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Association Among Plasma Levels of Monocyte Chemoattractant Protein-1, Traditional Cardiovascular Risk Factors, and Subclinical Atherosclerosis

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OBJECTIVES We sought to evaluate the association between plasma levels of monocyte chemoattractant protein (MCP)-1 and the risk for subclinical atherosclerosis.

BACKGROUND Monocyte chemoattractant protein is a chemokine that recruits monocytes into the developing atheroma and may contribute to atherosclerotic disease development and progression. Plasma levels of MCP-1 are independently associated with prognosis in patients with acute coronary syndromes, but few population-based data are available from subjects in earlier stages of atherosclerosis.

METHODS In the Dallas Heart Study, a population-based probability sample of adults in Dallas County ≤65 years old, plasma levels of MCP-1 were measured in 3,499 subjects and correlated with traditional cardiovascular risk factors, high-sensitivity C-reactive protein (hs-CRP), and coronary artery calcium (CAC) measured by electron beam computed tomography.

RESULTS Higher MCP-1 levels were associated with older age, white race, family history of premature coronary disease, smoking, hypertension, diabetes, hypercholesterolemia, and higher levels of hs-CRP ($p < 0.01$ for each). Similar associations were observed between MCP-1 and risk factors in the subgroup of participants without detectable CAC. Compared with the subjects in the lowest quartile of MCP-1, the odds of prevalent CAC (CAC score ≥10) for subjects in the second, third, and fourth quartiles were 1.30 (95% confidence interval [CI] 0.99 to 1.73), 1.60 (95% CI 1.22 to 2.11), and 2.02 (95% CI 1.54 to 2.63), respectively. The association between MCP-1 and CAC remained significant when adjusted for traditional cardiovascular risk factors, but not when further adjusted for age.

CONCLUSIONS In a large population-based sample, plasma levels of MCP-1 were associated with traditional risk factors for atherosclerosis, supporting the hypothesis that MCP-1 may mediate some of the atherogenic effects of these risk factors. These findings support the potential role of MCP-1 as a biomarker target for drug development. (J Am Coll Cardiol 2004;44:1812–8)

Monocytes/macrophages play a fundamental role in the initiation, progression, and complications of coronary atherosclerosis (1,2). Monocyte chemoattractant protein (MCP)-1 is the primary chemokine responsible for the recruitment of monocytes to sites of active inflammation, including the developing atheroma (3). In addition, MCP-1 activates monocytes to express tissue factor and superoxide anions (4,5), which may contribute to plaque instability and the development of acute coronary syndromes.

Mice susceptible to atherosclerosis that undergo targeted deletion of either the MCP-1 (6) or the MCP-1 receptor (CCR-2) gene (7) have less monocyte accumulation and reduced atherosclerotic plaque burden when fed a cholesterol-rich diet compared to mice without targeted deletion of these genes. In human autopsy specimens, MCP-1 expression has been demonstrated within atheromatous lesions (8). More recently, investigators have focused on circulating plasma levels of MCP-1 as a biomarker with potential clinical utility. Results from one large prospective study demonstrated an independent association between plasma levels of MCP-1 and clinical outcomes in patients with acute coronary syndromes (9). In this study, MCP-1 levels were also strongly associated with several traditional cardiovascular risk factors such as age, hypercholesterolemia, hypertension, diabetes, and renal insufficiency. These associations with atherosclerosis risk factors suggest that MCP-1 may also be an important biomarker earlier in the disease process, during the preclinical phase of atherosclerosis. Although small studies have reported an association between plasma MCP-1 levels and the extent of coronary atherosclerosis among patients with unstable angina (10), no studies have evaluated the association between MCP-1 and subclinical atherosclerosis.

