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The Association Between HDL Particle Concentration and Incident Metabolic Syndrome in the Multi-ethnic Dallas Heart Study

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Abstract

AIMS: Metabolic syndrome (MetS) increases atherosclerotic cardiovascular disease (ASCVD) risk. Low HDL cholesterol (HDL-C) is a diagnostic criterion of MetS and a major ASCVD risk factor. HDL particle concentration (HDL-P) associates with incident ASCVD independent of HDL-C, but its association with incident MetS has not been studied. We hypothesized that HDL-P would be inversely associated with incident metabolic syndrome independent of HDL-C and markers of adiposity and insulin resistance.

MATERIALS AND METHODS: HDL-P was measured by NMR and visceral fat by MRI in participants of the Dallas Heart Study, a probability-based population sample of adults age 30–65. Participants with prevalent MetS, DM, CVD, and any systemic illness were excluded. Incident MetS as defined by NCEP ATP III criteria was determined in all participants after median follow-up period of 7.0 years.

RESULTS: Among 1120 participants without DM or MetS at baseline (57% women, 45% Black, mean age 43), 22.8% had incident MetS at follow-up. HDL-P and HDL-C were modestly correlated ($r=0.54$, $p<0.0001$). In models adjusted for traditional risk factors and MetS risk factors including visceral fat, HS-CRP, triglyceride to HDL-C ratio, and HOMA-IR, the lowest quartile of HDL-P was associated with a 2-fold increased risk of incident MetS (OR 2.1, 95% CI 1.4–3.1; $p=0.0003$).

CONCLUSIONS: Low HDL-P is independently associated with incident MetS after adjustment for traditional risk factors, lipid parameters, adiposity, inflammation, and markers of insulin

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resistance. Further studies are warranted to validate these findings and elucidate the mechanisms underpinning this association.

Keywords

HDL particle concentration; Metabolic syndrome; Lipids

Introduction

Metabolic syndrome (MetS) affects more than 1 in 4 US adults(1) and increases the risk of diabetes 5-fold and the risk of atherosclerotic cardiovascular disease (ASCVD) by 1.5 to 3 fold over 5–10 years(2). In the Framingham cohort, MetS predicted 25% of new-onset ASCVD, with ten-year risk in men with MetS ranging from 10 to 20%(3). Unfortunately, it is not clear how to best identify patients who are at risk of developing MetS.

Characterization of abdominal obesity, whether by waist circumference or by visceral fat, can predict incident MetS independent of other risk factors and body mass index (BMI)(4, 5). However, the association between baseline lipid particle markers and incident MetS is unclear.

Low HDL cholesterol (HDL-C) is a known ASCVD risk factor and is also a component of MetS. Total HDL particle concentration (HDL-P) provides a more comprehensive assessment of HDL subspecies than HDL-C. Studies in several large cohorts, including MESA, JUPITER, and the Dallas Heart Study (DHS), have shown that HDL-P associates with ASCVD events independent of HDL-C(6–8), suggesting that HDL-P may be superior to HDL-C in predicting cardiovascular risk.

We therefore sought to determine the association between baseline levels of HDL-P and incident MetS within the Dallas Heart Study, a large multi-ethnic population cohort. We hypothesized that HDL-P would be inversely associated with incident MetS independent of HDL-C, adiposity, and other markers of insulin resistance.

Subjects

The Dallas Heart Study has previously been described in detail(9). Briefly, the Dallas Heart Study is a multi-ethnic, probability-based population cohort study of Dallas County residents. The random probability sample includes intentional oversampling of Black individuals to make up 50% of the cohort. Participants age 30–65 underwent risk factor assessment, fasting blood and urine collection, dual-energy x-ray absorptiometry (DEXA) to assess body composition, electron-beam computed tomography (CT) and magnetic resonance imaging (MRI) of the heart for cardiovascular phenotyping, and MRI of the abdomen to assess body fat distribution. Those meeting NCEP ATP III criteria for metabolic syndrome or diabetes mellitus at baseline were excluded for the current analysis. In addition, participants were excluded if they had a self-reported history of any CVD (myocardial infarction, stroke, arterial revascularization, heart failure, or arrhythmia), cirrhosis, cancer, HIV, niacin use, or renal failure, or if they died within 1 year of enrollment. Participants returned for a follow up visit after a median 7.0 years, during which they underwent repeat risk factor assessment, blood collection, and imaging for obesity. Of the 2971 participants

who completed baseline assessment, 2072 returned and completed follow up assessment. After the above exclusions, a total of 1120 participants were included in this study. Written informed consent was obtained from all participants and the protocol was approved by the institutional review board at the University of Texas Southwestern Medical Center, Dallas TX.

