 2.8 (2.2)      | 4.0 (2.8)      | 0.001 |
| HOMA-β                         | 108.0 (71.9)   | 138.5 (102.6)  | 87.0 (59.5)    | 122.4 (74.0)   | 0.000 |

### Lipids and Lipoproteins

- **Total cholesterol, mg/dL**: 198.0 (49.0) vs 194.0 (47.9), 0.645 vs 192.5 (42.8) vs 196.5 (45.0), 0.659 vs 177.5 (35.1) vs 174.0 (38.5), 0.613
- **Triglycerides, mg/dL**: 80.0 (56.0) vs 108.6 (73.0), 0.000 vs 114.5 (115.8) vs 126.0 (73.8), 0.295 vs 116.0 (83.0) vs 122.0 (82.5), 0.133
- **RLP-C, mg/dL**: 4.7 (4.2) vs 6.8 (6.4), 0.980 vs 7.9 (11.5) vs 9.0 (9.3), 0.626 vs 5.4 (6.4) vs 6.8 (8.8), 0.129
- **LDL-C, mg/dL**: 115.0 (40.1) vs 119.6 (39.4), 0.180 vs 117.6 (41.3) vs 113.9 (40.8), 0.918 vs 105.1 (39.9) vs 108.4 (31.7), 0.219
- **Calculated LDL-C, mg/dL**: 116.8 (41.4) vs 114.6 (45.5), 0.899 vs 108.6 (41.3) vs 115.2 (38.7), 0.381 vs 97.5 (32.0) vs 94.4 (32.5), 0.335
- **sdLDL-C, mg/dL**: 26.4 (15.0) vs 31.6 (19.4), 0.008 vs 33.6 (20.5) vs 34.5 (22.5), 0.952 vs 31.4 (18.8) vs 31.5 (20.2), 0.092
- **sdLDL-C/LDL-C ratio**: 0.226 (0.080) vs 0.256 (0.097), 0.003 vs 0.294 (0.132) vs 0.275 (0.115), 0.913 vs 0.285 (0.116) vs 0.293 (0.147), 0.122
- **lbLDL-C, mg/dL**: 87.8 (27.9) vs 87.5 (27.8), 0.824 vs 82.6 (32.1) vs 80.6 (25.8), 0.920 vs 72.3 (27.7) vs 75.6 (26.7), 0.673
- **LDL-TG, mg/dL**: 20.1 (8.3) vs 25.1 (9.1), 0.000 vs 23.4 (11.1) vs 26.2 (8.8), 0.139 vs 20.4 (7.6) vs 21.4 (8.6), 0.212
- **Non-HDL-C, mg/dL**: 131.3 (49.3) vs 137.3 (46.3), 0.241 vs 135.8 (44.5) vs 145.2 (38.9), 0.217 vs 121.6 (39.5) vs 122.0 (34.2), 0.988
- **HDL-C, mg/dL**: 60.8 (19.3) vs 55.6 (14.6), 0.000 vs 53.8 (17.0) vs 51.1 (12.8), 0.030 vs 53.0 (16.2) vs 51.8 (13.5), 0.157
- **HDL-C, mg/dL**: 36.0 (16.2) vs 30.8 (12.1), 0.000 vs 30.4 (12.7) vs 28.1 (9.2), 0.014 vs 30.1 (12.4) vs 28.9 (9.7), 0.050
- **HDL-C, mg/dL**: 25.2 (4.6) vs 24.9 (4.3), 0.037 vs 24.0 (5.4) vs 23.3 (5.2), 0.493 vs 23.0 (5.7) vs 22.6 (5.5), 0.957
- **ApoE-HDL, mg/dL**: 5.9 (2.4) vs 5.3 (1.8), 0.000 vs 5.3 (2.1) vs 4.8 (1.9), 0.029 vs 4.7 (2.0) vs 4.7 (1.8), 0.479

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*Obesity criteria based on Japanese criteria of < 25.0 kg/m², and all data are expressed as median (interquartile range). The prevalence of obesity was 26.4%, 36.2%, and 54.8% in the NGT, pre-diabetic, and diabetic subjects, respectively.

