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Lipoprotein Particles, Insulin, Adiponectin, C-Reactive Protein and Risk of Coronary Heart Disease among Men with Metabolic Syndrome

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Abstract

We tested the hypotheses whether nuclear magnetic resonance (NMR) determined lipoprotein particles, insulin and adiponectin, and C-reactive protein (CRP) and white blood cell (WBC) count as markers of inflammation predicted risk of coronary heart disease (CHD) death among 428 men age 35–57 years with metabolic syndrome (MetSyn) in a matched case control study within the Multiple Risk Factor Intervention Trial.

Blood samples collected at entry into the study and stored at –60° C were obtained from central storage for blood analyte analysis. 214 men with MetSyn who died of CHD were matched with 214 men with MetSyn who did not die of CHD during 18 years of follow-up. Cases were matched to controls on age, study group, number of factors present in the MetSyn, and presence or absence of a non-fatal CVD event during the trial. Mortality follow up was determined using the National Death Index.

Higher levels of high density lipoprotein particles (HDL-P), especially medium-sized HDL-P, [hazard ratio (95% confidence interval) 0.45 (0.25–0.83, $p < 0.01$), quartile 1 as compared to quartile 4], were associated with lower risk of CHD death. Low density lipoprotein (LDL) particles were not associated with increased risk of CHD. Elevated LDL cholesterol (LDL-C), smoking and WBC count were, but levels of adiponectin, insulin and CRP were not significantly related to CHD death. In multivariate models adjusting for smoking and LDL-C, medium HDL-P and WBC count remained independent predictors of CHD death.

Number of HDL particles, especially medium-sized HDL particles and WBC count were independent predictors of CHD death among men with MetSyn.

Keywords

Lipoproteins; metabolic syndrome; coronary heart disease; white blood cell count; C-reactive protein

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Introduction

The long term follow-up (25 years following enrollment) of men in the Multiple Risk Factor Intervention Trial (MRFIT) has provided an opportunity to evaluate the relationship of metabolic syndrome (MetSyn) (1) to coronary heart disease (CHD) mortality in a large group of men ages 35–57 years. (2–4) In the initial report of 10,950 men who survived for at least 6 years (until the end of the intervention phase of the trial), the prevalence of the MetSyn was 41.9%. The multivariate-adjusted hazards ratios (HRs) (MetSyn versus no MetSyn) were 1.21 (95% confidence interval [CI]: 1.13–1.29), 1.49 (CI: 1.35–1.61) and 1.51 (CI: 1.31–1.70) for total, cardiovascular disease (CVD) and CHD mortality. (4) Smoking and elevated low density lipoprotein cholesterol (LDL-C) further increased risk of CVD and CHD mortality above MetSyn. Risk increased with the number of MetSyn conditions.

In this paper we have tested the hypothesis that among men with MetSyn as previously described in the MRFIT (4), lipoprotein abnormalities as measured by nuclear magnetic resonance (NMR) spectroscopy (5–13), higher numbers of LDL particles (LDL-P), specifically higher number of small LDL-P, and lower high density lipoprotein particles (HDL-P); lower adiponectin and higher insulin (14–20) and markers of inflammation, higher CRP and WBC were independent determinants of CHD death among men with MetSyn.

Methods

Previous reports have described the MRFIT in detail. (2–4). MRFIT was a primary prevention trial of CHD mortality among men, baseline ages 35–57 years, at higher risk but free of clinical CHD. Men were randomized between 1973 and 1975 at 22 clinical centers in the United States. Men were selected for the study based on being in the upper 10–15% of risk based on a Framingham Risk Score (FRS) of levels of serum cholesterol, diastolic blood pressure (BP) and cigarette smoking. Men with a history of CHD, treatment of diabetes, diastolic BP >115 mmHg or serum cholesterol over 350 mg/dL were ineligible. Of those eligible 12,866 men were randomized to either a special intervention (SI) or usual care (UC) group. The trial was carried out until February 1982 during which men were seen for clinic visits at least annually. Thereafter, all men were followed for vital status. (21)

