

WEB MATERIAL.

erythritol		
covariate	β (standard error)	p value
age	1.29(0.12)	<0.001
gender	0.13(0.04)	0.005
CHD	0.38(0.13)	0.003
smoking	0.02(0.05)	0.635
physical activity	-0.13(0.03)	<0.001
education	-0.11(0.04)	0.004
BMI	0.44(0.13)	0.001
SBP	1.95(0.45)	<0.001
BP med	0.32(0.05)	<0.001
glucose	0.47(0.05)	<0.001
diabetes	0.44(0.06)	<0.001
TC : HDL ratio	0.28(0.03)	<0.001
lipid med	0.02(0.22)	0.913
LVH	0.41(0.11)	<0.001
eGFR	-6.28(0.36)	<0.001

pyroglutamine*		
covariate	β (standard error)	p value
age	0.62(0.12)	<0.001
gender	1.36(0.07)	<0.001
CHD	0.40(0.13)	0.002
smoking	0.34(0.05)	<0.001
physical activity	-0.01(0.03)	0.782
education	0.00(0.04)	0.965
BMI	-1.09(0.12)	<0.001
SBP	1.57(0.46)	0.001
BP med	-0.04(0.04)	0.420
glucose	-0.32(0.05)	<0.001
diabetes	-0.33(0.06)	<0.001
TC : HDL ratio	0.17(0.03)	<0.001
lipid med	-0.17(0.22)	0.447
LVH	0.16(0.10)	0.120
eGFR	-5.03(0.37)	<0.001

N-acetylalanine		
covariate	β (standard error)	p value
age	0.93(0.12)	<0.001
gender	0.10(0.04)	0.020
CHD	0.21(0.12)	0.083
smoking	0.02(0.05)	0.714
physical activity	-0.10(0.03)	0.001
education	-0.13(0.04)	<0.001
BMI	0.53(0.13)	<0.001
SBP	2.13(0.45)	<0.001
BP med	0.32(0.05)	<0.001
glucose	-0.22(0.05)	<0.001
diabetes	-0.18(0.06)	0.002
TC : HDL ratio	0.13(0.03)	<0.001
lipid med	-0.02(0.22)	0.911
LVH	0.35(0.11)	0.001
eGFR	-6.83(0.35)	<0.001

phenylacetylglutamine		
covariate	β (standard error)	p value
age	0.96(0.12)	<0.001
gender	-0.03(0.04)	0.567
CHD	0.40(0.13)	0.002
smoking	-0.17(0.05)	<0.001
physical activity	-0.13(0.03)	<0.001
education	-0.16(0.04)	<0.001
BMI	-0.06(0.13)	0.625
SBP	0.74(0.46)	0.104
BP med	0.18(0.05)	<0.001
glucose	0.17(0.05)	0.001
diabetes	0.14(0.06)	0.019
TC : HDL ratio	0.01(0.03)	0.698
lipid med	0.22(0.22)	0.331
LVH	0.26(0.10)	0.011
eGFR	-4.05(0.37)	<0.001

Metabolite values are in the form of quartile ordinal scores; continuous variables used liner model (e.g. age= intercept+ β *quartile scores); categorical variables used logistic model (e.g. logit(CHD)= quartile scores).

Abbreviations: CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; BP med, anti-hypertensive medication use; TC : HDL ratio, serum total cholesterol to high-density-cholesterol lipoprotein ratio; lipid med, lipid-lowering medication use; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate.