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides; non HDL-C, Non HDL cholesterol.
Supplemental Table 3. Comparison of variables between normal participants with or without using statin*

| Variables                      | Male Participants | Female Participants |   |
|--------------------------------|-------------------|---------------------|---|
|                                | Statin − (n = 207) | Statin + (n = 62)   | P | Statin − (n = 324) | Statin + (n = 60) | P |
| Age, year                      | 52.2 (18.3)       | 66.0 (16.2)         | 0.000 | 49.3 (12.9)       | 69.5 (13.0) | 0.000 |
| BMI, kg/m²                     | 23.9 (4.1)        | 24.7 (3.4)          | 0.044 | 22.5 (4.0)        | 24.0 (4.1) | 0.001 |
| Obesity Prevalence             | 36 (17.4%)        | 14 (22.6%)          | 0.009 | 25 (7.7%)         | 10 (16.7%) | 0.003 |
| Systolic BP, mmHg              | 122.0 (15.8)      | 130.0 (15.3)        | 0.097 | 117.0 (19.0)      | 129.5 (18.3) | 0.000 |
| Diastolic BP, mmHg             | 74.0 (13.0)       | 75.0 (10.8)         | 0.348 | 68.0 (14.0)       | 76.0 (10.5) | 0.020 |
| Fasting Glucose, mg/dL         | 92.0 (7.5)        | 94.0 (7.0)          | 0.182 | 89.5 (8.0)        | 92.0 (8.5) | 0.000 |
| HbA1c, %                       | 5.5 (0.4)         | 5.6 (0.3)           | 0.584 | 5.4 (0.4)         | 5.6 (0.5) | 0.000 |
| Insulin, g/L                   | 7.9 (7.4)         | 8.5 (6.8)           | 0.494 | 7.9 (5.6)         | 10.1 (7.6) | 0.004 |
| HOMA-IR                        | 1.8 (1.6)         | 1.9 (1.5)           | 0.578 | 1.8 (1.3)         | 2.3 (1.7) | 0.001 |
| HOMA-β                         | 99.5 (96.2)       | 104.0 (68.5)        | 0.271 | 110.7 (76.0)      | 128.9 (85.5) | 0.483 |
| Lipids and Lipoproteins        |                   |                     |     |                   |                     | |
| Total cholesterol, mg/dL       | 196.1 (50.5)      | 175.5 (57.2)        | 0.056 | 198.0 (47.3)      | 193.8 (56.0) | 0.767 |
| Triglycerides, mg/dL           | 103.0 (79.5)      | 100.5 (47.3)        | 0.260 | 81.0 (57.5)       | 107.6 (68.3) | 0.000 |
| RLP-C, mg/dL                   | 6.3 (8.2)         | 5.7 (5.6)           | 0.309 | 4.8 (4.2)         | 7.4 (5.8) | 0.842 |
| LDL-C, mg/dL                   | 116.7 (44.8)      | 102.1 (46.0)        | 0.194 | 117.7 (39.2)      | 112.5 (40.6) | 0.285 |
| calculated LDL-C, mg/dL        | 119.2 (44.3)      | 100.6 (51.9)        | 0.078 | 117.3 (40.7)      | 111.2 (52.1) | 0.342 |
| sdLDL-C, mg/dL                 | 30.7 (22.9)       | 27.5 (15.0)         | 0.216 | 26.5 (16.8)       | 30.0 (17.2) | 0.218 |
| sdLDL-C/LDL-C ratio            | 0.256 (0.118)     | 0.265 (0.070)       | 0.460 | 0.226 (0.081)     | 0.278 (0.091) | 0.000 |
| lbLDL-C, mg/dL                 | 84.9 (33.0)       | 76.0 (32.7)         | 0.324 | 89.8 (27.4)       | 81.7 (31.4) | 0.019 |
| LDL-TG, mg/dL                  | 22.1 (11.3)       | 22.0 (8.2)          | 0.419 | 20.1 (9.9)        | 23.8 (6.1) | 0.001 |
| Non HDL-C, mg/dL               | 142.9 (52.2)      | 122.9 (51.7)        | 0.062 | 133.4 (48.1)      | 135.9 (53.9) | 0.696 |
| HDL-C, mg/dL                   | 51.6 (18.1)       | 49.9 (16.0)         | 0.729 | 59.9 (18.8)       | 58.2 (15.4) | 0.088 |
| HDL₃-C, mg/dL                  | 27.6 (13.0)       | 26.4 (12.9)         | 0.961 | 34.7 (16.1)       | 32.1 (11.1) | 0.074 |
| HDL₄-C, mg/dL                  | 23.0 (5.8)        | 22.8 (4.2)          | 0.279 | 25.1 (4.7)        | 24.9 (3.9) | 0.534 |
| ApoE-HDL, mg/dL                | 4.6 (2.1)         | 4.5 (2.5)           | 0.962 | 5.7 (2.3)         | 5.8 (2.0) | 0.354 |

*Data are expressed as median (interquartile range).