At their second visit prior to randomization an aliquot of serum was stored at -60°C for future studies. At the year 6 visit, measures obtained at the second visit were repeated but no aliquots were stored. The measurements at the 6th annual visit were used to determine presence of MetSyn while stored bloods at 2nd screening visit were used for measurement of lipoproteins, adiponectin, CRP and insulin. Approximately 70% of men classified as MetSyn at 6th visit also meet criteria based on second screen measurements. A 12-hour fasting blood sample was obtained for each participant and centrally analyzed for serum glucose and plasma cholesterol, triglycerides, HDL-C and LDL-C. (22) BP was measured and smoking status was ascertained, and alcohol use and physical activity were assessed. (2)

Participants were classified for analysis by whether they did or did not have a nonfatal CVD event during the trial. Nonfatal CVD was defined by any of the following before the 6th annual visit: coronary bypass surgery, nonfatal stroke, nonfatal myocardial infarction (MI), silent MI or left ventricle hypertrophy on electrocardiogram (ECG), peripheral artery disease, impaired renal function, angina or intermittent claudication by Rose questionnaire. (23)

CHD mortality between the 6th annual visit and December 1999 was the primary outcome investigated. Mortality was determined using the National Death Index. For CHD mortality, International Classification of Diseases (ICD)-9 codes 410–414 and 429.2 and ICD-10 codes I20–I25 were used. (4,24)

Selection of Cases and Controls

A total of 11,490 participants attended the year 6 MRFIT visit. The 1,376 participants who did not attend the year 6 visit included 430 men who died during the trial prior to Year 6. An additional 496 men were excluded due to missing data. The remaining 10,994 men were followed for mortality from year 6 to December 1999, a median of 18 years of follow up. (4)

The MetSyn was defined according to Adult Treatment Panel III guidelines using measurements made at the year 6 examination -- 3 or more of the following: body mass index (BMI) $>30 \text{ kg/m}^2$ (waist circumference was not measured), triglycerides $>150 \text{ mg/dL}$, HDL $\leq 40 \text{ mg/dL}$, systolic BP $\geq 130 \text{ mmHg}$, fasting glucose $\geq 110 \text{ mg/dL}$. (25) This criteria for MetSyn has recently been modified. (26)

Cases were the 214 men with MetSyn who died of CHD between 1982 and 1999 and who had baseline blood analytes available for study. Nine of these CHD deaths occurred in 1982–84, 22 in 1985–89, 81 in 1990–94 and 102 in 1995–99. These 214 CHD deaths were matched with 214 controls with MetSyn who did not die of CHD (or CVD). Cases and controls were matched by age (within 4 years), treatment group (SI or UC), number of MetSyn conditions present at year 6 (3, 4, or 5), and whether a non-fatal CVD event occurred during the trial through year 6. In addition, controls must have been alive at the follow-up time the case died. Approximately 11% of the controls (23) died during the 18 year follow up, none of CHD. There was no significant difference in CHD death by intervention groups through December 31, 1999. Stored serum from many of the CHD deaths as well as deaths from other causes has been used for previous MRFIT serum study analyses. This accounts for the long time period in this study between collection of the serum at 2nd screen and the CHD deaths. Also, the controls had to survive at least to the time of death of the case accounting, in part, for the low number of deaths among the controls since most of the CHD deaths occurred toward the end of follow up, i.e. 1995–99. In spite of the long time period to CHD deaths and the absence of data on changes in risk factors following the end of the intervention phase of the trial, the traditional CHD risk factors such as hypertension, blood cholesterol levels and cigarette smoking continued to be strong predictors of CHD deaths. However, risk factors that contribute only to short term risk of CHD death or in which the change in the risk factors but not the baseline levels are the primary determinants of risk of CHD cannot be evaluated in this study.