Materials and Methods

Assessment of Circulating Markers

Blood was collected from all participants in a fasting state at baseline and follow up visits by venipuncture and plasma was stored at -70°C . Plasma lipids were measured after fasting as previously described(9). HDL particle concentration (HDL-P) was measured at baseline using nuclear magnetic resonance spectroscopy by LipoScience (Raleigh, NC, U.S.A.) as previously described(10). The homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated as fasting insulin ($\mu\text{IU/ml}$) $\times$ fasting glucose (mmol/l)/22.5(11). High sensitivity C-reactive protein was measured as previously described(12).

Assessment of Obesity

Measurements of body fat distribution and imaging measurements were made as previously described(13). BMI (body mass index) was calculated as weight (kilograms)/height (meters)². Waist circumference was measured 1cm above the iliac crest and hip circumference was measured at the widest circumference of the buttocks at the greater trochanters. Visceral abdominal fat mass was measured using a 1.5-T MRI system (Intera, Philips Medical Systems, Best, the Netherlands) using a validated method of fat mass prediction from one MRI slice at the L2–L3 intervertebral level(14).

Primary End Point

The primary end point was incident MetS at the return visit, defined by NCEP ATP III criteria as having 3 or more of the following: abdominal obesity (waist circumference >102 cm in men or 88 cm in women), hypertriglyceridemia (>150 mg/dl), low high-density lipoprotein cholesterol (HDL-C <40 mg/dl in men or <50 mg/dl in women), hypertension ($>130/85$ mmHg), or elevated fasting glucose (>110 mg/dl)(15).

Statistical Analysis

Demographic and clinical variables at baseline were compared across quartiles of HDLP using the Jonckheere-Terpstra trend test. Correlations between HDL-P and continuous markers measured at baseline were assessed with nonparametric Spearman coefficients. The primary exposure variable was baseline sex- and race-specific quartiles of HDL-P, analyzing quartile 1 vs quartiles 2–4. Conditional logistic regression models were used to determine the association between baseline HDL-P and incident MetS. Models were adjusted for traditional ASCVD risk factors such as age, sex, race, systolic blood pressure, use of blood-pressure lowering medication, and smoking, as well as MetS risk factors such as BMI, triglyceride/HDL-C, hs-CRP, visceral fat, and HOMA-IR. The correlation coefficient between waist circumference and visceral fat was 0.78, therefore only visceral fat was included in the models. Sensitivity analyses included assessment of HDL-P as a continuous

variable per one standard deviation increase. Two-sided p-values of 0.05 or less were considered to indicate statistical significance. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Raleigh, NC, U.S.A.).

Results

Among the 1120 participants without baseline MetS or diabetes, the mean age was 43, with 57% women and 45% black. The clinical characteristics and cardiovascular risk factor profile across quartiles of baseline HDL-P are summarized in Table 1. The lowest quartile of HDL-P was associated with younger age ($p < 0.0001$), male gender ($p < 0.0001$), and Hispanic ethnicity ($p = 0.001$). This group had lower total cholesterol, HDL-C, HDL size, and LDL size (all $p < 0.0001$), as well as lower waist to hip ratio and systolic and diastolic blood pressure (all $p < 0.0001$). The lowest quartile of HDL-P was associated with significantly lower self-reported alcohol intake ($p < 0.0001$) but not self-reported physical activity. In continuous analysis, HDL-P was correlated with HDL-C ($r = 0.54$, $p < 0.0001$) and only weakly correlated with other variables (Table 2).

