Plasminogen Activator Inhibitor-1 and Diagnosis of the Metabolic Syndrome in a West African Population

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Background—Metabolic syndrome (MetS) is diagnosed by the presence of at least 3 of the following: obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein. Individuals with MetS also typically have elevated plasma levels of the antifibrinolytic factor, plasminogen activator inhibitor-1 (PAI-1), but the relationships between PAI-1 and MetS diagnostic criteria are not clear. Understanding these relationships can elucidate the relevance of MetS to cardiovascular disease risk, because PAI-1 is associated with ischemic events and directly involved in thrombosis.

Methods and Results—In a cross-sectional analysis of 2220 Ghanaian men and women from urban and rural locales, we found the age-standardized prevalence of MetS to be as high as 21.4% (urban women). PAI-1 level increased exponentially as the number of diagnostic criteria increased linearly \((P<10^{-15})\), supporting the conclusion that MetS components have a joint effect that is stronger than their additive contributions. Body mass index, triglycerides, and fasting glucose were more strongly correlated with PAI-1 than with canonical MetS criteria, and this pattern did not change when pair-wise correlations were conditioned on all other risk factors, supporting an independent role for PAI-1 in MetS. Finally, whereas the correlations between conventional risk factors did not vary significantly by sex or across urban and rural environments, correlations with PAI-1 were generally stronger among urban participants.

Conclusions—MetS prevalence in the West African population we studied was comparable to that of the industrialized West. PAI-1 may serve as a key link between MetS, as currently defined, and the endpoints with which it is associated. Whether this association is generalizable will require follow-up. (J Am Heart Assoc. 2016;5:e003867 doi: 10.1161/JAHA.116.003867)

Key Words: diabetes mellitus • epidemiology • fibrinolysis • hypertension • lipids • obesity
There is, however, at least 1 aspect of the syndrome that may distinguish it from its component conditions: Patients diagnosed with MetS typically suffer from a hypercoagulable condition of the blood, caused by supranormal levels of clotting and antifibrinolytic factors. Among the most prominent of these factors is plasminogen activator inhibitor 1 (PAI-1), which hinders clot degradation by inhibiting plasminogen activators in the fibrinolytic pathway. PAI-1 appears to be connected to MetS in multiple ways beyond this antifibrinolytic role. For example, at high levels, PAI-1 promotes a chronic state of low-grade inflammation, one of the proposed underlying causes of MetS. A number of proinflammatory factors are known to stimulate PAI-1 production, including interleukins, tumor necrosis factor alpha, transforming growth factor beta, and C-reactive protein. Although circulating PAI-1 is mainly released by hepatic and endothelial cells, adipose tissue becomes a major source as visceral adiposity increases, which also has been implicated in increased inflammation and coronary heart disease. High PAI-1 may also predispose patients to premature atherosclerosis not only through inflammatory pathways, but also by interfering with cell migration. Other PAI-1 stimulants related to MetS include plasma glucose, insulin, very low-density lipoprotein (VLDL) cholesterol, and the vasopressive hormone, angiotensin II.

Perhaps, most important, PAI-1 represents a natural link between MetS risk factors and acute phases of cardiovascular disease. Circadian spikes in PAI-1 levels likely explain the morning peak in the incidence of myocardial infarction and stroke, and epidemiological studies have demonstrated a positive association between elevated plasma PAI-1 levels and adverse cardiovascular events. Thus, understanding how PAI-1 levels respond to the risk factors of MetS (and vice versa) should provide insight into how the components of the syndrome individually—and jointly—increase the risk of cardiovascular disease.

There have been relatively few studies of MetS in West Africa, and no large study, to our knowledge, has addressed the association between PAI-1 and MetS in the region. Prevalence and etiology of MetS, including its relationship with PAI-1, vary among ethnic groups, making it important to study these factors simultaneously in different populations. In addition, urbanization and the changes that accompany it, such as the adoption of sedentary lifestyle and nutrient-poor, calorie-rich diets, are major factors in MetS prevalence and etiology, but no study, to our knowledge, has examined how urban-rural differences may affect the relationship between PAI-1 and MetS.

Here, we present a multivariate analysis of MetS and PAI-1, using cardiovascular risk factor data from 3331 men and women in Ghana from both urban and rural locales. We assess the correlational architecture of MetS risk factors and estimate their potential relevance to thrombotic endpoints by using strength and independence of association with PAI-1 as a proxy. Because correlational analyses do not require any assumptions of direction of effect, they are well suited for the study of metabolic systems. Partial correlations in particular can distinguish independent (and possibly direct) interactions among risk factors from merely incidental associations. In addition, we assess the possibility of nonlinear relationships among risk factors, such as at the extremes of their distributions, which may be especially pertinent to clinical outcomes. Throughout, we evaluate how the patterns of association we observe may be influenced by differences in sex and environment (urban vs rural), both of which have been shown to affect cardiovascular disease risk. The overriding goal of this study was to assess the extent to which PAI-1 may play a central or connecting role in the diagnosis of MetS.

**Methods**

**Study Population**

Participants were recruited from Sunyani, the capital of the Brong Ahafo region of Ghana (population 250,000 as of the 2012 census), and from surrounding rural villages of fewer than 5000 people. Urban recruitment occurred from 2002 to 2007. Rural participants were recruited in 2008. Participants learned about the study at public venues, including local churches and markets. Individuals <18 years of age or who were first- or second-degree relatives of someone already enrolled in the study were excluded. Participants provided information by in-person interviews regarding their medical histories and other demographic and socioeconomic factors, including education level, smoking status, alcohol consumption, and current medications. All participants provided informed consent. Institutional review boards at Dartmouth College (Hanover, NH), Vanderbilt University (Nashville, TN), and Regional Hospital, Sunyani approved all protocols.

**Anthropometric Measurements and Biochemical Analyses**

The mean of 2 measurements for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) was calculated. Blood was drawn between 8:00 and 10:00 AM, after a fast ≥8 hours, and used to assess fasting glucose, fasting lipids, and PAI-1 levels. Glucose was measured from blood drops using a SureStep monitor by LifeScan (Milpitas, CA). Total cholesterol (TC), triglycerides (TG), and HDL levels were measured in plasma. PAI-1 antigen was measured using an enzyme-linked immunoassay (Biopool AB, Umea, The...
Netherlands). Here, only total PAI-1 was measured (comprising free PAI-1 as well as its complexes with plasminogen activators), given that the short half-life of the active molecule in plasma makes it less useful for studies of chronic disease. Body mass index (BMI) was calculated with weight and height measurements (kg/m²).