**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides
# Supplemental Table 4. Comparison of variables between prediabetic participants with or without using statin*

| Variables                      | Male Participants | Female Participants |  |
|--------------------------------|-------------------|---------------------|---|
|                                | Statin - (n = 117) | Statin + (n = 79)  | P | Statin - (n = 90) | Statin + (n = 52) | P |
| Age, year                      | 54.5 (18.5)       | 66.0 (12.7)         | 0.000 | 54.7 (19.2)       | 68.0 (12.8)         | 0.000 |
| BMI, kg/m²                      | 25.3 (4.0)        | 25.0 (4.1)          | 0.067 | 24.1 (5.2)        | 23.5 (4.5)          | 0.079 |
| Obesity Prevalence             | 36 (30.8%)**      | 16 (20.3%)**        | 0.888 | 23 (25.5%)**      | 8 (15.4%)**         | 0.371 |
| Systolic BP, mmHg              | 130.0 (22.0)      | 127.0 (12.0)        | 0.309 | 120.0 (17.0)      | 130.0 (10.0)        | 0.041 |
| Diastolic BP, mmHg             | 77.0 (17.0)       | 75.0 (11.0)         | 0.170 | 70.5 (11.8)       | 77.0 (12.0)         | 0.136 |
| Fasting Glucose, mg/dL         | 105.0 (10.0)      | 106.0 (8.5)         | 0.563 | 105.0 (11.0)      | 104.5 (10.3)        | 0.158 |
| HbA1c, %                       | 5.8 (0.5)         | 5.9 (0.4)           | 0.807 | 5.8 (0.7)         | 5.9 (0.4)           | 0.544 |
| Insulin,                        | 10.6 (8.9)        | 11.2 (8.0)          | 0.319 | 11.9 (8.2)        | 13.4 (10.2)         | 0.566 |
| HOMA-IR                        | 2.7 (2.3)         | 3.0 (2.1)           | 0.449 | 3.2 (2.2)         | 3.4 (2.6)           | 0.899 |
| HOMA-β                         | 85.1 (63.5)       | 90.4 (51.9)         | 0.254 | 95.7 (64.5)       | 116.4 (75.1)        | 0.065 |
| Lipids and Lipoproteins        |                   |                     |     |                   |                     |    |
| Total cholesterol, mg/dL       | 192.0 (32.0)      | 184.0 (56.0)        | 0.306 | 194.5 (38.5)      | 193.5 (54.5)        | 0.234 |
| Triglycerides, mg/dL           | 133.0 (99.0)      | 111.0 (69.0)        | 0.119 | 106.5 (82.8)      | 131.5 (106.3)       | 0.002 |
| RLP-C, mg/dL                   | 10.1 (11.6)       | 7.4 (8.3)           | 0.029 | 7.0 (8.4)         | 9.5 (14.6)          | 0.012 |
| LDL-C, mg/dL                   | 115.5 (40.9)      | 106.7 (48.8)        | 0.579 | 118.1 (39.5)      | 110.0 (49.0)        | 0.124 |
| calculated LDL-C, mg/dL        | 114.1 (38.0)      | 106.9 (47.7)        | 0.912 | 113.5 (36.2)      | 106.3 (55.2)        | 0.055 |
| sdLDL-C, mg/dL                 | 34.9 (26.1)       | 33.4 (22.4)         | 0.369 | 32.5 (22.5)       | 35.8 (21.4)         | 0.271 |
| sdLDL-C/LDL-C ratio            | 0.310 (0.164)     | 0.288 (0.121)       | 0.356 | 0.272 (0.103)     | 0.330 (0.136)       | 0.002 |
| lbLDL-C, mg/dL                 | 79.7 (32.5)       | 73.8 (31.0)         | 0.902 | 84.4 (22.7)       | 72.2 (29.5)         | 0.004 |
| LDL-TG, mg/dL                  | 23.4 (10.9)       | 22.9 (8.8)          | 0.259 | 23.3 (10.6)       | 26.9 (10.1)         | 0.168 |
| Non HDL-C, mg/dL               | 141.6 (33.2)      | 131.1 (50.3)        | 0.320 | 139.7 (38.8)      | 138.5 (54.9)        | 0.614 |
| HDL-C, mg/dL                   | 51.4 (18.0)       | 49.4 (13.8)         | 0.846 | 53.6 (16.7)       | 51.0 (12.6)         | 0.054 |
| HDL⊥-C, mg/dL                  | 26.3 (12.4)       | 27.1 (7.9)          | 0.851 | 29.8 (13.7)       | 26.1 (9.1)          | 0.059 |
| HDL⊥-C, mg/dL                  | 22.9 (5.5)        | 22.5 (5.3)          | 0.888 | 23.9 (5.4)        | 22.8 (4.9)          | 0.205 |
| ApoE-HDL, mg/dL                | 4.8 (2.1)         | 4.6 (1.9)           | 0.919 | 5.2 (2.3)         | 4.9 (1.4)           | 0.259 |