Measurements on Stored Serum Specimens

Prior to randomization, blood samples were obtained and stored centrally at -60°C for future use. Previous papers have been published utilizing these stored blood samples and have documented the stability of the samples over time. (27–30) The following metabolites were measured for this study on the stored samples: lipoprotein particle concentration and distribution by NMR spectroscopy at Liposcience, Inc. in Raleigh, NC (Dr. James Otvos). (6) The lipoprotein subclasses were categorized as large (60–200 nm), medium (35–60 nm), and small (27–35 nm) VLDL; large (21.3–23.0 nm), medium (19.8–21.2 nm), small (<18.2 –19.7 nm) LDL; and large (8.8–13 nm), medium (8.2–8.8 nm) and small (7.3–8.2 nm) HDL. It is also important to note that we are measuring the number of particles and not the cholesterol or triglycerides within any single particle. The amount of cholesterol in any large HDL-P is much greater than in the small particles. The distribution of number of NMR particles does not depend on the cholesterol or triglyceride content of the particles but on the size distribution of the particles.

CRP as a measure of inflammation by high sensitivity CRP measurement (Dr. Russell Tracy, University of Vermont) (27) and measures of adiponectin (31,32) and insulin (33) at the Heinz Nutrition Laboratory at the University of Pittsburgh, Graduate School of Public Health (Dr. Rhobert Evans).

The NMR spectroscopy methodology, including repeatability in measurements, has been previously published (6). LDL and HDL subclasses determined by gradient gel electrophoresis (GGE) and NMR are highly correlated. (13) The distribution of NMR lipoprotein levels in the MRFIT were similar to those recently reported from the Framingham Heart Study (34) and the VA High density lipoprotein Intervention trial (VA-HIT) (35) and from the Multi-Ethnic Study of Atherosclerosis. (36) Even though distribution of NMR particles was similar to other studies, we cannot be certain that protein degradation with storage may have occurred during the 25 years of storage at -70°C . It is unlikely that there was a selection bias.

Approximately 70% of the MRFIT men classified as MetSyn at year 6 also met the criteria for MetSyn at the time that the serum samples were analyzed for NMR. The differences in the risk factors between baseline and year 6 (Table 1) were an increase in triglycerides and glucose to year 6 (due, in part, to high dose diuretic therapies in MRFIT and weight gain following smoking cessation).

Statistical Methods

Paired t-tests and conditional logistic regression for matched pairs were used to summarize the association of lipoproteins, particle concentrations, particle sizes, CRP, insulin, adiponectin, and other continuous risk factors with CHD mortality. Quartiles of the distribution of each selected measure were formed and odds ratios for quartiles 2–4 compared with quartile 1 were estimated. A test for linear trend was also performed using each factor as a continuous variable. Logistic regression models included smoking status and WBC count at year 6 as covariates. Both of these factors were significant in univariate analyses. In addition to considering each putative risk factor separately, models were also considered that included combinations of the risk factors. A significance level of 0.05 was used to guide the interpretation of the results. All analyses were done using SAS, Version 8.2.

Results

Traditional Risk Factors, WBC and CHD Death

By design, cases and controls were well-matched on age, treatment group, number of MetSyn conditions present at year 6, and the occurrence of a non-fatal CVD event through year 6 of the trial (Table 1). In univariate analyses, WBC count differed significantly between cases and controls at both baseline and year 6. At year 6, fasting glucose, percent smokers, and HDL-C differed between cases and controls. At baseline, 2nd screening visit, there was no difference in HDL-C or glucose between cases and controls and a small non-significant difference in cigarette smoking. The LDL-C was higher for cases than controls, significant at baseline but not at year 6. (Table 1)

Lipid Particles, Lipoproteins and CHD Death

In both the univariate analyses shown in Table 1 and the matched multiple logistic regression analysis shown in Table 2, total HDL-P, medium HDL-P and baseline LDL-C were significant predictors of CHD death. LDL-P and VLDL-P were not significantly related to CHD death. Size of VLDL, LDL, or HDL-P was also not significantly related to CHD death (not shown).

The incidence of a nonfatal CVD event during the trial (year 1–6) could effect the levels of risk factors at year 6. Also, short term risk of CHD events within the first 6 years, i.e. during the study, may be different than for the long term follow up of CHD deaths over the next 18 years. We, therefore, reanalyzed the data in Table 3 excluding any individuals who had a nonfatal CVD event between years 1–6. All deaths, as noted, between year 1–6 were also excluded from this study irrespective of cause. Medium HDL-P and baseline LDL-C were significantly related to risk of CHD death, as were levels of large LDL-P. Neither total HDL-

P nor HDL-C by chemical methods differed between cases and controls. (Table 3) VLDL-P, and size of VLDL, LDL or HDL-P were not related to risk of CHD death.