The primary end point of incident MetS occurred in 256 participants (23%). The lowest sex- and race-adjusted quartile of HDL-P had the highest incidence of MetS (29% vs. 21%, Q1 vs Q2–4: $p = 0.0008$) (Figure 1), translating into an unadjusted 50% increased risk of incident MetS (Figure 2). In models adjusted for age, sex, race/ethnicity, smoking, and BMI (Figure 2), the lowest quartile of HDL-P compared to quartiles 2–4 remained associated with incident MetS ($p = 0.0003$). Visceral fat, triglyceride/HDL-C ratio, BMI, and HOMA-IR each independently associated with incident MetS (Table 3). However, serial adjustment for these metabolic risk markers did not attenuate the inverse association between HDL-P and incident MetS (Figure 2). In a fully adjusted model including visceral fat, triglyceride to HDL-C ratio, BMI, HOMA-IR, and hs-CRP, the lowest quartile of HDL-P was associated with a 2-fold increased risk of incident MetS (95% CI 1.4–3.1) (Figure 2). There was no interaction between HDL-P and race/ethnicity ($p_{\text{interaction}} = 0.59$ for Black/White; $p_{\text{interaction}} = 0.36$ for Hispanic/White,). In sensitivity analyses modeling HDL-P as a continuous variable, a 1 standard deviation increase in HDL-P led to a fully-adjusted 32% decrease in risk of incident MetS (95% CI 0.56–0.82).

Discussion

In a large population-based multi-ethnic cohort, individuals with low HDL-P are at significantly increased risk of developing MetS. The inverse association between HDL-P and incident MetS is independent of traditional and MetS risk factors, including markers of insulin resistance, visceral adiposity, and inflammation.

MetS is a known risk factor for the development of diabetes and cardiovascular disease. Patients with MetS but without diabetes are at very high risk of developing diabetes, likely due to the presence of glucose dysregulation (impaired fasting glucose or impaired glucose tolerance). While diabetes increases risk of coronary heart disease and stroke by two to four fold(16–18), MetS also independently raises risk of cardiovascular disease(19–24). Despite the risks associated with MetS, there is no clear way to identify those most likely to develop

MetS. A few studies have found that adiposity, as measured by waist circumference and visceral fat, is a better predictor of incident MetS than other components(4, 5). Although a recent study assessed the relationship between lipoprotein particle size and incident diabetes(25), no studies have determined the association between lipoprotein particles and incident MetS.

Low HDL-C is a component of MetS and reflects an atherogenic dyslipidemia phenotype. Atherogenic dyslipidemia can cause impairments in insulin metabolism by causing dysfunction and apoptosis of pancreatic beta cells(26–28). Furthermore, patients with diabetes often have low HDL-C and impaired HDL function, including reductions in reverse cholesterol transport and reduced antioxidant capacity(29–33). Impaired reverse cholesterol transport within pancreatic beta cells can lead to altered function and impaired insulin secretion(34). While the relationships between HDL function and MetS are less well established, it is likely that the relationships between HDL and insulin resistance also impact development of MetS.

Low HDL-C is also an established ASCVD risk factor; however, the failure of HDL-C modulation to impact risk of cardiovascular events(35, 36) has drawn attention to the idea that HDL-C may not be a good target for risk reduction. HDL particle concentration (HDL-P) by NMR is readily available for clinical testing and provides a more comprehensive assessment of HDL subspecies than HDL-C. Several large cohort studies have shown that low levels of HDLP predict incident cardiovascular events and coronary heart disease death independent of traditional risk factors including HDL-C(6–8). In fact, HDL-P has been shown to be superior to HDL-C in predicting cardiovascular disease even after accounting for LDL particle measures(6–8, 37–39). However, the association between HDL-P and incident MetS has not been previously studied.

We report in a large multi-ethnic cohort that low HDL-P was associated with a 2-fold increased risk of incident MetS. This association was independent not only of traditional ASCVD risk factors but also MetS risk factors, including several robust markers of insulin resistance. Visceral adiposity correlates with adverse metabolic markers better than measures of overall adiposity and predicts incident diabetes among obese individuals(40). In our study, directly measured visceral adiposity by MRI also predicted incident MetS. However, adjustment for visceral adiposity did not attenuate the inverse association between HDL-P and incident MetS, suggesting that the pathways by which low HDL-P confers increased metabolic risk is distinct from the pathways reflected by metabolically dysfunctional fat depots. In addition, other markers of insulin resistance such as triglyceride/HDL-C ratio and HOMA-IR also associated with incident MetS but did not attenuate the inverse association between HDL-P and MetS. These observations suggest that the mechanism by which low HDL-P associates with incident MetS is not reflected by markers of insulin resistance or adiposity, supporting the need for further investigation.