*Data are expressed as median (interquartile range).**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides
**Supplemental Table 5.** Comparison of variables between diabetic participants with or without using statin*

| Variables                  | Male Participants | Female Participants |
|----------------------------|-------------------|---------------------|
|                            | Statin − (n = 281) | Statin + (n = 206)  | p          | Statin − (n = 208) | Statin + (n = 227) | p          |
| Age, year                  | 61.9 (13.4)       | 62.4 (15.2)         | 0.521      | 63.6 (11.9)       | 64.3 (13.1)         | 0.286      |
| BMI, kg/m²                 | 25.4 (4.7)        | 26.6 (4.9)          | 0.007      | 24.8 (4.8)        | 26.2 (5.4)          | 0.001      |
| Obesity Prevalence         | 94 (33.5%)**      | 88 (42.7%)**        | 0.001      | 57 (27.4%)**      | 94 (41.4%)**        | 0.058      |
| Systolic BP, mmHg          | 130.0 (14.0)      | 130.0 (10.0)        | 0.945      | 130.0 (19.5)      | 130.0 (10.0)        | 0.352      |
| Diastolic BP, mmHg         | 76.0 (10.0)       | 70.0 (10.0)         | 0.419      | 70.0 (10.0)       | 70.0 (10.0)         | 0.257      |
| Fasting Glucose, mg/dL     | 134.0 (35.0)      | 132.0 (39.8)        | 0.311      | 132.0 (39.5)      | 131.0 (42.0)        | 0.618      |
| HbA1c, %                   | 6.9 (1.1)         | 6.8 (1.4)           | 0.657      | 7.0 (1.2)         | 6.9 (1.3)           | 0.189      |
| Insulin, mg/L              | 10.5 (10.7)       | 10.4 (7.9)          | 0.495      | 12.0 (9.4)        | 13.7 (10.5)         | 0.644      |
| HOMA-IR                    | 3.3 (3.7)         | 3.5 (3.0)           | 0.611      | 4.0 (3.6)         | 4.6 (3.9)           | 0.757      |
| HOMA-β                     | 55.2 (61.7)       | 60.0 (56.7)         | 0.522      | 60.9 (60.0)       | 69.2 (72.7)         | 0.155      |
| Lipids and Lipoproteins    |                   |                     |            |                   |                     |            |
| Total cholesterol, mg/dL   | 171.0 (33.0)      | 168.0 (50.8)        | 0.214      | 178.0 (31.1)      | 172.0 (41.0)        | 0.971      |
| Triglycerides, mg/dL       | 116.0 (91.0)      | 118.0 (88.3)        | 0.579      | 118.0 (75.0)      | 120.0 (78.0)        | 0.126      |
| RLP-C, mg/dL               | 5.6 (8.0)         | 7.3 (9.4)           | 0.133      | 5.3 (6.1)         | 6.8 (8.7)           | 0.073      |
| LDL-C, mg/dL               | 107.2 (30.1)      | 104.7 (40.9)        | 0.087      | 108.4 (29.7)      | 104.1 (39.6)        | 0.655      |
| calculated LDL-C, mg/dL    | 94.1 (30.9)       | 92.7 (40.5)         | 0.141      | 101.0 (27.1)      | 91.3 (34.7)         | 0.099      |
| sdLDL-C, mg/dL             | 31.8 (18.8)       | 33.2 (21.0)         | 0.056      | 29.4 (19.9)       | 32.8 (16.9)         | 0.039      |
| sdLDL-C/LDL-C ratio        | 0.288 (0.139)     | 0.304 (0.140)       | 0.298      | 0.272 (0.124)     | 0.301 (0.131)       | 0.011      |
| lbLDL-C, mg/dL             | 74.6 (25.2)       | 72.4 (26.8)         | 0.394      | 76.4 (24.1)       | 71.7 (27.8)         | 0.304      |
| LDL-TG, mg/dL              | 18.1 (6.6)        | 20.0 (8.1)          | 0.003      | 19.3 (7.9)        | 21.7 (8.6)          | 0.000      |
| Non HDL-C, mg/dL           | 122.8 (30.9)      | 119.5 (44.6)        | 0.257      | 124.4 (33.5)      | 117.3 (36.8)        | 0.454      |
| HDL-C, mg/dL               | 46.0 (13.6)       | 46.8 (14.1)         | 0.587      | 50.3 (17.2)       | 54.0 (13.9)         | 0.034      |
| HDLs-C, mg/dL              | 25.2 (8.3)        | 25.4 (8.4)          | 0.736      | 28.4 (11.8)       | 30.3 (10.2)         | 0.144      |
| HDLs-C, mg/dL              | 20.5 (5.1)        | 20.9 (5.3)          | 0.409      | 22.2 (5.2)        | 23.4 (5.3)          | 0.002      |
| ApoE-HDL, mg/dL            | 3.7 (1.5)         | 4.1 (1.8)           | 0.039      | 4.4 (2.0)         | 5.0 (1.8)           | 0.000      |