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Abbreviations and Acronyms

CAC = coronary artery calcium
CAD = coronary artery disease
EBCT = electron beam computed tomography
HDL = high-density lipoprotein
hs-CRP = high-sensitivity C-reactive protein
LDL = low-density lipoprotein
LVEF = left ventricular ejection fraction
MCP = monocyte chemoattractant protein

Given the multiple lines of experimental evidence implicating MCP-1 in atherogenesis, and the association between plasma MCP-1 levels and cardiovascular risk factors observed in clinical studies, we sought to determine whether plasma MCP-1 levels correlate with subclinical atherosclerosis. In addition, we sought to clarify the associations between MCP-1 levels and traditional cardiovascular risk factors using data from the Dallas Heart Study, a large and well-phenotyped population-based sample.

METHODS

Study population. The Dallas Heart Study is a population-based, multiethnic probability sample of 6,101 subjects in Dallas County designed to study cardiovascular disease. Details of the study design and characteristics of the enrolled cohort have been described previously (11). Briefly, a stratified random sample of Dallas County residents age 18 to 65 years was obtained from a pool of 841,943 eligible subjects using the U.S. Postal Service Delivery Sequence File, with deliberate oversampling of African Americans. An initial visit for 6,101 participants included a detailed in-home interview for demographic and health-related data, as well as measurements of weight, heart rate, and five sequential blood pressure measures. All subjects between the ages of 30 and 65 years who completed the initial visit were invited to return for a second visit to collect fasting venous blood and urine samples. If they completed the second visit they were invited to return for a third detailed clinic visit, consisting of a 12-lead electrocardiogram, cardiac and aortic magnetic resonance imaging, electron beam computed tomography (EBCT) to assess coronary artery calcification, and dual-energy X-ray absorbiometry scanning to evaluate fat distribution and bone density. A total of 3,557 subjects completed the second visit, and 2,971 subjects completed the third visit. No significant differences were noted in demographics, medical history, blood pressure, or body mass index between subjects participating in the home interview and the phlebotomy visit. Moreover, laboratory values were similar between those participating in the phlebotomy and clinic visits (11).

MCP-1 assay. Blood samples were obtained after an overnight fast in EDTA tubes and were stored for ≤4 h at 4°C before processing. Plasma aliquots were frozen at −80°C until assays were performed. Monocyte chemoattractant protein-1 measurements were performed in duplicate on thawed samples at Biosite Inc. (San Diego, California) on a high-throughput robotic platform (TECAN Genesis RSP 200/8). Details of the MCP-1 immunoassay have been previously reported (9). The minimal detectable concentration for the assay is 40 pg/ml, and the upper end of the reportable range is 2,000 pg/ml.

EBCT scans. Electron beam computed tomography measurements were performed on 2,763 subjects who were ≥30 years old. Measurements were obtained at 80% of the RR interval using an Imatron 150 XP (Imatron Inc., San Bruno, California), 30 cm FOV, 512 matrix with sharp kernel reconstruction. Calcium scoring followed the protocol of the Multi Ethnic Study of Atherosclerosis (12), and detection of calcium was based on a focus of calcium with ≥3 contiguous pixels and a computed tomography threshold of 130 Hounsfield units. Electron beam computed tomography scores were expressed in Agatston units (13,14) and the mean of two consecutive scans was used as the final EBCT score, unless only one scan was obtained. To minimize false-positive coronary artery calcium (CAC) classifications due to tissue-associated artifact, a mean EBCT score ≥10 Agatston units was defined as CAC-positive status in this study; at 10 Agatston units, more than 95% of subjects were concordant for positive (≥10) or negative (<10) scores in the replicate EBCT scans.

Definitions of variables. Complete medication profiles were obtained at the first visit. Hypercholesterolemia was defined as a calculated low-density lipoprotein (LDL) cholesterol ≥160 mg/dl on a fasting sample, direct LDL ≥160 mg/dl on a non-fasting sample, total cholesterol ≥240 mg/dl, or use of statin medication. Hypertriglyceridemia was defined as a fasting triglyceride concentration ≥200 mg/dl and low high-density lipoprotein (HDL) was defined as HDL <40 mg/dl in men and < 50 mg/dl in women. Five sequential blood pressure measurements were averaged for the first subject visit. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Diabetes was defined by a fasting glucose level ≥126 mg/dl or use of any hypoglycemic medication. C-reactive protein measurements were performed using a commercially available high-sensitivity assay (Roche Diagnostics, Indianapolis, Indiana).