Strengths of our study include use of a large, multi-ethnic population cohort, a large number of incident MetS cases to detect relevant associations, and comprehensive phenotyping with regard to insulin resistance and adiposity. Importantly, our findings were not attenuated by baseline MetS risk factors. Limitations include inability to assess change in HDL-P and risk

of incident MetS. Our findings should be confirmed in other large cohorts and support further investigation of the etiology of the association between HDL-P and incident MetS as well as whether increasing HDL-P with lipid-modifying therapies can reduced the risk for developing MetS.

In summary, our study demonstrates a clear association between low HDL-P, a marker of increased ASCVD risk, and incident MetS that is independent of traditional risk factors, visceral adiposity, and markers of insulin resistance. Low HDL-P may be one link by which MetS increases risk of ASCVD. Improving the ability to identify individuals at risk for developing MetS would allow for early implementation of lifestyle modifications and therapeutics to reduce the risk of MetS and thereby risk of ASCVD events in this particularly vulnerable population.

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References

1. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and Trends of Metabolic Syndrome in the Adult U.S. Population, 1999–2010. *Journal of the American College of Cardiology*. 2013 2013/8;62(8):697–703. [PubMed: 23810877]
2. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC Medicine*. 2011 2011/5/05;9(1).
3. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation*. 1998 1998/5/19;97(18):1837–47. [PubMed: 9603539]
4. Palaniappan L, Carnethon MR, Wang Y, Hanley AJG, Fortmann SP, Haffner SM, et al. Predictors of the Incident Metabolic Syndrome in Adults: The Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2004 2004/2/26;27(3):788–93. [PubMed: 14988303]
5. Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB, et al. Visceral Adiposity and the Risk of Metabolic Syndrome Across Body Mass Index. *JACC: Cardiovascular Imaging*. 2014 2014/12/7(12):1221–35. [PubMed: 25440591]
6. Mackey RH, Greenland P, Goff DC, Lloyd-Jones D, Sibley CT, Mora S. High-Density Lipoprotein Cholesterol and Particle Concentrations, Carotid Atherosclerosis, and Coronary Events. *Journal of the American College of Cardiology*. 2012 2012/8;60(6):508–16. [PubMed: 22796256]
7. Mora S, Glynn RJ, Ridker PM. High-Density Lipoprotein Cholesterol, Size, Particle Number, and Residual Vascular Risk After Potent Statin Therapy. *Circulation*. 2013 2013/9/03;128(11):1189–97. [PubMed: 24002795]
8. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events. *New England Journal of Medicine*. 2014 2014/12/18;371(25):2383–93. [PubMed: 25404125]
9. Victor RG, Haley RW, Willett DL, Peshock RM, Vaeth PC, Leonard D, et al. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *The American Journal of Cardiology*. 2004 2004/6;93(12):1473–80. [PubMed: 15194016]
10. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein Particle Analysis by Nuclear Magnetic Resonance Spectroscopy. *Clinics in Laboratory Medicine*. 2006 2006/12;26(4):847–70. [PubMed: 17110242]