Study Variables

Five categorical metabolic risk factors (hypertriglyceridemia, low HDL, hypertension, hyperglycemia, and obesity) were defined according to the updated National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) criteria, as follows: TG ≥150 mg/dL; HDL <40 mg/dL in males or <50 mg/dL in females; SBP and DBP ≥130/85 mm Hg or on antihypertensive medication; fasting glucose (GLUC) ≥100 mg/dL or on antidiabetic medication; and BMI ≥30. None of the study participants reported taking statins. Mean arterial pressure (MAP) was calculated using the formula: MAP = (SBP + DBP)/3, which approximates the average arterial pressure during a single cardiac cycle. Because MAP has been shown to predict future MetS more accurately than SBP, DBP, or pulse pressure, it was used in the correlational analyses. Pearson’s correlation coefficients and tests of correlational homogeneity are sensitive to deviations from normality. Quantitative variables used in the correlational analyses were therefore log-transformed after observing that this improved approximations to normality (using the Shapiro-Wilk test as a criterion). For clarity of presentation, however, mention in the text does not reflect these transformations (eg, as “ln-glucose” or “ln-PAI-1,” etc).

For calculating prevalence of MetS, the study participants for whom no data were missing (N=2220) and who had at least 3 of the 5 conditions (as per the NCEP ATP-III guidelines) were deemed cases. The missing data for 1111 participants (598 urban, 513 rural) resulted from a supply failure for HDL cholesterol assay during the collection process.

Statistical Analyses

Prevalence rates of MetS were age-standardized to the World Health Organization 2000–2025 standard population using recommended age bins that pertained to our data (18–24, 25–34, 35–44, 45–54, and ≥55 years-old). Relative risks (RRs) of MetS (for urban vs rural and female vs male) were also estimated. To check for possible bias in the participants with missing HDL data versus complete cases, the age-adjusted means and variances of all other variables were compared (by t test and Levene’s test, respectively) for both groups.

Pair-wise correlations between BMI, MAP, GLUC, TG, HDL, and PAI-1 were calculated, using the residuals after linear regression on age, sex, and residence. Pair-wise correlations were also calculated separately for (1) individuals stratified by residence (after age and sex adjustment) and (2) individuals stratified by sex (after age and residence adjustment). Tests for homogeneity of correlation between groups (ie, urban vs rural, male vs female) were conducted by t test after Fisher transformation of correlation coefficients. For every pair of variables in the set of BMI, MAP, GLUC, TG, HDL, and PAI-1, partial correlations were calculated controlling for the remaining variables in the set, after which the above analyses were repeated. For clarity, only these higher-order partial correlations are referred to as “partial correlations” in the text, although all correlations in this study are controlled for age and sex and/or residence.

The following approach was used to assess visually whether the strengths of association between MetS traits (BMI, MAP, GLUC, TG, and HDL) and PAI-1 were consistent over the entirety of their respective ranges, and to identify patterns of nonlinear association: (1) Age-, sex-, and residence-adjusted regression residuals of the five MetS traits were standardized: ranked in ascending order, and paired with corresponding standardized PAI-1 values; (2) the 25th percentile, median, and 75th percentile of PAI-1 (period=100) were plotted against the corresponding median (period=100) of each MetS trait; (3) smooth curves of the plots were generated, using a cubic spline method. Briefly, for n observations, where \( \bar{x} \) is the ith standardized median (period 100) of a risk factor, \( i \epsilon [1, n–99] \), and \( \hat{P} \) the corresponding quantile value of PAI-1, such that \( \hat{P} = \mu(\bar{x}) \), the smoothing function \( \mu \) estimated \( \mu \) by minimizing

\[
\sum_{i=1}^{n} (\hat{P}_i - \mu(\bar{x}))^2 + \lambda \int_{x_1}^{x_99} \hat{\mu}^2(x) dx
\]

The first term represents the sum of squares error and the second term the penalty for “roughness.” The parameter \( \lambda \) controls the bias-variance trade-off and was set to 10. PAI-1 quartiles were used in these analyses rather than mean values to minimize the influence of outliers caused by the characteristic kurtosis of the PAI-1 distribution, and to gain insight into whether PAI-1 levels at upper or lower quartiles associate differently with changes in the other risk factors.

For further analysis, an ordinal variable, defined as the number of conditions with which an individual was diagnosed (ie, 0 through 5), was created to augment the dichotomous characterization of MetS (ie, as the presence or absence of at least 3 conditions). Mean PAI-1 was calculated for each of these groups, using the standardized age-, sex-, and residence-adjusted residuals. The association between
MetS progression and PAI-1 was then assessed in 2 ways. First, the number of MetS conditions was modeled as a function of PAI-1, using ordinal regression (with cumulative logit link), adding age, sex, and residence as covariates. PAI-1 was then added as an explanatory variable, and the fit of the quadratic versus the linear model was compared using the likelihood ratio test. Second, mean PAI-1 levels were compared by t test for each sequential pair of groups (ie, 0 vs 1 conditions, 1 vs 2, etc). A curve was also fitted to the PAI-1 means using polynomial regression (quadratic). Statistical analyses were performed using JMP Pro (12.1; SAS Institute Inc., Cary, NC), STATA (12; StataCorp LP, College Station, TX), and R software (3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 3331 participants in this study, 2276 (68%) were urban residents, of whom 1298 (57%) were female and 978 male. Of the 1055 rural residents, 583 (55%) were female and 472 male. Ages ranged from 18 to 99 and were similarly distributed among urban and rural men and women (P=0.23, Kruskal–Wallis test). In analyses that depended on the total number of categorical risk factors, participants with missing data were excluded, lowering the sample size to 2220. The decrease in sample size resulted from the lack of supplies for testing HDL cholesterol during the collection process. However, the distributions of measured variables between participants with and without missing data were not significantly different (Table S1), consistent with the sporadic and random timing of the supply shortages. Age-standardized MetS prevalence by group and summary data of associated variables are presented in Table 1 and Figure S1.

Table 1. Prevalence of MetS and Its Component Risk Factors Among 2220 Urban and Rural Men and Women From Brong Ahafo, Ghana

|                  | Males                        | Females                     |
|------------------|------------------------------|------------------------------|
|                  | Urban (N=721)                 | Rural (N=225)                | Urban (N=957) | Rural (N=317)          |
| MetS*            | 0.126 (0.102, 0.151)          | 0.078 (0.043, 0.113)         | 0.214 (0.188, 0.240) | 0.112 (0.077, 0.147) |
| Obesity          | 0.065 (0.049, 0.086)          | 0.00 (0.00, 0.017)           | 0.265 (0.238, 0.294) | 0.050 (0.031, 0.080)  |
| Hypertension     | 0.130 (0.108, 0.157)          | 0.111 (0.076, 0.159)         | 0.097 (0.080, 0.118) | 0.088 (0.062, 0.125)  |
| Hyperglycemia    | 0.413 (0.378, 0.450)          | 0.267 (0.213, 0.328)         | 0.389 (0.358, 0.420) | 0.293 (0.246, 0.346)  |
| High TG          | 0.239 (0.209, 0.271)          | 0.173 (0.129, 0.228)         | 0.315 (0.286, 0.345) | 0.293 (0.246, 0.346)  |
| Low HDL-C        | 0.437 (0.401, 0.473)          | 0.391 (0.330, 0.456)         | 0.588 (0.557, 0.619) | 0.612 (0.557, 0.664)  |

HDL-C indicates high-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.  
*Prevalence was age-standardized to the World Health Organization 2000–2025 standard population; N=sample size of participants for whom no data were missing; in parentheses: 95% CIs.