Inflammation, Insulin and CHD Death

CRP, adiponectin and insulin were not significantly different between the cases and the controls in univariate or multivariate analyses. (Table 1 and 3) Neither was the ratio of insulin to adiponectin related to risk of CHD death (not shown).

Multivariate Models

Further analyses were explored to determine if HDL-P and WBC were independent predictors of CHD. Medium HDL-P and WBC remained significant predictors of CHD when adjusting for smoking and LDL-C (Table 4, Model 4). A one standard deviation higher level of medium HDL-P was associated with a 30% lower risk of CHD (OR=0.70, 95%CI: 0.55–0.90). The OR and 95% CI for a one standard deviation higher WBC (1800 per cu mm) was 1.40 (1.10–1.77). Total HDL-P was not significant (P=0.07, Model 3) when adjusted for smoking, WBC count and LDL-C. Cigarette smoking was not a significant predictor of CHD death in either HDL-P models.

Discussion

The results of the MRFIT suggest that the long term risk of CHD among men with MetSyn is not related to the levels of CRP, insulin, adiponectin or to number of small LDL-P. The latter result is consistent with the recent report from the Framingham Heart Study (34). Like MRFIT, in the FHS there was an increase in small LDL-P among individuals with MetSyn but not a significant relationship of the number of small LDL-P particles to the risk of CHD among men with MetSyn.

Chemical levels of LDL-C were, on average, high and related to the risk of CHD. The high LDL-C levels are due to the selection of high risk men for the MRFIT trial based on a high FRS.

In the MRFIT, high levels of HDL-P and especially medium HDL-P were associated with a reduced risk of CHD. In the report from the VA-HIT (35), gemfibrozil therapy was associated with an increase in HDL particles and in small HDL particles and with reduced risk of CHD based on both the baseline and the on-trial levels of these measures. Medium HDL particles in the VA-HIT, baseline OR=0.96 (CL: 0.84–1.09) p=0.54, was not related to risk of CHD. Levels of HDL-C in the VA-HIT were very low compared with the MRFIT MetSyn study.

Heterogeneity of discrete sizes of HDL particles in humans is well recognized. (34). Several approaches have been used to classify HDL. (37,38) Differences in distribution and size of HDL-P have been related to CVD risk. (39–46) Whether there is a unique important protective effect of size of HDL-P measured by NMR spectroscopy requires better assessment of the characteristics and metabolism by size of HDL-P. (39)

Large rather than small LDL-P were more strongly related to risk of CHD death for MRFIT men with MetSyn, especially among men without morbid CV events in the first 6 years of the trial. Recent reports from the MESA (36) and the VA-HIT trial (35) have shown that markers of LDL-P rather than size may be a more important determinant of the risk of CHD. In the MRFIT analysis, we compared individuals who already had MetSyn which is characterized by high levels of small LDL-P. Therefore, it is possible that within MetSyn, small LDL-P do not discriminate those who did or did not develop or die of CHD over the next 18 years. The addition of large LDL-P to the high levels of small LDL will increase the total number of

particles and could be associated with an increased risk of CHD death. As noted, the total number of particles was related to risk only within the 1st versus the 4th quartile. (Table 2, 3)

The levels of LDL-P in the MRFIT are high compared with other populations (36). There are two reasons: 1) MRFIT selected men with higher LDL-C; and 2) men with MetSyn in the MRFIT and other studies (34) have higher number of LDL-P. For example, mean LDL-P was 1740 ± 396 nmol/L for MRFIT men with MetSyn and nonCVD during the trial and 1363 ± 323 nmol/L for men in MRFIT without MetSyn. It is possible then by truncating the distribution of LDL-P to higher levels, the power of LDL-P to predict CHD is reduced.