Statistical analysis. Categorical data are reported as proportions and continuous data as median values with interquartile ranges (25th to 75th percentile). Baseline demographic variables and cardiovascular risk factors were compared across quartiles of MCP-1 using the chi-square trend test for categorical variables and the test for trend across ordered groups for continuous variables. The associations between MCP-1 levels and continuous variables were explored using Spearman correlation coefficients, without adjustment for lipid-lowering or antihypertensive therapies. Multivariate linear regression analysis was used to identify variables independently associated with log MCP-1 levels. Log MCP-1 levels were used in this analysis because of a rightward skew of MCP-1 values. Associations between

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Table 1. Association Between MCP-1 Levels and Demographic and Clinical Variables (n = 3,499)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p Trend
Subjects (n)	875	877	874	873	
Range (pg/ml)	≤123.1	123.2–167.9	168–226.1	>226.1	
Age (yrs)	40 [34, 48]	43 [36, 51]	44 [36, 52]	47 [39, 54]	<0.0001
Male gender	363 (42)	423 (48)	400 (46)	398 (46)	0.05
Race					
Black	526 (60)	423 (48)	421 (48)	438 (50)	<0.0001
White	192 (22)	265 (30)	273 (31)	294 (34)	<0.0001
Hispanic	140 (16)	171 (20)	158 (18)	125 (14)	0.26
Other	17 (2)	18 (2)	22 (3)	16 (2)	0.95
Medical history					
Hypertension	246 (28)	270 (31)	298 (35)	360 (42)	<0.0001
Diabetes	73 (8)	97 (11)	108 (12)	124 (14)	<0.0001
Cholesterol (mg/dl)	172 [150, 198]	176 [154, 202]	180 [156, 204]	181 [155, 208]	0.0002
Triglycerides (mg/dl)	82 [60, 127]	96 [66, 146]	98 [69, 151]	104 [74, 153]	0.0001
HDL (mg/dl)	48 [41, 59]	47 [40, 56]	47 [39, 57]	47 [39, 56]	0.04
LDL (mg/dl)	101 [82, 124]	103 [83, 123]	106 [85, 128]	108 [83, 130]	0.02
Current smoker	218 (25)	232 (26)	280 (32)	283 (32)	<0.0001
Family history of CAD	258 (29)	278 (32)	286 (33)	317 (36)	0.002
CrCl (ml/min)	118 [99, 144]	118 [100, 145]	117 [96, 145]	113 [91, 143]	<0.0001
LVH (n = 2,746)	91 (13)	82 (12)	85 (12)	104 (15)	0.33
LVEF <55% (n = 2,746)	20 (3)	15 (2)	26 (4)	21 (3)	0.51
BMI	28 [24, 33]	28 [25, 33]	28 [25, 33]	29 [25, 34]	0.01
% fat by DEXA	32 [25, 40]	33 [25, 40]	33 [25, 40]	33 [24, 41]	0.59
Median hs-CRP (mg/l)	2.4 [1, 6.1]	2.7 [1.3, 6.5]	3 [1.2, 6.9]	3.6 [1.4, 8.7]	<0.0001

Categorical data are presented as number (percent) and continuous data are presented as median [25th, 75th percentile].

BMI = body mass index; CAD = coronary artery disease; CrCl = creatinine clearance; DEXA = dual-energy X-ray absorbiometry; HDL = high-density lipoprotein cholesterol; hs-CRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MCP-1 = monocyte chemoattractant protein-1.

MCP-1 quartiles and CAC were determined using a series of univariable and multivariable logistic regression models, with adjustment for traditional risk factors and for age. The trend across MCP-1 quartiles was evaluated using the test for linear trend of the log odds.