Prevalence and RR of MetS

Male and female urban residents had a significantly higher RR of MetS than their rural counterparts (1.61 with 95% CI, 1.02–2.53, and 1.72 with 95% CI, 1.28–2.3, males and females,
Table 2. Pearson Correlation Coefficients Between Cardiovascular Risk Factors Associated With MetS in Urban and Rural Ghanaians

| Trait 1       | Trait 2       | \( r^* \) | CI          | N  | \( P \) Value | Rural | \( r^1 \) | CI          | N  | \( P \) Value | Urban | \( P \) Value | Homogeneity of Correlation | \( P \) Value |
|---------------|---------------|----------|-------------|----|---------------|-------|----------|-------------|----|---------------|-------|---------------|--------------------------|-------------|
| BMI           | PAI-1         | 0.43     | (0.40, 0.45)| 3331 | <0.0001       | 0.29  | (0.23, 0.34)| 542 | <0.0001       | 0.47  | (0.44, 0.51)| 2276 | <0.0001       | 4.90E-09                 |
| BMI           | GLUC          | 0.15     | (0.12, 0.18)| 3331 | <0.0001       | 0.20  | (0.14, 0.25)| 1055| <0.0001       | 0.13  | (0.09, 0.17)| 2276 | <0.0001       | 0.0621                   |
| BMI           | HDL           | -0.15    | (-0.19, -0.11)| 2225 | <0.0001       | -0.08 | (-0.17, 0.00)| 543 | 0.0522        | -0.18 | (-0.23, -0.13)| 1682 | <0.0001       | 0.0472                   |
| BMI           | MAP           | 0.30     | (0.27, 0.33)| 3331 | <0.0001       | 0.28  | (0.22, 0.33)| 1055| <0.0001       | 0.31  | (0.27, 0.34)| 2276 | <0.0001       | 0.4186                   |
| BMI           | TG            | 0.25     | (0.22, 0.28)| 3321 | <0.0001       | 0.18  | (0.13, 0.24)| 1051| <0.0001       | 0.27  | (0.23, 0.31)| 2270 | <0.0001       | 0.0122                   |
| GLUC          | PAI-1         | 0.20     | (0.16, 0.23)| 3331 | <0.0001       | 0.11  | (0.05, 0.17)| 1055| 0.0004        | 0.23  | (0.19, 0.27)| 2270 | <0.0001       | 0.0001                  |
| GLUC          | HDL           | -0.12    | (-0.16, -0.08)| 2225 | <0.0001       | -0.14 | (-0.22, -0.05)| 543 | 0.0014        | -0.12 | (-0.16, -0.07)| 1682 | <0.0001       | 9.90E-04                 |
| GLUC          | MAP           | 0.13     | (0.10, 0.17)| 3331 | <0.0001       | 0.17  | (0.11, 0.23)| 1055| <0.0001       | 0.11  | (0.07, 0.16)| 2276 | <0.0001       | 0.1416                   |
| GLUC          | TG            | 0.17     | (0.14, 0.21)| 3321 | <0.0001       | 0.20  | (0.14, 0.26)| 1051| <0.0001       | 0.16  | (0.12, 0.20)| 2270 | <0.0001       | 0.2878                   |
| HDL           | PAI-1         | -0.17    | (-0.21, -0.13)| 2225 | <0.0001       | -0.17 | (-0.25, -0.08)| 543 | 0.0001        | -0.18 | (-0.22, -0.13)| 1682 | <0.0001       | 0.8302                   |
| HDL           | MAP           | 0.03     | (-0.01, 0.07)| 2225 | 0.1376       | 0.05  | (-0.03, 0.14)| 543 | 0.2110        | 0.03  | (-0.02, 0.07)| 1682 | 0.2752        | 0.5818                   |
| HDL           | TG            | -0.27    | (-0.31, -0.23)| 2220 | <0.0001       | -0.30 | (-0.37, -0.22)| 542 | <0.0001       | -0.26 | (-0.31, -0.22)| 1678 | <0.0001       | 0.4726                   |
| MAP           | PAI-1         | 0.23     | (0.20, 0.26)| 3331 | <0.0001       | 0.24  | (0.18, 0.29)| 1055| <0.0001       | 0.23  | (0.19, 0.27)| 2276 | <0.0001       | 0.7878                   |
| MAP           | TG            | 0.16     | (0.13, 0.20)| 3321 | <0.0001       | 0.19  | (0.13, 0.25)| 1051| <0.0001       | 0.15  | (0.11, 0.19)| 2270 | <0.0001       | 0.2561                   |
| TG            | PAI-1         | 0.35     | (0.32, 0.38)| 3321 | <0.0001       | 0.28  | (0.22, 0.33)| 1051| <0.0001       | 0.38  | (0.35, 0.42)| 2270 | <0.0001       | 2.10E-03                  |

BMI indicates body mass index; GLUC, glucose; HDL, high-density lipoprotein cholesterol; MAP, mean arterial pressure; MetS, metabolic syndrome; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides.

*Pearson correlation coefficient, calculated using residuals after adjustment for age, sex, and residence.
†Pearson correlation coefficient, calculated for urban and rural participants separately, using residuals after adjustment for age and sex; CI=95% confidence interval (in parenthesis); \( P \) value=probability of \( r \) if true correlation is zero; Homogeneity of Correlation \( P \) value=probability of these data if true correlation is equal for urban and rural populations.
respectively). Urban women, who had the highest prevalence of obesity among all groups (26.5%), also had the highest age-standardized prevalence of MetS (21.4%; Table 1), with an RR of 1.68 (CI, 1.36–2.07) compared to urban men (P<0.0001), and 1.72 compared to rural women (P=0.0002). Among rural participants, risk of MetS did not differ by sex.

**Relationship Between PAI-1 and Number of MetS Conditions**

Mean PAI-1 (log-normalized and adjusted for age, sex, and residence) rose exponentially as the number of MetS risk factors increased linearly. The quadratic fit to the means was virtually perfect (R²=0.996). Among participants who had at least 1 MetS risk factor, mean PAI-1 increased significantly with each additional condition, with the most significant increase occurring when the number of conditions increased from 2 to 3, consistent with the NCEP ATP-III definition (Figure 1). Ordinal polynomial regression was also used to model the number of MetS risk factors as a function of PAI-1. The improvement of the quadratic fit over the linear fit was highly significant (P<10⁻¹³), confirming the strong exponential relationship between the logarithm of PAI-1 level and number of MetS criteria.