*Data are expressed as median (interquartile range).

**Data are expressed as number of obese participant (percentage of obese participants) (BMI ≥ 27 kg/m²).

Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, LDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; NGT, normal glucose tolerance; preDM, pre-diabetes mellitus; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides
**Supplemental Table 6.** Correlations in all subjects***

|                  | TG       | RLP-C    | LDL-C    | Calculated LDL-C | sdLDL-C   | sdLDL-C/LDL-C | lbLDL-C   | LDL-TG    | HDL-C    | HDL2-C   | HDL3-C   | ApoE-HDL |
|------------------|----------|----------|----------|------------------|-----------|----------------|-----------|-----------|-----------|-----------|-----------|----------|
| Age              | -0.013   | -0.017   | -0.143** | -0.142**         | -0.088    | -0.131**       | -0.024    | -0.105**  | -0.052**  | -0.196**  | -0.135**  |
| BMI              | 0.205**  | 0.089**  | 0.026    | -0.084**         | 0.174**   | 0.23**         | -0.087**  | 0.138**   | -0.274**  | -0.288**  | -0.153**  | -0.254** |
| Systolic BP      | 0.152**  | 0.089**  | 0.014    | -0.009           | 0.154**   | 0.219**        | -0.088**  | 0.165**   | -0.153**  | -0.174**  | -0.043**  | -0.136** |
| Diastolic BP     | 0.118**  | 0.051    | 0.052    | 0.033            | 0.157**   | 0.176**        | -0.037    | 0.145**   | -0.131**  | -0.164**  | 0.001     | -0.106** |
| Fasting Glucose  | 0.245**  | 0.097**  | -0.055*  | -0.194**         | 0.154**   | 0.26**         | -0.183**  | 0.013     | -0.129**  | -0.117**  | -0.115**  | -0.158** |
| HbA1c            | 0.198**  | 0.071**  | -0.052*  | -0.186**         | 0.126**   | 0.21**         | -0.16**   | -0.007    | -0.15**   | -0.132**  | -0.142**  | -0.183** |
| Insulin          | 0.228**  | 0.115**  | -0.009   | -0.07**          | 0.115**   | 0.182**        | -0.094**  | 0.134**   | -0.178**  | -0.167**  | -0.146**  | -0.168** |
| HOMA-IR          | 0.272**  | 0.138**  | -0.024   | -0.101**         | 0.116**   | 0.196**        | -0.114**  | 0.109**   | -0.152**  | -0.141**  | -0.128**  | -0.149** |
| HOMA-β           | 0.104**  | 0.107**  | 0.036    | 0.024            | 0.063**   | 0.059**        | 0.004     | 0.173**   | -0.11**   | -0.099**  | -0.09**   | -0.09**  |