High WBC rather than CRP was an independent predictor of the risk of CHD. The levels of CRP among men with MetSyn are probably primarily determined by the extent of obesity. (47)

Neither fasting insulin nor adiponectin were related to risk of CHD death. Our previous publications from the MRFIT (29), including deaths more proximate to the baseline blood draw also failed to find an increased risk of CHD deaths associated with higher fasting blood insulin levels. Fasting blood glucose at year 6 was a risk factor for CHD death. (Table 1)

In summary, among men with MetSyn, higher levels of HDL-P and especially medium HDL-P were associated with decreased risk of death from CHD. Elevated levels of LDL-C and perhaps large LDL, cigarette smoking, and WBC were also associated with an increased risk of CHD death. Levels of adiponectin and insulin, markers of possible IR, and CRP, a measure of inflammation, were not independently related to the risk of CHD death among these men with MetSyn. WBC count may be an important marker of risk among men with MetSyn.

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Baseline (Year 1) and Post-Intervention (Year 6) Characteristics of CHD Deaths and Matched Controls for Men With Metabolic Syndrome (MetSyn) at Year 6

Table 1

	CHD Deaths	Baseline (Year 1) Controls	P	CHD Deaths	Year 6 Controls	P
Matching Factors for Cases and Controls						
Age (y)	48.3	47.5	--	54.3	53.6*	--
Number of Factors in MetSyn, % with MetSyn	2.97 (70)	2.98 (69)	--	3.7 (100)	3.7 (100)*	--
Study Group (% SI)	48.1	48.1*	--	--	--	--
In-trial CVD (%) (Year 1–6)	--	--	--	36.4	36.4*	--
Other Risk Factors						
Race (% Black)	6.1	5.6	0.84	--	--	0.75
Systolic BP (mmHg)	138.2	139.9	0.24	125.8	126.2	0.11
Diastolic BP (mmHg)	92.1	93.5	0.08	82.7	84.1	0.68
BMI (kg/m ²)	29.5	29.2	0.33	30.0	29.8	<.01
Current Smoker (%)	59.3	50.9	0.08	37.6	23.9	0.04
Fasting Glucose (mg/dL)	104.1	102.2	0.21	123.0	116.3	0.01
WBC (#/cu mm)	7738	6761	<.01	7170	6714	0.01
Resting ECG abnormality (%)	29.9	29.6	0.45	--	--	0.50
Exercise ECG abnormality (%)	14.2	17.2	0.42	--	--	0.15
Lipids						
Plasma Cholesterol (mg/dL)	244.1	241.2	0.40	233.3	235.9	0.01
LDL-C (mg/dL)	160.5	152.6	0.03	148.8	144.2	0.18
HDL-C (mg/dL)	37.0	37.5	0.55	33.6	35.5	0.18
Triglycerides (mg/dL)	240.8	259.0	0.31	271.1	315.3	0.18
Lipoprotein Particle Numbers (P), Size (nm)						
LDL-P (nmol/L)	130.5 ± 38.1	130.2 ± 38.2	0.93	--	--	--
LDL-P (nmol/L)	1780.4 ± 423.6	1744.1 ± 372.0	0.31	--	--	--
Large LDL-P (nmol/L), 21.3–23.0	500.7 ± 218.3	465.8 ± 233.2	0.10	--	--	--
Small LDL-P (nmol/L), <18.2–19.7	1207.1 ± 449.5	1200.2 ± 398.8	0.86	--	--	--
HDL-P (μmol/L)	25.4 ± 6.6	26.9 ± 6.6	0.01	--	--	--
Large HDL-P (μmol/L), 8.8–13	1.8 ± 1.7	2.0 ± 1.7	0.18	--	--	--
Medium HDL-P (μmol/L), 8.2–8.8	2.0 ± 2.5	3.0 ± 3.3	<.01	--	--	--
Small HDL-P (μmol/L), 7.3–8.2	21.6 ± 5.3	21.9 ± 5.0	0.52	--	--	--
Other Blood Levels						
CRP (μg/mL)	4.6 ± 4.3	4.5 ± 6.3	0.87	--	--	--
Adiponectin (μg/mL)	7.6 ± 4.6	7.7 ± 3.2	0.84	--	--	--
Insulin (Iu/mL)	17.1 ± 10.8	16.5 ± 9.1	0.55	--	--	--
Number of Men	214	214		--	--	--