**Pair-wise Correlations of Risk Factors**

All pair-wise correlations between risk factors adjusted for age, sex, and residence were statistically significant (P<0.0001), except for the correlation between MAP and HDL (Table 2 and Figure 2). Seven of 15 correlations were at least 0.20 in magnitude: BMI-PAI-1; BMI-TG; BMI-MAP; TG-PAI-1; TG-HDL; MAP-PAI-1; and GLUC-PAI-1. Among pair-wise correlations with PAI-1, only 2 of 10 pairs were significantly different: BMI-HDL (P=0.047) and BMI-TG (P=0.012), with both correlations again stronger in the urban population (Table 2 and Figure 2). When participants were stratified by sex, no P value for homogeneity of correlation was smaller than 0.01 (Table 3 and Figure 2). Of the 3 significant at the 0.05 level, the GLUC-PAI-1 correlation was higher in women than in men, and the correlations of both BMI and PAI-1 with MAP were higher in men.

**Pair-wise Partial Correlations of Risk Factors**

Partial correlations between pairs of risk factors (including PAI-1) that controlled for all other risk factors (in addition to age and sex and/or residence, as above) were calculated to assess strengths of independent association. All partial correlations were statistically significant, with 4 greater than 0.20 in magnitude: BMI-PAI-1; TG-PAI-1; BMI-MAP; and TG-HDL (Table 4 and Figure 3). Three of 15 partial correlations were significantly different between urban and rural residents (BMI-PAI-1, P=0.0002; GLUC-PAI-1, P=0.001; and BMI-GLUC, P=0.005), with the stronger correlations in the urban group (Table 4 and Figure 3). Only 1 of 15 partial correlations was significantly different between men and women (GLUC-PAI-1, P=0.023; Table 5 and Figure 3). The partial correlational analyses were repeated for MetS risk factors without PAI-1 and yielded comparable results (Tables S2 through S4).
Table 3. Pearson Correlation Coefficients Between Cardiovascular Risk Factors Associated With MetS, Including PAI-1, by Sex

| Trait 1   | Trait 2 | Females       | Males       | Homogeneity of Correlation |
|-----------|---------|---------------|-------------|----------------------------|
|           |         | r       | CI         | N  | P Value | r       | CI         | N  | P Value | P Value |
| BMI       | PAI-1   | 0.44   | (0.41, 0.48) | 1881 | <0.0001 | 0.41   | (0.36, 0.45) | 1450 | <0.0001 | 0.2008 |
| BMI       | GLUC    | 0.15   | (0.10, 0.19) | 1881 | <0.0001 | 0.17   | (0.12, 0.22) | 1450 | <0.0001 | 0.5756 |
| BMI       | HDL     | −0.15  | (−0.20, −0.10) | 1275 | <0.0001 | −0.17  | (−0.23, −0.11) | 950 | <0.0001 | 0.6037 |
| BMI       | MAP     | 0.27   | (0.23, 0.32) | 1881 | <0.0001 | 0.35   | (0.30, 0.39) | 1450 | <0.0001 | 0.0186 |
| BMI       | TG      | 0.24   | (0.19, 0.28) | 1878 | <0.0001 | 0.27   | (0.23, 0.32) | 1443 | <0.0001 | 0.2610 |
| GLUC      | PAI-1   | 0.23   | (0.19, 0.28) | 1881 | <0.0001 | 0.15   | (0.10, 0.20) | 1450 | <0.0001 | 0.0116 |
| GLUC      | HDL     | −0.13  | (−0.18, −0.07) | 1275 | <0.0001 | −0.12  | (−0.18, −0.05) | 950 | 0.0003  | 0.7984 |
| GLUC      | MAP     | 0.11   | (0.07, 0.16) | 1881 | <0.0001 | 0.16   | (0.11, 0.21) | 1450 | <0.0001 | 0.1371 |
| GLUC      | TG      | 0.19   | (0.14, 0.23) | 1878 | <0.0001 | 0.15   | (0.10, 0.20) | 1443 | <0.0001 | 0.3103 |
| HDL       | PAI-1   | −0.20  | (−0.25, −0.15) | 1275 | <0.0001 | −0.14  | (−0.20, −0.08) | 950 | <0.0001 | 0.1569 |
| HDL       | MAP     | 0.05   | (0.00, 0.11) | 1275 | 0.0604  | 0.01   | (−0.06, 0.07) | 950 | 0.8036  | 0.2993 |
| HDL       | TG      | −0.26  | (−0.31, −0.20) | 1274 | <0.0001 | −0.28  | (−0.34, −0.23) | 946 | <0.0001 | 0.4758 |
| MAP       | PAI-1   | 0.20   | (0.15, 0.24) | 1881 | <0.0001 | 0.27   | (0.22, 0.32) | 1450 | <0.0001 | 0.0239 |
| MAP       | TG      | 0.13   | (0.09, 0.18) | 1878 | <0.0001 | 0.19   | (0.14, 0.24) | 1443 | <0.0001 | 0.0830 |
| TG        | PAI-1   | 0.34   | (0.30, 0.38) | 1878 | <0.0001 | 0.36   | (0.31, 0.40) | 1443 | <0.0001 | 0.5472 |

*r*=Pearson correlation coefficient, calculated using residuals after adjustment for age and residence by sex; CI=95% confidence interval (in parenthesis); *P* value=probability of *r* if true correlation is zero; Homogeneity of Correlation *P* value=probability of these data if true correlation is equal for men and women. BMI indicates body mass index; GLUC, glucose; HDL, high-density lipoprotein cholesterol; MAP, mean arterial pressure; MetS, Metabolic Syndrome; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides.
Relationship Between PAI-1 Quartiles and MetS Risk Factors

Consistent with the strong correlations, median PAI-1 increased most with BMI and TG, from ≈0.5 SD below the mean to 1.0 SD above (Figure 4). Notably, median PAI-1 did not vary when BMI was less than ≈1 SD below its mean. The relationship between PAI-1 quartiles and glucose displayed an abrupt shift at a glucose value of ≈+1.5 SD, from strongly positive to flat (Figure 4). The moving quartiles of PAI-1 were also evaluated for data stratified by sex and residence (Figure 5), revealing pronounced differences in the urban/rural PAI-1 quartiles. In contrast, the male-female trajectories of PAI-1 were almost indistinguishable, regardless of risk factor. The significantly different correlations by sex observed for PAI-1-MAP and PAI-1-GLUC, however, were likely reflected in the slight discordances at the right tails of their distributions (Figure 5).

To complement the partial correlational analyses, which assessed the independence of association among risk factors, PAI-1 quartiles were also plotted against each risk factor after adjustment for all others (Figure 4). The relationship of PAI-1 quartiles with all variables except BMI changed qualitatively with these additional adjustments. The most consistent difference was that independent associations with PAI-1 were much weaker when risk factors were below their means (Figure 4). Over their entire ranges, MAP and HDL had the weakest independent associations with PAI-1, corresponding to weak partial correlations (r<0.10). In contrast, the independent association between glucose and median PAI-1 was relatively strong, despite a similarly weak GLUC-PAI-1 partial correlation (r<0.10; Figure 4).