| Total cholesterol| 0.189**  | 0.197**  | 0.779**  | 0.907**          | 0.603**   | 0.167**        | 0.626**   | 0.461**   | 0.323**   | 0.214**   | 0.473**   | 0.438**  |
| TG               | 0.618**  | 0.069**  | 0.027    | 0.377**          | 0.481**   | 0.173**        | 0.332**   | 0.102**   | -0.121**  | -0.025**  | -0.035    |         |
| RLP-C            | 0.618**  | 0.069**  | 0.027    | 0.377**          | 0.481**   | 0.173**        | 0.332**   | 0.102**   | -0.121**  | -0.025**  | -0.035    |         |
| LDL-C            | 0.023    | 0.069**  | 0.779**  | 0.447**          | 0.694**   | 0.106**        | 0.86**    | 0.476**   | 0.136**   | 0.064**   | 0.26**    | 0.241**  |
| Calculated LDL-C | -0.084** | 0.027    | 0.779**  | -0.065**         | -0.065**  | 0.772**        | 0.381**   | 0.111**   | 0.026     | 0.276**   | 0.208**   |         |
| sdLDL-C          | 0.513**  | 0.377**  | 0.694**  | 0.447**          | 0.76**    | 0.23**         | 0.677**   | -0.083**  | -0.178**  | 0.168**   | 0.05**    |         |
| sdLDL-C/LDL-C    | 0.737**  | 0.481**  | 0.106**  | -0.065**         | 0.76**    | -0.396**       | 0.532**   | -0.256**  | -0.328**  | -0.003**  | -0.156**  |         |
| lbLDL-C          | -0.333** | -0.173** | 0.86**   | 0.772**          | 0.23**    | -0.396**       | 0.164**   | 0.243**   | 0.213**   | 0.232**   | 0.291**   |         |
| LDL-TG           | 0.534**  | 0.332**  | 0.476**  | 0.381**          | 0.677**   | 0.532**        | 0.122**   | -0.202**  | -0.257**  | -0.003**  | -0.08**   |         |
| non HDL-C        | 0.311**  | 0.247**  | 0.770**  | 0.920**          | 0.668**   | 0.275**        | 0.568**   | 0.564**   | -0.044**  | -0.144**  | 0.207**   | 0.089**  |
| HDL-C            | -0.292** | -0.102** | 0.136**  | 0.111**          | -0.083**  | -0.250**       | 0.243**   | -0.202**  | 0.961**   | 0.76**    | 0.971**   |         |
| HDL2-C           | -0.323** | -0.121** | 0.064**  | 0.026            | -0.178**  | -0.328**       | 0.213**   | -0.257**  | 0.961**   | 0.551**   | 0.904**   |         |
| HDL3-C           | -0.122** | -0.025   | 0.26**   | 0.276**          | 0.168**   | -0.003         | 0.232**   | -0.003**  | 0.76**    | 0.551**   | 0.809**   |         |
| ApoE-HDL         | -0.207** | -0.035   | 0.241**  | 0.208**          | 0.05**    | -0.156**       | 0.291**   | -0.08**   | 0.971**   | 0.904**   | 0.809**   |         |