11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985 1985/7;28(7):412–9. [PubMed: 3899825]
12. Abdullah SM, Khera A, Leonard D, Das SR, Canham RM, Kamath SA, et al. Sex differences in the association between leptin and CRP: Results from the Dallas Heart Study. *Atherosclerosis*. 2007 2007/12;195(2):404–10. [PubMed: 17141244]
13. Neeland IJ, Winders BR, Ayers CR, Das SR, Chang AY, Berry JD, et al. Higher Natriuretic Peptide Levels Associate With a Favorable Adipose Tissue Distribution Profile. *Journal of the American College of Cardiology*. 2013 2013/8;62(8):752–60. [PubMed: 23602771]
14. Abate N, Garg A, Coleman R, Grundy SM, Peshock RM. Prediction of total subcutaneous abdominal, intraperitoneal, and retroperitoneal adipose tissue masses in men by a single axial magnetic resonance imaging slice. *Am J Clin Nutr*. 1997 2;65(2):403–8. [PubMed: 9022523]
15. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002 12 17;106(25):3143–421. [PubMed: 12485966]
16. Saydah SH. Age and the Burden of Death Attributable to Diabetes in the United States. *American Journal of Epidemiology*. 2002 2002/10/15;156(8):714–9. [PubMed: 12370159]
17. Hyperglycaemia Nakagami T. and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia*. 2004 2004/3/01;47(3):385–94. [PubMed: 14985967]
18. Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM. Cause-Specific Mortality in a Population With Diabetes: South Tees Diabetes Mortality Study. *Diabetes Care*. 2002 2002/1/01;25(1):43–8. [PubMed: 11772899]
19. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular Morbidity and Mortality Associated With the Metabolic Syndrome. *Diabetes Care*. 2001 2001/4/01;24(4):683–9. [PubMed: 11315831]
20. Hu G Prevalence of the Metabolic Syndrome and Its Relation to All-Cause and Cardiovascular Mortality in Nondiabetic European Men and Women. *Archives of Internal Medicine*. 2004 2004/5/24;164(10):1066. [PubMed: 15159263]
21. Lakka H-M. The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-aged Men. *JAMA*. 2002 2002/12/04;288(21):2709. [PubMed: 12460094]
22. Hunt KJ. National Cholesterol Education Program Versus World Health Organization Metabolic Syndrome in Relation to All-Cause and Cardiovascular Mortality in the San Antonio Heart Study. *Circulation*. 2004 2004/9/07;110(10):1251–7. [PubMed: 15326061]
23. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The Metabolic Syndrome and 11-Year Risk of Incident Cardiovascular Disease in the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2005 2005/1/27;28(2):385–90. [PubMed: 15677797]
24. Sattar N Metabolic Syndrome With and Without C-Reactive Protein as a Predictor of Coronary Heart Disease and Diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003 2003/7/29;108(4):414–9. [PubMed: 12860911]
25. Fízelova M, Miilunpohja M, Kangas AJ, Soininen P, Kuusisto J, Ala-Korpela M, et al. Associations of multiple lipoprotein and apolipoprotein measures with worsening of glycemia and incident type 2 diabetes in 6607 non-diabetic Finnish men. *Atherosclerosis*. 2015 2015/5;240(1):272–7. [PubMed: 25818853]
26. von Eckardstein A, Sjöström RA. Possible contributions of lipoproteins and cholesterol to the pathogenesis of diabetes mellitus type 2. *Current Opinion in Lipidology*. 2011 2011/2;22(1):26–32. [PubMed: 21102330]
27. Rütli S, Ehses JA, Sjöström RA, Prazak R, Rohrer L, Georgopoulos S, et al. Low- and High-Density Lipoproteins Modulate Function, Apoptosis, and Proliferation of Primary Human and Murine Pancreatic β -Cells. *Endocrinology*. 2009 2009/10;150(10):4521–30. [PubMed: 19628574]
28. Siebel AL, Natoli AK, Yap FYT, Carey AL, Reddy-Luthmoodoo M, Sviridov D, et al. Effects of High-Density Lipoprotein Elevation With Cholesteryl Ester Transfer Protein Inhibition on Insulin Secretion. *Circulation Research*. 2013 2013/5/15;113(2):167–75. [PubMed: 23676183]