RESULTS

In the Dallas Heart Study, 3,499 patients (mean age 44 ± 10 years) underwent measurement of MCP-1 levels. The median MCP-1 concentration was 167.9 pg/ml, and the 25th, 75th, 90th, and 95th percentiles were 123.1, 226.1, 304, and 380.5 pg/ml, respectively. Of these 3,499 patients, 2,723 had EBCT scans performed to measure CAC scores. Coronary artery calcium was present (CAC score ≥10) in 572 patients and absent in 2,151 patients.

Association with baseline risk factors. In univariable analyses, increasing quartiles of MCP-1 were associated with older age, white race, hypertension, diabetes, smoking, family history of coronary artery disease (CAD), lower creatinine clearance, and higher levels of LDL cholesterol, triglycerides, and CRP. In contrast, there was no association with left ventricular hypertrophy, left ventricular dysfunction, or the total percent of body fat (Table 1). In the subgroup of patients without detectable coronary calcification (CAC <10), similar associations were observed between quartiles of MCP-1 and older age, white race, hypertension, smoking, family history of CAD, lower creatinine clearance, and higher triglyceride and CRP levels (Table 2).

When MCP-1 was considered as a continuous variable, significant correlations were observed with age, systolic blood pressure, total cholesterol, LDL, HDL, triglycerides, and CRP (Table 3). In the subgroup without detectable CAC, significant correlations were observed between MCP-1 and age, total cholesterol, triglycerides, and CRP (Table 3). In a linear regression model that included all subjects, independent associations were observed between log MCP-1 and older age, white race, hypertension, CRP, and smoking (Table 4).

Association between MCP-1 and subclinical atherosclerosis. The proportion of patients with detectable coronary calcium increased in a stepwise fashion across quartiles of MCP-1, from 17.7% in the first quartile to 32.4% in the fourth quartile (unadjusted p for trend <0.0001) (Fig. 1). In a logistic regression model adjusting for traditional atherosclerosis risk factors (male gender, smoking, diabetes, hypercholesterolemia, hypertension, and family history of CAD) and for CRP, higher MCP-1 levels remained independently associated with CAC status. After further adjustment for age, however, MCP-1 was no longer independently associated with CAC (Table 5). When these analyses were repeated after excluding subjects receiving statin therapy, similar results were observed (data not shown).

DISCUSSION

In a large probability-based population sample, increasing plasma concentrations of MCP-1 were associated with several cardiovascular risk factors: older age, hypertension, diabetes,

Table 2. Association Between MCP-1 Levels and Demographic and Clinical Variables in Subjects Without Evidence of Subclinical Atherosclerosis (CAC score <10; n = 2,151)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p Trend
Subjects (n)	538	539	536	538	
Range (pg/ml)	≤120.7	120.8–163.8	163.9–220.8	>220.8	
Age (yrs)	41 [35, 47]	41 [36, 48]	42 [36, 49]	44 [37, 51]	<0.0001
Male gender	211 (38)	234 (42)	216 (41)	211 (42)	0.20
Race					
Black	309 (57)	238 (44)	229 (43)	238 (44)	<0.0001
White	127 (24)	171 (32)	185 (35)	192 (36)	<0.0001
Hispanic	93 (17)	118 (22)	106 (20)	96 (18)	0.96
Other	9 (2)	13 (2)	16 (3)	12 (2)	0.44
Medical history					
Hypertension	142 (27)	129 (24)	131 (25)	175 (33)	0.03
Diabetes	36 (7)	43 (8)	49 (9)	43 (8)	0.33
Cholesterol (mg/dl)	175 [152, 200]	178 [155, 204]	181 [157, 206]	182 [156, 209]	<0.0001
Triglycerides (mg/dl)	83 [60, 131]	96 [66, 146]	98 [70, 151]	104 [74, 152]	0.0001
HDL (mg/dl)	50 [41, 59]	47 [40, 56]	47 [39, 58]	48 [39, 56]	0.03
LDL (mg/dl)	103 [82, 126]	105 [82, 128]	107 [85, 130]	108 [83, 130]	0.13
Current smoker	111 (21)	130 (24)	149 (28)	155 (29)	0.0007
Family history of CAD	148 (28)	146 (27)	149 (28)	183 (34)	0.02
CrCl (ml/min)	119 [99, 140]	119 [101, 145]	117 [98, 143]	113 [92, 141]	0.01
LVH (n = 1,983)	60 (12)	51 (10)	38 (8)	57 (11)	0.49
LVEF <55% (n = 1,983)	12 (2)	9 (2)	7 (1)	12 (2)	0.90
BMI	28 [24, 32]	28 [25, 32]	28 [25, 32]	28 [25, 33]	0.35
% fat by DEXA	33 [26, 40]	33 [25, 40]	34 [25, 41]	33 [24, 41]	0.80
Median hs-CRP	2.4 [1, 5.7]	2.6 [1.2, 6.2]	2.7 [1.1, 5.7]	2.8 [1.1, 6.8]	0.01