Discussion

A much-discussed topic has been whether the clustering of factors associated with MetS increases total cardiovascular disease risk in an additive or exponential way.35–38 If, as observed here, PAI-1 increases exponentially as MetS diagnostic conditions increase linearly, then the question of whether MetS is “more than the sum of its parts” can be reduced, in part, to the clinical consequences of elevated PAI-1. Although the added value of using elevated PAI-1 as a prognostic indicator of adverse cardiac events has been debated,39 its connection with increased cardiovascular risk has been demonstrated convincingly by many clinical and epidemiological studies.7,40–44 Our results therefore support the basis of MetS as a clinical entity with distinct outcomes. We also observed the most significant increase in PAI-1 when the number of risk factors increased from 2 to 3, which supports the current NCEP ATP-III definition.

We found that the correlations between PAI-1 and the factors that define MetS (BMI, MAP, HDL, TG, and GLUC) were generally stronger than the correlations between the factors themselves. Given that MetS is essentially defined by the association of multiple risk factors, our results raise the question of whether PAI-1 should also be incorporated into its definition and diagnosis. For example, the strongest pair-wise correlations that included BMI, TG, or glucose were all with PAI-1. Moreover, this pattern did not change when we controlled for the influence of other factors, suggesting an independent role for PAI-1 in the clinical pathology of MetS.
| Trait 1  | Trait 2  | \( r^* \)  | CI          | \( P \) Value | Rural \( r^* \)  | CI          | N  | \( P \) Value | Urban \( r^* \)  | CI          | N  | \( P \) Value | Homogeneity of Correlation \( P \) Value |
|----------|----------|-------------|--------------|---------------|----------------|--------------|----|---------------|----------------|--------------|----|---------------|--------------------------|
| BMI      | PAI-1    | 0.33        | (0.29, 0.37) | <0.0001       | 0.21           | (0.12, 0.29) | 542 | <0.0001       | 0.37           | (0.33, 0.41) | 1678 | <0.0001       | 0.0002                     |
| BMI      | GLUC     | 0.04        | (0.00, 0.08) | 0.0564        | 0.13           | (0.05, 0.21) | 542 | 0.0023        | -0.01          | (-0.05, 0.04) | 1678 | 0.7965        | 0.0054                     |
| BMI      | HDL      | -0.09       | (-0.13, -0.04) | <0.0001      | -0.03          | (-0.12, 0.05) | 542 | 0.4282        | -0.12          | (-0.16, -0.07) | 1678 | <0.0001       | 0.1003                     |
| BMI      | MAP      | 0.22        | (0.18, 0.26) | <0.0001       | 0.20           | (0.12, 0.28) | 542 | <0.0001       | 0.23           | (0.19, 0.28)  | 1678 | <0.0001       | 0.4607                     |
| BMI      | TG       | 0.07        | (0.03, 0.11) | 0.0007        | 0.05           | (-0.03, 0.14) | 542 | 0.2241        | 0.07           | (0.03, 0.12)  | 1678 | 0.0027        | 0.6733                     |
| GLUC     | PAI-1    | 0.10        | (0.06, 0.14) | <0.0001       | -0.01          | (-0.09, 0.07) | 542 | 0.8199        | 0.15           | (0.10, 0.20)  | 1678 | <0.0001       | 0.0010                     |
| GLUC     | HDL      | -0.08       | (-0.12, -0.04) | 0.0003       | -0.09          | (-0.18, -0.01) | 542 | 0.0299        | -0.07          | (-0.12, -0.02) | 1678 | 0.0030        | 0.6723                     |
| GLUC     | MAP      | 0.08        | (0.04, 0.12) | 0.0002        | 0.11           | (0.02, 0.19) | 542 | 0.0113        | 0.07           | (0.02, 0.11)  | 1678 | 0.0058        | 0.3994                     |
| GLUC     | TG       | 0.08        | (0.04, 0.12) | 0.0001        | 0.12           | (0.04, 0.20) | 542 | 0.0046        | 0.06           | (0.01, 0.11)  | 1678 | 0.0126        | 0.2171                     |
| HDL      | PAI-1    | -0.05       | (-0.09, -0.01) | 0.0156       | -0.11          | (-0.20, -0.03) | 542 | 0.0085        | -0.03          | (-0.08, 0.01) | 1678 | 0.1626        | 0.1090                     |
| HDL      | MAP      | 0.12        | (0.08, 0.16) | <0.0001       | 0.14           | (0.05, 0.22) | 542 | 0.0014        | 0.12           | (0.07, 0.17)  | 1678 | <0.0001       | 0.7363                     |
| HDL      | TG       | -0.22       | (-0.26, -0.18) | <0.0001      | -0.26          | (-0.33, -0.18) | 542 | <0.0001       | -0.21          | (-0.25, -0.16) | 1678 | <0.0001       | 0.3053                     |
| MAP      | PAI-1    | 0.09        | (0.05, 0.13) | <0.0001       | 0.15           | (0.07, 0.23) | 542 | 0.0004        | 0.07           | (0.03, 0.12)  | 1678 | 0.0024        | 0.1068                     |
| MAP      | TG       | 0.08        | (0.04, 0.12) | <0.0001       | 0.13           | (0.04, 0.21) | 542 | 0.0034        | 0.06           | (0.02, 0.11)  | 1678 | 0.0094        | 0.2049                     |
| TG       | PAI-1    | 0.24        | (0.20, 0.28) | <0.0001       | 0.18           | (0.10, 0.26) | 542 | <0.0001       | 0.26           | (0.22, 0.31)  | 1678 | <0.0001       | 0.0810                     |

BMI indicates body mass index; GLUC, glucose; HDL, high-density lipoprotein cholesterol; MAP, mean arterial pressure; MetS, metabolic syndrome; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides. *Pearson correlation coefficient, calculated using residuals after adjustment for age, sex, and residence. †Pearson correlation coefficient, calculated for urban and rural participants separately, using residuals after adjustment for age and sex; CI=95% confidence interval (in parenthesis); \( P \) value=probability of \( r \) if true partial correlation is zero; Homogeneity of Correlation \( P \) value=probability of these data if true partial correlation is equal for urban and rural.
Because PAI-1 plays a direct biochemical role in thrombosis, each MetS factor’s strength of correlation with PAI-1 may be indicative of its relevance to MetS-related cardiac events. Partial correlations with PAI-1 may be particularly relevant, because independent associations are more likely to reflect direct biochemical and physiological connections. In this regard, the strongest partial correlation we observed, that between PAI-1 and BMI, is consistent with the known biological mechanism of PAI-1 release from adipocytes. Adipokines also amplify PAI-1 expression through inflammatory pathways, whereas PAI-1 itself may promote accumulation of visceral fat, perhaps by mediating insulin signaling. The second strongest partial correlation we observed was between PAI-1 and TG, likely influenced by the fact that the PAI-1 promoter is responsive to VLDL, which transports TG. A similar connection exists between PAI-1 and the renin-angiotensin system, involved in hypertension.