29. Asleh R, Miller-Lotan R, Aviram M, Hayek T, Yulish M, Levy JE, et al. Haptoglobin Genotype Is a Regulator of Reverse Cholesterol Transport in Diabetes In Vitro and In Vivo. *Circulation Research*. 2006 2006/12/08;99(12):1419–25. [PubMed: 17082477]
30. Asleh R, Levy AP. Divergent Effects of α -Tocopherol and Vitamin C on the Generation of Dysfunctional HDL Associated with Diabetes and the Hp 2–2 Genotype. *Antioxidants & Redox Signaling*. 2010 2010/1/15;12(2):209–17. [PubMed: 19769483]
31. Patel DC, Albrecht C, Pavitt D, Paul V, Pourreyron C, Newman SP, et al. Type 2 Diabetes Is Associated with Reduced ATP-Binding Cassette Transporter A1 Gene Expression, Protein and Function. *PLoS ONE*. 2011 2011/7/27;6(7):e22142. [PubMed: 21829447]
32. Oram JF, Vaughan AM. ATP-Binding Cassette Cholesterol Transporters and Cardiovascular Disease. *Circulation Research*. 2006 2006/11/10;99(10):1031–43. [PubMed: 17095732]
33. Getz GS, Reardon CA. High-Density Lipoprotein Function in Regulating Insulin Secretion: Possible Relevance to Metabolic Syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2010 2010/7/14;30(8):1497–9.
34. Dullaart RPF, Annema W, de Boer JF, Tietge UJF. Pancreatic β -cell function relates positively to HDL functionality in well-controlled Type 2 diabetes mellitus. *Atherosclerosis*. 2012 2012/6;222(2):567–73. [PubMed: 22541874]
35. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011 12 15;365(24):2255–67. [PubMed: 22085343]
36. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014 7 17;371(3):203–12. [PubMed: 25014686]
37. El Harchaoui K High-Density Lipoprotein Particle Size and Concentration and Coronary Risk. *Annals of Internal Medicine*. 2009 2009/1/20;150(2):84. [PubMed: 19153411]
38. Kuller LH, Grandits G, Cohen JD, Neaton JD, Prineas R. Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. *Atherosclerosis*. 2007 2007/11;195(1):122–8. [PubMed: 17011566]
39. Otvos JD. Low-Density Lipoprotein and High-Density Lipoprotein Particle Subclasses Predict Coronary Events and Are Favorably Changed by Gemfibrozil Therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation*. 2006 2006/3/28;113(12):1556–63. [PubMed: 16534013]
40. Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional Adiposity and the Risk of Prediabetes and Type 2 Diabetes in Obese Adults. *JAMA*. 2012 2012/9/19;308(11):1150. [PubMed: 22990274]

Figure 1. Incident metabolic syndrome by sex/race adjusted quartiles of HDL-P

Figure 2. Multi-variable models of incident metabolic syndrome

BMI: body mass index, hs-CRP: C-reactive protein, TG/HDL-C: Triglyceride/HDL cholesterol ratio, HOMA-IR: homeostasis model assessment of insulin resistance index

*OR for sex- and race-adjusted quartile 1 of HDL-P versus quartiles 2–4

Table 1.