***Pearson correlations.
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides
*Significance between 0.05 and 0.01
**Significance less than 0.01
Supplemental Table 7. Correlations in male subjects

|                  | TG    | RLP-C | LDL-C | Calculated LDL-C | sdLDL-C | sdLDL-C/LDL-C | lbLDL-C | LDL-TG | HDL-C | HDL2-C | HDL3-C | ApoE-HDL |
|------------------|-------|-------|-------|------------------|---------|---------------|---------|--------|-------|--------|--------|----------|
| Age              | -0.159** | -0.063* | -0.129** | -0.099** | -0.205** | -0.172** | -0.024 | -0.152** | -0.016 | 0.076* | -0.206** | -0.068* |
| BMI              | 0.225** | 0.068* | 0.05 | -0.055 | 0.221** | -0.092** | 0.143** | -0.26** | -0.272** | -0.145** | -0.225** |
| Systolic BP      | 0.092* | 0.052 | 0.043 | 0.017 | 0.147** | 0.167** | -0.047 | 0.148** | -0.003 | 0.035 | 0.068 | 0.019 |
| Diastolic BP     | 0.089* | -0.002 | 0.088 | 0.079 | 0.15** | 0.128** | 0.013 | 0.137** | -0.057 | -0.104* | 0.069 | -0.017 |
| Fasting Glucose  | 0.199** | 0.064* | -0.074* | -0.193** | 0.109** | 0.221** | -0.176** | -0.047 | -0.108** | -0.082** | -0.128** | -0.145** |
| HbA1c            | 0.114** | 0.014 | -0.035 | -0.154** | 0.074* | 0.13** | -0.1** | -0.091** | -0.099** | -0.064** | -0.138** | -0.142** |
| Insulin          | 0.195** | 0.08* | 0.041 | -0.059 | 0.142** | 0.16** | -0.047 | 0.123** | -0.18** | -0.161** | -0.159** | -0.166** |
| HOMA-IR          | 0.203** | 0.081** | 0.009 | -0.099** | 0.131** | 0.173** | -0.082** | 0.08** | -0.176** | -0.151** | -0.169** | -0.175** |
| HOMA-β           | 0.104** | 0.048 | 0.071* | 0.04 | 0.091** | 0.065* | 0.03 | 0.161** | -0.13** | -0.125** | -0.096** | -0.098** |
| Total cholesterol| 0.192** | 0.217** | 0.785** | 0.905** | 0.628** | 0.201** | 0.595** | 0.503** | 0.331** | 0.204** | 0.484** | 0.459** |
| TG               | 0.564** | 0.113** | 0.059 | 0.408** | 0.477** | -0.142** | 0.377** | -0.067** | -0.093** | 0.012 | 0.01 | 0.01 |
| RLP-C            | 0.564** | 0.113** | 0.059 | 0.408** | 0.477** | -0.142** | 0.377** | -0.067** | -0.093** | 0.012 | 0.01 | 0.01 |
| LDL-C            | 0.015 | 0.113** | 0.78** | 0.673** | 0.084** | 0.848** | 0.461** | 0.157** | 0.084** | 0.258** | 0.269** | 0.269** |
| Calculated LDL-C | -0.12** | 0.059 | 0.78** | 0.438** | -0.077** | 0.767** | 0.427** | 0.135** | 0.043 | 0.285** | 0.239** |
| sdLDL-C          | 0.548** | 0.408** | 0.673** | 0.438** | 0.767** | 0.178** | 0.681** | -0.021 | -0.138** | 0.234** | 0.13** |
| sdLDL-C/LDL-C    | 0.771** | 0.477** | 0.884** | -0.077** | 0.767** | 0.438** | 0.545** | -0.181** | -0.28** | 0.091** | -0.065** |
| lbLDL-C          | -0.373** | -0.142** | 0.848** | 0.767** | 0.178** | -0.438** | 0.125** | 0.224** | 0.21** | 0.175** | 0.265** |
| LDL-TG           | 0.6** | 0.377** | 0.461** | 0.427** | 0.681** | 0.545** | 0.125** | -0.167** | -0.233** | 0.028 | -0.031 |
| non HDL-C        | 0.296 | 0.253 | 0.777 | 0.917 | 0.672 | 0.276 | 0.551 | 0.592 | -0.001 | -0.118 | 0.246 | 0.146 |
| HDL-C            | -0.263** | -0.067* | 0.157** | 0.135** | -0.021 | -0.181** | 0.224** | -0.167** | 0.951** | 0.759** | 0.968** |
| HDL2-C           | -0.311** | -0.093** | 0.084** | 0.043 | -0.138** | -0.28** | 0.21** | -0.233** | 0.951** | 0.521** | 0.883** |
| HDL3-C           | -0.072* | 0.012 | 0.258** | 0.285** | 0.234** | 0.091** | 0.175** | 0.028 | 0.759** | 0.521** | 0.813** |
| ApoE-HDL         | -0.164** | 0.01 | 0.269** | 0.239** | 0.13** | -0.065** | 0.265** | -0.031 | 0.968** | 0.883** | 0.813** |