Categorical data are presented as number (percent) and continuous data are presented as median [25th, 75th percentile].
Abbreviations as in Table 1.

hypercholesterolemia, smoking, family history of premature CAD, lower creatinine clearance, and higher levels of CRP. The MCP-1 levels were also higher in whites than African Americans. These results extend previous observations among patients with acute coronary syndromes (9,15–17) to a low-risk population-based cohort. Similar findings were observed among patients with no evidence of CAC, suggesting that the association between MCP-1 and atherosclerosis risk factors was not due to the presence of concomitant coronary atherosclerosis. Although we cannot exclude the possibility that the association between risk factors and MCP-1 was due to atherosclerosis in noncoronary vascular beds, prior population-based studies have demonstrated a very low prevalence of noncoronary atherosclerosis in patients without detectable CAC (18). In a multivariable linear regression model, older age, white race, hypertension, CRP and smoking were independently associated with higher MCP-1 levels. Although MCP-1 and CRP were associated with each other, the correlation between these two inflammatory markers was modest, suggesting that they reflect different inflammatory pathways.

In this study, MCP-1 was associated with CAC in multivariable analyses adjusting for traditional coronary risk factors; however, when further adjustment was made for age, MCP-1 was no longer independently associated with the presence of subclinical atherosclerosis. These results suggest that MCP-1 may not be useful as a clinical tool that is additive to the assessment of age, traditional risk factors, and/or CRP for the detection of subclinical atherosclerosis. However, our findings may have important pathophysiologic implications.

Table 3. Unadjusted Correlation Between MCP-1 Levels and Continuous Variables

	Total Population (n = 3,499)		Patients With CAC <10 (n = 2,151)	
	Spearman ρ	p Value	Spearman ρ	p Value
Age (yrs)	0.18	<0.0001	0.12	<0.0001
Total cholesterol	0.08	<0.0001	0.05	0.02
LDL	0.05	0.003	0.03	0.23
HDL	−0.04	0.01	−0.04	0.09
Triglycerides	0.14	<0.0001	0.11	<0.0001
CrCl	−0.06	0.0004	−0.06	0.006
CRP	0.10	<0.0001	0.05	0.02
% fat by DEXA	0.01	0.7	0.005	0.82
SBP	0.08	<0.0001	0.04	0.07
DBP	0.02	0.2	0.003	0.89
Heart rate	0.01	0.4	0.01	0.53

CAC = coronary artery calcium; DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Table 1.

Table 4. Variables Independently Associated With Log MCP-1 (n = 2,777)

	β Coefficient	p Value
Age (per 10 yrs)	0.08	<0.0001
White race (vs. black race)	0.14	<0.0001
Hypertension	0.05	0.03
CRP (per mg/l)	0.007	0.0001
Smoking	0.07	0.002

Abbreviations as in Table 1.