* Cases and controls were matched on year 6 age (± 4 years), number of factors in MetSyn at year 6 (3, 4, or 5), study group (SI or UC), and in-trial CVD status at year 6 (nonfatal event during follow-up or no event)

Table 2

Summary of Matched Logistic Regression Analyses* Comparing Chemical Lipid Measurements and CHD Deaths and Controls by Lipoprotein Particle Numbers (P), C-reactive protein (CRP), Adiponectin and Insulin for Men with Metabolic Syndrome (MetSyn)

<i>Blood Determination at Baseline (25,50,75 percentiles)</i>	Q1	Q2	Q3	Q4	P (Trend)
VLDL-P (nmol/L) (103,130,153)	1.00	0.96 (0.54–1.68)	1.33 (0.76–2.33)	0.84 (0.46–1.52)	0.79
LDL-P (nmol/L) (1492,1725,2015)	1.00	0.87 (0.49–1.57)	0.89 (0.51–1.56)	1.41 (0.75–2.65)	0.26
Large LDL (nmol/L) (335,484,628)	1.00	1.09 (0.63–1.89)	1.13 (0.66–1.95)	1.31 (0.73–2.36)	0.11
Small LDL (nmol/L) (896,1163,1445)	1.00	0.91 (0.50–1.67)	0.62 (0.35–1.09)	1.14 (0.61–2.12)	0.75
HDL-P, μ mol/L (22,26,30)	1.00	0.82 (0.45–1.49)	0.56 (0.31–1.01)	0.50 (0.26–0.96)	0.03
Large HDL-P (nmol/L) (0.6,1.4,2.7)	1.00	1.00 (0.56–1.79)	0.64 (0.35–1.18)	0.70 (0.40–1.23)	0.16
Medium HDL-P (nmol/L) (0.4,1.3,3.4)	1.00	0.92 (0.51–1.66)	0.80 (0.45–1.43)	0.45 (0.25–0.83)	<.01
Small HDL-P (nmol/L) (18,21,25)	1.00	0.72 (0.41–1.26)	1.10 (0.62–1.96)	0.79 (0.44–1.42)	0.77
Triglycerides (mg/dl) (146,205,287)	1.00	1.06 (0.60–1.88)	0.89 (0.48–1.62)	0.72 (0.40–1.29)	0.49
HDL-C (mg/dl) (31,36,42)	1.00	1.53 (0.88–2.68)	2.19 (1.15–4.16)	1.00 (0.55–1.82)	0.82
LDL-C (mg/dl) (133,156,182)	1.00	1.15 (0.67–1.99)	1.95 (1.12–3.39)	1.74 (0.98–3.09)	0.01
CRP (ug/mL) (1.7,3.3,5.5)	1.00	1.75 (0.92–3.30)	1.73 (0.95–3.16)	1.52 (0.83–2.77)	0.52
Adiponectin (ug/mL) (5.4,7.0,9.2)	1.00	0.93 (0.52–1.66)	0.94 (0.55–1.62)	1.01 (0.56–1.81)	0.50
Insulin (Iu/mL) (11.2,14.7,19.4)	1.00	1.15 (0.67–1.97)	0.92 (0.53–1.60)	1.06 (0.61–1.84)	0.56

P-value for trend uses factor as a continuous variable in the regression model.

* Matched variables as in Table 1.

Models were adjusted for white blood cell count and smoking status at year 6.

Table 3

Summary of Matched Logistic Regression Analyses* Comparing Cases (CHD Deaths) and Controls for Lipoprotein Particle Numbers (P), CRP, Adiponectin and Insulin: Subset for Men with Metabolic Syndrome but Without In-Trial Nonfatal CVD* (Years 1–6)