None of the partial correlations among the 5 MetS risk factors varied by sex or urban/rural environment when PAI-1 was excluded from analyses, despite differences in the underlying male/female and urban/rural risk factor distributions. This correlational homogeneity among conventional MetS criteria suggests that the relationships among risk factors are likely stable over a wide range of values and fairly insensitive to differences in physiological background, environment, and lifestyle. In contrast, the positive correlation of BMI, TG, and glucose with PAI-1 was markedly stronger in the urban population. To the extent that elevated PAI-1 increases the risk of thrombotic endpoints, then, it is possible that high BMI, TG, and glucose confer greater risk in urban than in rural environments. It is therefore likely that undefined aspects of the urban environment influence the nature of the relationships between adiposity, fasting glucose, TG, and PAI-1. In addition to obesity, factors such as stress and nutrient-poor diets have been shown to influence PAI-1 expression directly in animal models, making these possible candidates as effect modifiers.

**Figure 4.** PAI-1 quartiles as a function of standardized MetS risk factor values. A, Medians (solid) and first and third quartiles (dotted) of standardized ln-PAI-1 after all data were adjusted for age, sex, and residence; in (B), data were further adjusted for the other risk factors. Period for quartiles = 100. Data smoothed using cubic spline. BMI indicates body mass index; GLUC, glucose; HDL, high-density lipoprotein cholesterol; MAP, mean arterial pressure; MetS, metabolic syndrome; TRIG, triglycerides.
Our results show that important physiological connections can be underestimated by a single correlation coefficient. For example, the correlation between glucose and PAI-1 was likely the result of 2 different patterns of association, which shifted at higher glucose values. Importantly, when glucose was less than \( 2 \) SDs above the mean, its relationship with PAI-1 quartiles was comparable to the stronger BMI-PAI-1 and TG-PAI-1 relationships. Similar analyses of PAI-1 quartiles using the residuals of the partial correlations confirmed this. The strong, independent connection over most of the normal glucose range may, in part, reflect increasing insulin resistance, which amplifies PAI-1 expression by accelerating the release of free fatty acids.54

Although we could not find similar studies with which to compare our higher-order partial correlations directly, a recent meta-analysis of 85 000 people (of whom 7.8% were African American and the remainder European) reported pair-wise correlations between MetS risk factors adjusted for age and sex.55 Among all 15 pair-wise correlations we assessed, only BMI-GLUC and BMI-HDL here (adjusted for age, sex, and residence) fell outside of the 95% CIs reported by the meta-analysis. That study reported \( r=-0.33 \) for BMI-HDL and \( r=0.28 \) for BMI-GLUC, in contrast to our results of \( r=-0.15 \) and 0.15, respectively. With respect to HDL, this may be because many Ghanaians with normal BMI had low HDL. For example, 49% of participants with BMI below the obesity threshold had low HDL, and 25% of the participants with at least 1 risk factor had low HDL as the isolated condition. There may therefore be aspects of the Ghanaian environment, perhaps including diets, that contribute to low HDL in the absence of other risk factors. Speculation regarding the difference in the GLUC-PAI-1 correlation is more difficult, but we note that a previous study found a difference in the insulin-PAI-1 relationship between African and European women, which might provide some insight.56

MetS was significantly more prevalent in the urban population than the rural, and urban women were particularly at risk. Excess adiposity is generally considered the primary cause of MetS,57 and the urban women had, by far,
It is true that BMI serves as a somewhat crude variable for assessing causal connection between excess adiposity and cause cannot be inferred from correlation; it can be ruled out by the absence of correlation; therefore, the hypothesis of obesity is also associated with the distribution of adipose tissue, which varies among populations and lower-order partial correlations were further complicated by asymmetric power, owing to different numbers of adjust-ments. Additionally, though we performed these adjustments by sex and residence. Nonetheless, we identi-cated highly significant findings in many of these stratified analyses. Our direct comparisons of higher- and lower-order partial correlations were further complicated by asymmetric power, owing to different numbers of adjust-ments. Additionally, though we performed these adjustments by sex and residence.

The weak connection between obesity and MetS was particularly evident among rural males. Their age-standardized prevalence of MetS (7.8%) was unexpectedly high, despite no rural male participant’s BMI being above the obesity threshold. Whereas “metabolically obese” individuals of normal weight are not uncommon in some populations (eg, South Asians), often MetS without obesity reflects insulin resistance caused by factors other than excess adiposity. However, 40% of the rural men who met the diagnostic criteria of MetS in our study did not have hyperglycemia in addition to hypertension and/or dyslipidemia (low HDL or high TG), making it unlikely that they were insulin resistant. MetS in the absence of obesity is also associated with the distribution of adipose tissue, which varies among populations and may affect PAI-1 expression. Thus, how comparable our findings in many African populations, and that, even when measured accurately, abdominal fat may have a weaker relationship with plasma PAI-1 in Africans than in European-descent populations.

The weak connection between obesity and MetS was particularly evident among rural males. Their age-standardized prevalence of MetS (7.8%) was unexpectedly high, despite no rural male participant’s BMI being above the obesity threshold. Whereas “metabolically obese” individuals of normal weight are not uncommon in some populations (eg, South Asians), often MetS without obesity reflects insulin resistance caused by factors other than excess adiposity. However, 40% of the rural men who met the diagnostic criteria of MetS in our study did not have hyperglycemia in addition to hypertension and/or dyslipidemia (low HDL or high TG), making it unlikely that they were insulin resistant. MetS in the absence of obesity is also associated with the distribution of adipose tissue, which varies among populations and may affect PAI-1 expression. Thus, how comparable our rural participants are to others diagnosed with MetS is unclear, either from the standpoint of pathophysiology or clinical prognosis.

Some limitations of our study need to be acknowledged. The cross-sectional design of our study reduced our ability to elucidate causal relationships. Also, though our total sample size was relatively large, power was somewhat diminished after participants were stratified by sex and residence. Nonetheless, we identified highly significant findings in many of these stratified analyses. Our direct comparisons of higher- and lower-order partial correlations were further complicated by asymmetric power, owing to different numbers of adjustments. Additionally, though we performed these adjustments by sex and residence.