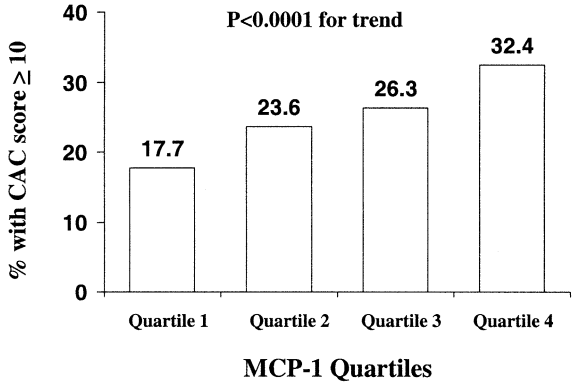

Figure 1. Association between quartiles of monocyte-chemoattractant protein-1 (MCP-1) and the prevalence of subclinical atherosclerosis detected by electron beam computed tomography (coronary artery calcium [CAC] score ≥10).

Pathophysiologic implications. Initial evidence implicating MCP-1 in atherogenesis was developed in mouse models. In mice rendered susceptible to atherosclerosis by knockout of the apolipoprotein E gene, overexpression of MCP-1 results in enhanced lipid staining and an increased burden of macrophages in atherosclerotic lesions (19). Conversely, mice with MCP-1 gene deletions have less lipid deposition and macrophage infiltration in their aortas than do those with normal MCP-1 expression (6). Similarly, deletion of the gene for the CCR-2 receptor (the ligand for MCP-1) also results in reduced atherosclerotic burden in mouse models (7). These studies provide substantial evidence for a role of MCP-1 in atherogenesis, yet the interplay between MCP-1 and traditional cardiovascular risk factors has been less well defined.

Traditional cardiovascular risk factors may mediate some of their effects on atherosclerosis via MCP-1 dependent pathways. Low-density lipoprotein upregulates CCR-2 receptor expression, which enhances monocyte chemotaxis (20). In addition, minimally modified LDL (a non-oxidative degradation product of LDL) increases MCP-1 levels and monocyte activity (21). Animal models also reveal reduced MCP-1 levels and macrophage infiltration in the neointima and media of mice treated with HMG-CoA reductase inhibitors (22). Finally, statin agents have been shown to lower plasma levels of MCP-1 in humans (23).

We observed an independent association between hypertension and MCP-1 levels. It is plausible that hypertension may also predispose humans to atherosclerosis in part via effects on MCP-1. Angiotensin II, which is upregulated in hypertension, activates nuclear factor kappa-B, a regulator of MCP-1 gene transcription (24). Angiotensin-converting enzyme inhibitors, therefore, may exert atheroprotective effects in part by inhibiting MCP-1 transcription (25).

Smoking was also independently associated with MCP-1 levels in the present study. Cigarette smoking has been shown to directly and indirectly activate macrophages to release MCP-1 in animal models and in humans with chronic obstructive lung disease (26). Smoking may contribute to atherosclerosis in part by modifying collagen and other vascular wall proteins so that they activate macrophages to secrete MCP-1. In addition, indirect effects, such as oxidation or modification of LDL (27), may contribute to the effects of smoking on MCP-1 levels.

Age is the variable most closely associated with MCP-1 levels in the present study. A previous study of healthy subjects showed an age-dependent increase in MCP-1 across each decade of life (28). Although it could be argued that the plasma concentration of MCP-1 may reflect the cumulative burden of atherosclerosis, which is a function of age, the present study demonstrates that MCP-1 levels increase with age even among those without evidence of atherosclerosis. Older age results in the formation of reactive oxygen species and progression of vascular endothelial dysfunction, both of which may occur via MCP-1–dependent pathways (29,30). The strong correlation seen between increasing MCP-1 levels and older age among patients with and without coronary calcification suggests that MCP-1 may mediate age-related effects on the vasculature.