Blood Determination at Baseline (25,50,75 percentiles)	Quartile Odds Ratios (versus Quartile 1)				P (Trend)
	Q1	Q2	Q3	Q4	
VLDL-P (nmol/L) (103,130,153)	1.00	0.91 (0.46–1.80)	1.36 (0.69–2.67)	0.89 (0.42–1.86)	0.54
LDL-P (nmol/L) (1492,1725,2015)	1.00	1.12 (0.54–2.31)	0.95 (0.43–2.09)	2.14 (0.93–4.89)	0.11
Large LDL-P (nmol/L) (335,484,628)	1.00	1.11 (0.56–2.20)	1.22 (0.60–2.47)	1.61 (0.76–3.42)	0.04
Small LDL-P (nmol/L) (896,1163,1445)	1.00	0.86 (0.39–1.86)	0.61 (0.29–1.29)	1.18 (0.50–2.82)	0.62
HDL-P, μ mol/L (22,26,30)	1.00	0.74 (0.34–1.61)	0.68 (0.32–1.44)	0.71 (0.33–1.53)	0.38
Large HDL-P (μ mol/L) (0.6,1.4,2.7)	1.00	0.96 (0.46–2.00)	0.96 (0.46–2.03)	0.70 (0.34–1.42)	0.37
Medium HDL-P (μ mol/L) (0.4,1.3,3.4)	1.00	0.86 (0.39–1.88)	0.64 (0.30–1.38)	0.43 (0.20–0.93)	0.005
Small HDL-P (μ mol/L) (18,21,25)	1.00	0.86 (0.43–1.73)	1.13 (0.56–2.28)	1.26 (0.61–2.63)	0.44
Triglycerides (mg/dl) (146,205,287)	1.00	1.07 (0.52–2.19)	0.80 (0.38–1.69)	1.03 (0.45–2.34)	0.98
HDL-C (mg/dl) (31,36,42)	1.00	1.20 (0.58–2.52)	1.84 (0.84–4.00)	1.00 (0.47–2.12)	0.77
LDL-C (mg/dl) (133,156,182)	1.00	0.89 (0.44–1.81)	2.31 (1.14–4.67)	1.90 (0.89–4.04)	0.019
CRP (ug/mL) (1.7,3.3,5.5)	1.00	1.55 (0.71–3.40)	1.90 (0.88–4.13)	1.91 (0.86–4.25)	0.23
Adiponectin (ug/mL) (5.4,7.0,9.2)	1.00	1.37 (0.63–2.98)	1.20 (0.61–2.34)	1.39 (0.64–3.04)	0.71
Insulin (tu/mL) (11.2,14.7,19.4)	1.00	1.50 (0.77–2.93)	0.70 (0.35–1.39)	1.17 (0.58–2.37)	0.69

P-value for trend uses factor as a continuous variable in the regression model.

* Matched variables as in Table 1.

Models were adjusted for white blood cell count and smoking status at year 6.

Table 4

Multiple Matched Logistic Regression Analysis of Cases (CHD Deaths) vs. Controls: Men with Metabolic Syndrome*

	Odds Ratio (95%CI)			
	Model 1	Model 2	Model 3	Model 4
Log insulin	1.04 (0.85–1.28)	1.07 (0.86–1.31)	--	--
Log CRP	1.04 (0.83–1.30)	1.03 (0.82–1.30)	--	--
Log adiponectin	0.95 (0.76–1.18)	0.87 (0.69–1.10)	--	--
HDL particle number	0.78 (0.62–0.97)	--	0.82 (0.65–1.03)	--
Medium. HDL particle number	--	0.64 (0.50–0.82)	--	0.70 (0.55–0.90)
Smoking (y/n)	1.06 (0.66–1.71)	0.99 (0.61–1.61)	1.14 (0.73–1.78)	1.06 (0.67–1.67)
WBC	1.32 (1.04–1.67)	1.40 (1.10–1.79)	1.33 (1.05–1.69)	1.40 (1.10–1.77)
LDL-C	--	--	1.23 (1.00–1.51)	1.14 (0.91–1.44)

Odds ratio is for a 1 SD difference for all variables except smoking where the odds ratio compares smokers versus non-smokers. All variables used are at baseline.

* Model 1 includes insulin, CRP, adiponectin, total HDL-P; Model 2 includes medium HDL-P rather than total HDL-P; Model 3 includes variables in Model 1 and LDL-C; and Model 4 includes variables in Model 2 plus LDL-C. All models also include WBC and smoking status at year 6.