Table 5. Pearson Partial Correlation Coefficients Between Cardiovascular Risk Factors Associated With MetS, Including PAI-1, by Sex

| Trait 1 | Trait 2 | Females | Males | Homogeneity of Correlation P Value |
|---------|---------|---------|-------|-----------------------------------|
|         |         | r       | CI    | N       | P Value | r       | CI    | N       | p Value |
| BMI     | PAI-1   | 0.35    | (0.30, 0.40) | 1274   | <0.0001 | 0.29    | (0.23, 0.34) | 946   | <0.0001 | 0.0814 |
| BMI     | GLUC    | 0.02    | (−0.03, 0.08) | 1274   | 0.4626  | 0.07    | (0.00, 0.13) | 946   | 0.0430  | 0.2920 |
| BMI     | HDL     | −0.08   | (−0.13, −0.02) | 1274   | 0.0052  | −0.11   | (−0.17, −0.05) | 946   | 0.0008  | 0.4682 |
| BMI     | MAP     | 0.21    | (0.16, 0.26) | 1274   | <0.0001 | 0.26    | (0.20, 0.32) | 946   | <0.0001 | 0.2487 |
| BMI     | TG      | 0.07    | (0.01, 0.12) | 1274   | 0.0142  | 0.09    | (0.02, 0.15) | 946   | 0.0067  | 0.6497 |
| GLUC    | PAI-1   | 0.14    | (0.09, 0.20) | 1274   | <0.0001 | 0.05    | (−0.02, 0.11) | 946   | 0.1410  | 0.0233 |
| GLUC    | HDL     | −0.07   | (−0.12, −0.01) | 1274   | 0.0128  | −0.08   | (−0.14, −0.01) | 946   | 0.0202  | 0.8921 |
| GLUC    | MAP     | 0.06    | (0.01, 0.12) | 1274   | 0.0241  | 0.10    | (0.04, 0.17) | 946   | 0.0014  | 0.3414 |
| GLUC    | TG      | 0.10    | (0.04, 0.15) | 1274   | 0.0006  | 0.07    | (0.00, 0.13) | 946   | 0.0447  | 0.4765 |
| HDL     | PAI-1   | −0.09   | (−0.14, −0.03) | 1274   | 0.0020  | −0.01   | (−0.08, 0.05) | 946   | 0.6987  | 0.0842 |
| HDL     | MAP     | 0.13    | (0.07, 0.18) | 1274   | <0.0001 | 0.12    | (0.05, 0.18) | 946   | 0.0004  | 0.7427 |
| HDL     | TG      | −0.20   | (−0.25, −0.14) | 1274   | <0.0001 | −0.25   | (−0.31, −0.19) | 946   | <0.0001 | 0.2210 |
| MAP     | PAI-1   | 0.07    | (0.02, 0.13) | 1274   | 0.0094  | 0.12    | (0.06, 0.19) | 946   | 0.0001  | 0.2363 |
| MAP     | TG      | 0.07    | (0.01, 0.12) | 1274   | 0.0134  | 0.09    | (0.02, 0.15) | 946   | 0.0078  | 0.6872 |
| TG      | PAI-1   | 0.22    | (0.17, 0.27) | 1274   | <0.0001 | 0.25    | (0.19, 0.31) | 946   | <0.0001 | 0.4270 |

r = Pearson partial correlation coefficient, calculated using residuals after adjustment for age and residence, by sex; CI = 95% confidence interval; P value = probability of r if true partial correlation is zero; Homogeneity of Correlation P value = probability of these data if true partial correlation is equal for men and women. BMI indicates body mass index; GLUC, glucose; HDL, high-density lipoprotein cholesterol; MAP, mean arterial pressure; MetS, metabolic syndrome; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides.
to distinguish direct interactions among risk factors from merely incidental associations, we could only control for conventional risk factors, and, moreover, these risk factors have generally been defined on the bases of European studies.69,70

Our study explored the role of PAI-1 in MetS from multiple perspectives in an understudied population. Although urban residence and sex had dramatic effects on the mean values of cardiovascular risk factors, our partial correlational analyses revealed that the relationships among the factors used to diagnose MetS are remarkably stable. In contrast, the relationships between these factors and PAI-1 were more sensitive to such differences. Thus, urban-rural differences impacted not only MetS prevalence, but also patterns of clustering and association with PAI-1. Identifying the specific factors responsible for these phenomena should provide unique insight into MetS etiology and, where modifiable, could inform public health measures. The patterns we have identified, such as the exponential relationship between mean PAI-1 and MetS diagnostic conditions, and the nonlinear relationships between PAI-1 and some of the MetS risk factors, improve our understanding of how MetS may mediate cardiovascular disease risk, although generalizability to other populations will require further study. In summation, we provide evidence that the prothrombotic state may be more than a mere epiphemomenon of MetS, possibly playing a major role in its etiology and its clinical sequelae.

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Disclosures

None.

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Supplemental Material
Table S1. Comparison of risk factor distributions between participants with missing HDL measurements (N=1111) and those with full data (N=2220), by sex and residence.

| Group          | N, complete/missing | Trait | standardized mean difference | 95% CIL     | 95% CIU     | p-value (t-test) | p-value (Levene's test) |
|----------------|---------------------|-------|------------------------------|-------------|-------------|------------------|------------------------|
| URBAN MALES    | 721/257             | PAI-1 | -0.026                       | -0.169      | 0.117       | 0.721            | 0.132                  |
|                |                     | BMI   | 0.064                        | -0.079      | 0.206       | 0.381            | 0.956                  |
|                |                     | MAP   | 0.092                        | -0.031      | 0.216       | 0.143            | 0.299                  |
|                |                     | TRIG  | -0.106                       | -0.230      | 0.018       | 0.094            | 0.307                  |
|                |                     | GLUC  | -0.047                       | -0.170      | 0.077       | 0.461            | 0.76                   |
| RURAL MALES    | 225/247             | PAI-1 | 0.029                        | -0.153      | 0.210       | 0.756            | 0.725                  |
|                |                     | BMI   | -0.124                       | -0.305      | 0.057       | 0.178            | 0.216                  |
|                |                     | MAP   | 0.143                        | -0.038      | 0.324       | 0.122            | 0.677                  |
|                |                     | TRIG  | 0.083                        | -0.098      | 0.265       | 0.368            | 0.204                  |
|                |                     | GLUC  | 0.031                        | -0.150      | 0.213       | 0.734            | 0.428                  |
| URBAN FEMALES  | 957/341             | PAI-1 | -0.134                       | -0.258      | -0.011      | 0.033            | 0.255                  |
|                |                     | BMI   | -0.026                       | -0.150      | 0.098       | 0.68             | 0.186                  |
|                |                     | MAP   | 0.040                        | -0.103      | 0.182       | 0.586            | 0.011                  |
|                |                     | TRIG  | -0.129                       | -0.273      | 0.014       | 0.077            | 0.906                  |
|                |                     | GLUC  | -0.126                       | -0.268      | 0.017       | 0.084            | 0.485                  |
| RURAL FEMALES  | 317/266             | PAI-1 | 0.017                        | -0.147      | 0.180       | 0.841            | 0.867                  |
|                |                     | BMI   | 0.084                        | -0.079      | 0.248       | 0.311            | 0.057                  |
|                |                     | MAP   | 0.006                        | -0.157      | 0.170       | 0.938            | 0.242                  |
|                |                     | TRIG  | 0.182                        | 0.019       | 0.346       | 0.029            | 0.853                  |
|                |                     | GLUC  | 0.116                        | -0.047      | 0.279       | 0.164            | 0.916                  |
Table S2. Pearson partial correlation coefficients between the five components of the metabolic syndrome. (PAI-1 excluded from analysis.)