*** Pearson correlations.
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides

* Significance between 0.05 and 0.01
** Significance less than 0.01
|                      | TG    | RLP-C | LDL-C | Calculated LDL-C | sdLDL-C | sdLDL-C/LDL-C | lbLDL-C | LDL-TG | HDL-C | HDL2-C | HDL3-C | ApoE-HDL |
|----------------------|-------|-------|-------|------------------|---------|---------------|---------|--------|-------|--------|--------|----------|
| Age                  | 0.138** | 0.047 | -0.156** | -0.184**         | 0.03    | 0.177**       | -0.237** | 0.104** | -0.181** | -0.154** | -0.186** | -0.194** |
| BMI                  | 0.176** | 0.105** | 0.014    | -0.103**         | 0.116** | 0.165**       | -0.062   | 0.148** | -0.236** | -0.254** | -0.108** | -0.224** |
| Systolic BP          | 0.173** | 0.114** | -0.001   | -0.026           | 0.136** | 0.236**       | -0.093** | 0.176** | -0.197** | -0.209** | -0.083** | -0.185** |
| Diastolic BP         | 0.107*  | 0.087*  | 0.034    | 0.001            | 0.131** | 0.171**       | -0.041   | 0.147** | -0.098** | -0.125** | 0.017   | -0.082*  |
| Fasting Glucose      | 0.288** | 0.13**  | -0.034   | -0.193**         | 0.195** | 0.303**       | -0.184** | 0.076*  | -0.13**  | -0.13**  | -0.086** | -0.155** |
| HbA1c                | 0.289** | 0.136** | -0.068*  | -0.218**         | 0.181** | 0.306**       | -0.221   | 0.085** | -0.193** | -0.188** | -0.138** | -0.221** |
| Insulin              | 0.267** | 0.153** | -0.05    | -0.082**         | 0.1**   | 0.221**       | -0.14**  | 0.143** | -0.206** | -0.196** | -0.157** | -0.199** |
| HOMA-IR              | 0.341** | 0.193** | -0.049   | -0.105**         | 0.114** | 0.239**       | -0.148** | 0.13**  | -0.163** | -0.158** | -0.12**  | -0.16**  |
| HOMA-β               | 0.119** | 0.162** | 0.012    | 0.008            | 0.055   | 0.074**       | -0.022   | 0.187** | -0.137** | -0.118** | -0.135** | -0.123** |
| Total cholesterol    | 0.204** | 0.184** | 0.775**  | 0.913**          | 0.598** | 0.158**       | 0.654**  | 0.411** | 0.287**  | 0.188**  | 0.441**  | 0.399**  |
| TG                   | 0.684** | 0.021   | 0.021    | -0.018           | 0.336** | 0.480**       | -0.206** | 0.285** | -0.129** | -0.141** | -0.054** | -0.066** |
| RLP-C                | 0.684** | 0.021   | 0.779**  | 0.727**          | 0.727** | 0.144**       | 0.876**  | 0.49**  | 0.108**  | 0.034**  | 0.26**   | 0.216**  |
| Calculated LDL-C     | -0.035 | -0.018  | 0.779**  | -0.042           | 0.779** | 0.334**       | 0.072*   | -0.01   | 0.26**   | 0.171**  | 0.012    | 0.331**  |
| sdLDL-C              | 0.468** | 0.336** | 0.727**  | -0.463           | 0.753** | 0.306**       | 0.683**  | -0.115** | -0.196** | 0.133**  | 0.012    | 0.331**  |
| sdLDL-C/LDL-C        | 0.69**  | 0.486** | 0.144**  | -0.042           | 0.753** | 0.306**       | -0.328** | 0.541** | -0.299** | -0.349** | -0.064** | -0.205** |
| lbLDL-C              | -0.277** | -0.206** | 0.876**  | -0.779**         | 0.306** | -0.328**      | 0.2**    | 0.231** | 0.184**  | 0.268**  | 0.29**   | 0.012    |
| LDL-TG               | 0.471** | 0.285** | 0.49**   | 0.334**          | 0.683** | 0.541**       | 0.0**    | -0.277** | -0.323** | -0.06   | -0.161** |
| non HDL-C            | 0.331   | 0.242   | 0.784    | 0.924            | 0.284** | 0.667**       | 0.280**  | 0.591   | 0.535    | -0.089  | -0.179  | 0.173    |
| HDL-C                | -0.308** | -0.129** | 0.108**  | -0.072*          | -0.115** | -0.299**      | 0.231**  | 0.277** | 0.965**  | 0.73**   | 0.97**   | 0.012    |
| HDL2-C               | -0.326** | -0.141** | 0.034**  | -0.01            | -0.196** | -0.349**      | 0.184**  | 0.323** | 0.965**  | 0.532**  | 0.908**  | 0.012    |
| HDL3-C               | -0.153** | -0.054  | 0.26**   | 0.26**           | 0.133** | -0.064*       | 0.268**  | 0.737** | 0.532**  | 0.786**  | 0.012    | 0.331**  |
| ApoE-HDL             | -0.23**  | -0.066* | 0.216**  | 0.171**          | 0.012   | -0.203**      | 0.29**   | -0.161** | 0.97**   | 0.908**  | 0.786**  | 0.012    |

*** Pearson correlations.
Apo, apolipoprotein; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment on Insulin Resistance; HOMA-β, homeostatic model assessment on beta-cell; HDL-C, HDL cholesterol; lbLDL-C, large buoyant LDL cholesterol; LDL-C, LDL cholesterol; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense LDL cholesterol; TG, triglycerides
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** Significance less than 0.01