Demographics and cardiovascular risk factors by quartiles of HDL-P

	Q1 (16.11–29.41)	Q2 (29.41 – 33.45)	Q3 (33.47–37.69)	Q4 (37.75–56.61)	p-value
<i>Age (years)</i>	37 [32, 44]	41 [35, 47]	42 [36, 49]	46 [38.5, 52.5]	<0.0001
<i>Male (%)</i>	50	49	42	30	<0.0001
<i>White (%)</i>	33	35	44	44	0.001
<i>Black (%)</i>	45	49	39	47	0.67
<i>Hispanic (%)</i>	19	13	15	9	0.001
<i>Weight (kg)</i>	79.4 [67.1, 90.3]	81.2 [70.6, 91.6]	76.7 [64.0, 90.7]	73.5 [64.0, 85.7]	0.001
<i>BMI (kg/m²)</i>	26.1 [23.6, 29.7]	26.6 [24.0, 30.3]	26.4 [23.0, 29.7]	26.0 [23.0, 29.8]	0.22
<i>Total cholesterol (mg/dl)</i>	160 [140, 188]	175 [153, 201]	178 [159, 198]	187 [165, 208]	<0.0001
<i>HDL-C (mg/dl)</i>	44 [38, 51]	48 [43, 56]	54 [47, 63]	63 [54, 74]	<0.0001
<i>LDL-C (mg/dl)</i>	99 [80, 121]	108 [87, 131]	104 [86, 124]	101.5 [79, 125]	0.68
<i>Triglycerides (mg/dl)</i>	79 [58, 113]	82 [61, 114]	82 [63, 110]	84 [61, 116]	0.10
<i>HDL size (nm)</i>	9.04 [8.7, 9.4]	9.01 [8.8, 9.3]	9.11 [8.8, 9.4]	9.14 [8.9, 9.47]	<0.0001
<i>LDL size (nm)</i>	21.04 [20.5, 21.6]	21.15 [20.7, 21.6]	21.27 [20.9, 21.8]	21.37 [20.9, 21.8]	<0.0001
<i>WHR</i>	0.93 [0.8, 1.1]	0.97 [0.8, 1.2]	0.98 [0.9, 1.2]	1.03 [0.9, 1.3]	<0.0001
<i>SBP (mmHg)</i>	114 [107, 124]	116 [109, 126]	115 [108, 125]	120 [111, 129]	<0.0001
<i>DBP (mmHg)</i>	72 [67, 80]	75 [69, 81]	75 [69, 80]	76 [71, 82]	<0.0001
<i>Glucose (mg/dl)</i>	89 [82, 95]	89 [83, 95]	89 [83, 95]	90 [84, 96]	0.08
<i>HOMA-IR</i>	2.0 [1.3, 3.6]	2.3 [1.4, 3.5]	1.9 [1.3, 3.4]	1.9 [1.1, 3.3]	0.16
<i>Fructosamine (umol/L)</i>	204 [194, 218]	210 [197, 223]	208 [195, 221]	209 [197, 222]	0.03
<i>HS-CRP (mg/L)</i>	1.7 [0.7, 4.4]	1.8 [0.7, 4.1]	2.0 [0.8, 4.6]	2.4 [0.9, 6.4]	0.03
<i>Alcohol intake (gm/week)</i>	2.2 [0, 22.5]	6.0 [0.8, 39.0]	7.5 [0.4, 42.0]	15.0 [0.8, 91.0]	<0.0001
<i>Exercise dose (met*min/week)</i>	240 [0, 750]	239.5 [0, 720]	159 [0, 720]	327 [0, 840]	0.32
<i>HxofHTN (%)</i>	11	16	15	24	0.0001
<i>HTN meds (%)</i>	6.6	9	9.2	16	0.0007
<i>Statins (%)</i>	1.1	2.2	3.7	4.8	0.007
<i>Smoking (%)</i>	26	26	23	27	0.88

BMI: body mass index, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, WHR: waist to hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HS-CRP: high sensitivity C-reactive protein, HTN: hypertension

Table 2.

Spearman correlation coefficients between HDL-P and cardiovascular risk factors

	Rho	p-value
<i>HDL-C</i>	0.54	<0.0001
<i>Age</i>	0.27	<0.0001
<i>Total Cholesterol</i>	0.23	<0.0001
<i>LDL size</i>	0.19	<0.0001
<i>Alcohol intake (gm/wk)</i>	0.15	<0.0001
<i>HDL size</i>	0.14	<0.0001
<i>DBP</i>	0.13	<0.0001
<i>SBP</i>	0.11	<0.0001
<i>Weight</i>	-0.11	0.0003
<i>HS-CRP</i>	0.07	0.02
<i>Waist Circumference</i>	-0.07	0.03
<i>HOMA-IR</i>	-0.06	0.05
<i>Triglycerides</i>	0.05	0.10
<i>Fructosamine</i>	0.05	0.08
<i>Glucose</i>	0.04	0.15
<i>BMI</i>	-0.04	0.24
<i>Exercise</i>	0.03	0.35
<i>LDL-C</i>	-0.02	0.58

HDL-C: high density lipoprotein cholesterol, LDL: low density lipoprotein, DBP: diastolic blood pressure, SBP: systolic blood pressure, HS-CRP: high sensitivity C-reactive protein, BMI: body mass index

Table 3.

Chi-Square values for multivariable models of incident metabolic syndrome

Variable	Chi-Square	p-value
<i>TG/HDL-C</i>	21.7	<0.0001
<i>HDL-P</i>	13.3	0.0003
<i>Anti-HTN Med</i>	11.1	0.0009
<i>Visceral fat</i>	11.3	0.0008
<i>Systolic BP</i>	5.5	0.02
<i>BMI</i>	6.3	0.01
<i>HOMA-IR</i>	4.4	0.04
<i>hs-CRP</i>	1.1	0.29

TG/HDL-C: Triglyceride/HDL cholesterol ratio, HDL-P: HDL particle concentration, BMI: body mass index, HOMA-IR: homeostasis model assessment of insulin resistance index, CRP: C-reactive protein

Models adjusted for age, sex, race/ethnicity, smoking, and all variables listed in the table.