| Trait | Trait | r     | CI            | N   | p-value |
|-------|-------|-------|---------------|-----|---------|
| MAP   | BMI   | 0.27  | (0.23, 0.31)  | 2220| <.0001  |
| HDL   | BMI   | -0.11 | (-0.15, -0.07)| 2220| <.0001  |
| HDL   | MAP   | 0.12  | (0.07, 0.16)  | 2220| <.0001  |
| TG    | BMI   | 0.16  | (0.12, 0.20)  | 2220| <.0001  |
| TG    | MAP   | 0.11  | (0.07, 0.15)  | 2220| <.0001  |
| TG    | HDL   | -0.24 | (-0.28, -0.20)| 2220| <.0001  |
| GLUC  | BMI   | 0.08  | (0.04, 0.12)  | 2220| 0.0002  |
| GLUC  | MAP   | 0.09  | (0.05, 0.13)  | 2220| <.0001  |
| GLUC  | HDL   | -0.08 | (-0.12, -0.04)| 2220| <.0001  |
| GLUC  | TRIG  | 0.11  | (0.07, 0.15)  | 2220| <.0001  |

\( r \) = Pearson partial correlation coefficient, calculated using residuals after adjustment for age, sex, and residence;

\( CI \) = 95% confidence interval;

\( p\text{-value} \) = probability of \( r \) if true partial correlation is zero.
Table S3. Pearson partial correlation coefficients between the five components of the metabolic syndrome, by urban or rural residence. (PAI-1 excluded from analysis.)

| Trait 1 | Trait 2 | Rural r | CI       | N     | p-value | Urban r | CI       | N     | p-value | Homogeneity of Correlation p-value |
|---------|---------|---------|----------|-------|---------|---------|----------|-------|---------|----------------------------------|
| MAP     | BMI     | 0.24    | (0.16, 0.32) | 542   | <.0001  | 0.28    | (0.24, 0.33) | 1678  | <.0001  | 0.3335                           |
| HDL     | BMI     | -0.06   | (-0.14, 0.02) | 542   | 0.1631  | -0.14   | (-0.19, -0.09) | 1678  | <.0001  | 0.1083                           |
| HDL     | MAP     | 0.12    | (0.04, 0.20) | 542   | 0.0042  | 0.12    | (0.07, 0.17)  | 1678  | <.0001  | 0.9314                           |
| TG      | BMI     | 0.09    | (0.01, 0.18) | 542   | 0.0297  | 0.19    | (0.14, 0.24)  | 1678  | <.0001  | 0.0430                           |
| TG      | MAP     | 0.16    | (0.07, 0.24) | 542   | 0.0002  | 0.09    | (0.04, 0.13)  | 1678  | 0.0004  | 0.1449                           |
| TG      | HDL     | -0.28   | (-0.36, -0.20) | 542   | <.0001  | -0.23   | (-0.27, -0.18) | 1678  | <.0001  | 0.2250                           |
| GLUC    | BMI     | 0.13    | (0.05, 0.21) | 542   | 0.0021  | 0.05    | (0.01, 0.10)  | 1678  | 0.0245  | 0.1180                           |
| GLUC    | MAP     | 0.11    | (0.02, 0.19) | 542   | 0.0116  | 0.08    | (0.03, 0.13)  | 1678  | 0.0011  | 0.5601                           |
| GLUC    | HDL     | -0.09   | (-0.17, -0.01) | 542   | 0.0356  | -0.08   | (-0.13, -0.03) | 1678  | 0.0011  | 0.8230                           |
| GLUC    | TRIG    | 0.12    | (0.04, 0.20) | 542   | 0.0044  | 0.11    | (0.06, 0.15)  | 1678  | <.0001  | 0.7341                           |

\( r \) = Pearson partial correlation coefficient, calculated using residuals after adjustment for age and sex, by residence;
CI = 95% confidence interval;

p-value = probability that the true partial correlation is zero;

Homogeneity of Correlation p-value = probability of these data if true partial correlation is equal for urban & rural.
Table S4. Pearson partial correlation coefficients between the five components of the metabolic syndrome, by sex. (PAI-1 excluded from analysis.)

| Trait 1 | Trait 2 | Females | | Males | | Homogeneity of Correlation p-value |
|---------|---------|---------|---------|---------|---------|----------------|
|         |         | r       | CI      | N       | p-value | r       | CI      | N       | p-value |           |
| MAP     | BMI     | 0.26    | (0.20, 0.31) | 1274 | <.0001 | 0.31    | (0.25, 0.37) | 946 | <.0001 | 0.1710 |
| HDL     | BMI     | -0.12   | (-0.17, -0.07) | 1274 | <.0001 | -0.12   | (-0.18, -0.05) | 946 | 0.0003 | 0.9642 |
| HDL     | MAP     | 0.13    | (0.07, 0.18)  | 1274 | <.0001 | 0.11    | (0.05, 0.18)  | 946 | 0.0004 | 0.7842 |
| TG      | BMI     | 0.16    | (0.11, 0.21)  | 1274 | <.0001 | 0.17    | (0.11, 0.23)  | 946 | <.0001 | 0.7575 |
| TG      | MAP     | 0.09    | (0.03, 0.14)  | 1274 | 0.0016 | 0.12    | (0.06, 0.18)  | 946 | 0.0002 | 0.4210 |
| TG      | HDL     | -0.22   | (-0.27, -0.17) | 1274 | <.0001 | -0.26   | (-0.32, -0.20) | 946 | <.0001 | 0.3481 |
| GLUC    | BMI     | 0.08    | (0.02, 0.13)  | 1274 | 0.0060 | 0.08    | (0.02, 0.15)  | 946 | 0.0106 | 0.8846 |
| GLUC    | MAP     | 0.08    | (0.02, 0.13)  | 1274 | 0.0074 | 0.11    | (0.05, 0.17)  | 946 | 0.0006 | 0.4021 |
| GLUC    | HDL     | -0.09   | (-0.14, -0.03) | 1274 | 0.0023 | -0.08   | (-0.14, -0.01) | 946 | 0.0189 | 0.8331 |
| GLUC    | TRIG    | 0.13    | (0.08, 0.19)  | 1274 | <.0001 | 0.08    | (0.02, 0.14)  | 946 | 0.0141 | 0.2184 |

\[ r = \text{Pearson partial correlation coefficient, calculated using residuals after adjustment for age and residence, by sex;} \]
$CI = 95\%$ confidence interval;

$p$-value = probability of $r$ if true partial correlation is zero;

Homogeneity of Correlation $p$-value = probability of these data if true partial correlation is equal for men & women.
Figure S1. Proportions of participants with \( N \in [0,5] \) component risk factors of the metabolic syndrome, by sex and environment. Lengths of rectangles represent the percentage of participants with \( N \) risk factors within each labeled group: Total= all 2220 participants for whom no data were missing; UM = urban males; UF= urban females; RM= rural males; RF= rural females. Areas of rectangles for UM, UF, RM, RF represent proportions with respect to all 2220 participants.
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