In summary, the finding that traditional cardiovascular risk factors are associated with MCP-1 levels adds support

Table 5. Odds of Subclinical Atherosclerosis (CAC ≥ 10)

	Model 1 OR [95% CI]	Model 2 OR [95% CI]	Model 3 OR [95% CI]	Model 4 OR [95% CI]
MCP quartile 2	1.30 [0.99–1.73]	1.29 [0.95–1.75]	1.18 [0.85–1.65]	1.14 [0.84–1.56]
MCP quartile 3	1.60 [1.22–2.11]	1.41 [1.04–1.90]	1.15 [0.83–1.60]	1.25 [0.92–1.69]
MCP quartile 4	2.02 [1.54–2.63]	1.58 [1.18–2.12]	1.14 [0.82–1.57]	1.31 [0.97–1.77]
Male gender	—	2.76 [2.22–3.43]	3.50 [2.75–4.46]	—
Hypertension	—	3.11 [2.52–3.84]	1.74 [1.37–2.20]	—
Diabetes	—	2.16 [1.63–2.87]	1.86 [1.37–2.54]	—
Hypercholesterolemia	—	2.25 [1.73–2.93]	1.53 [1.14–2.04]	—
Tobacco use	—	1.79 [1.44–2.22]	2.49 [1.96–3.17]	—
Family history of CAD	—	1.67 [1.36–2.06]	1.31 [1.05–1.65]	—
CRP (per mg/l)	—	1.03 [1.01–1.05]	1.02 [1.00–1.04]	—
Age (per 10 yrs)	—	—	3.84 [3.31–4.49]	3.73 [3.28–4.26]

Model 1: Unadjusted p trend across MCP-1 quartiles <0.0001; Model 2: Adjusted for traditional risk factors p trend across MCP-1 quartiles = 0.05; Model 3: Adjusted for traditional risk factors and age p trend across MCP-1 quartiles = 0.40; Model 4: Adjusted for age p trend across MCP-1 quartiles = 0.07.

CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; other abbreviations as in Tables 1 and 3.

to the hypothesis that MCP-1 may function in the causal pathway between risk factors and atherosclerosis, mediating some of the effects of these traditional risk factors. Thus, MCP-1 may have value in the future as a biomarker target for drug development. Further experimental studies are needed to evaluate this hypothesis.

Study limitations. Although this study represents the first large-scale evaluation of MCP-1 in a population-based cohort, it has a number of important limitations. First, we performed EBCT as the measure of atherosclerosis burden in the Dallas Heart Study. Given that age is so closely associated with coronary calcification (31–34), this relationship may have "dominated" a more subtle association between MCP-1 and CAC in multivariable models. Association studies with MCP-1 should be performed using other measures of subclinical atherosclerosis that may be less dependent on age, such as carotid intima-media thickness, magnetic resonance imaging of the vascular wall, and novel plaque imaging modalities. Second, the cross-sectional design of the present study does not permit assessment of the temporal associations among cardiovascular risk factors, MCP-1, and the development or progression of atherosclerosis. Many years would be required to analyze the longitudinal association between MCP-1 and the clinical complications of atherosclerotic disease. Finally, we were not able to evaluate the association between MCP-1 and prognosis with a cross-sectional study design. Prospective studies with both clinical and imaging endpoints will be needed to fully evaluate the clinical potential of MCP-1 as a biomarker of atherosclerosis.

Conclusions. In a population-based sample, plasma levels of MCP-1 were associated with traditional cardiovascular risk factors, both in subjects with and without evidence for subclinical coronary atherosclerosis. The association between MCP-1 levels and CAC was independent of traditional risk factors, but not of age. Based on sound experimental evidence linking MCP-1 with the development of atherosclerosis, strong associations between MCP-1 levels and risk factors for atherosclerosis observed in the present study, and prior demonstration that preventive therapies lower MCP-1 levels (35,36), MCP-1 holds promise as a biomarker target for drug development. Further prospective studies of this biomarker are warranted.

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