Regression Coefficients with Established Risk Factors for Quartile-score of Sixteen HF Related Metabolites in Model 3

p-cresol sulfate		
covariate	β (standard error)	p value
age	0.59(0.12)	<0.001
gender	-0.01(0.04)	0.841
CHD	0.14(0.12)	0.254
smoking	-0.16(0.05)	0.001
physical activity	-0.11(0.03)	0.001
education	-0.07(0.04)	0.044
BMI	-0.56(0.13)	<0.001
SBP	-0.01(0.46)	0.989
BP med	0.11(0.04)	0.018
glucose	0.03(0.05)	0.623
diabetes	-0.02(0.06)	0.679
TC : HDL ratio	0.02(0.03)	0.508
lipid med	-0.17(0.22)	0.447
LVH	0.17(0.10)	0.098
eGFR	-3.40(0.38)	<0.001

X - 11429		
covariate	β (standard error)	p value
age	1.00(0.12)	<0.001
gender	0.02(0.04)	0.672
CHD	0.12(0.12)	0.307
smoking	0.20(0.05)	<0.001
physical activity	-0.16(0.03)	<0.001
education	-0.12(0.04)	0.001
BMI	0.28(0.13)	0.026
SBP	1.54(0.46)	0.001
BP med	0.23(0.05)	<0.001
glucose	-0.36(0.05)	<0.001
diabetes	-0.34(0.06)	<0.001
TC : HDL ratio	0.02(0.03)	0.448
lipid med	-0.54(0.24)	0.028
LVH	0.30(0.10)	0.005
eGFE	-5.56(0.36)	<0.001

pro-hydroxy-pro		
covariate	β (standard error)	p value
age	0.69(0.12)	<0.001
gender	0.04(0.04)	0.370
CHD	0.15(0.12)	0.209
smoking	0.20(0.05)	<0.001
physical activity	-0.05(0.03)	0.131
education	-0.17(0.04)	<0.001
BMI	-0.64(0.13)	<0.001
SBP	1.44(0.46)	0.002
BP med	-0.10(0.04)	0.031
glucose	-0.13(0.05)	0.020
diabetes	-0.08(0.06)	0.190
TC : HDL ratio	-0.06(0.03)	0.064
lipid med	-0.02(0.22)	0.912
LVH	0.14(0.10)	0.177
eGFR	-3.20(0.38)	<0.001

X - 11687_200		
covariate	β (standard error)	p value
age	0.61(0.11)	<0.001
gender	0.06(0.04)	0.144
CHD	0.03(0.11)	0.810
smoking	0.19(0.04)	<0.001
physical activity	-0.11(0.03)	<0.001
education	-0.06(0.03)	0.098
BMI	0.00(0.12)	0.993
SBP	1.67(0.42)	<0.001
BP med	0.27(0.04)	<0.001
glucose	0.07(0.05)	0.132
diabetes	0.08(0.05)	0.132
TC : HDL ratio	0.12(0.03)	<0.001
lipid med	-0.19(0.21)	0.368
LVH	0.18(0.09)	0.050
eGFE	-3.64(0.35)	<0.001

Metabolite values are in the form of quartile ordinal scores; continuous variables used liner model (e.g. age= intercept+ β *quartile scores); categorical variables used logistic model (e.g. logit(CHD)= quartile scores).

Abbreviations: CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; BP med, anti-hypertensive medication use; TC : HDL ratio, serum total cholesterol to high-density-cholesterol lipoprotein ratio; lipid med, lipid-lowering medication use; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate.

Regression Coefficients with Established Risk Factors for Quartile-score of Sixteen HF Related Metabolites in Model 3

X – 12096		
covariate	β (standard error)	p value
age	0.92(0.12)	<0.001
gender	-0.06(0.04)	0.161
CHD	0.20(0.12)	0.106
smoking	0.02(0.05)	0.635
physical activity	-0.10(0.03)	0.001
education	-0.15(0.04)	<0.001
BMI	1.57(0.12)	<0.001
SBP	1.05(0.46)	0.021
BP med	0.35(0.05)	<0.001
glucose	0.22(0.05)	<0.001
diabetes	0.28(0.06)	<0.001
TC : HDL ratio	0.33(0.03)	<0.001
lipid med	-0.22(0.22)	0.330
LVH	0.37(0.11)	<0.001
eGFR	-4.51(0.37)	<0.001

X – 11334		
covariate	β (standard error)	p value
age	0.95(0.12)	<0.001
gender	0.31(0.05)	<0.001
CHD	0.23(0.12)	0.064
smoking	-0.13(0.05)	0.006
physical activity	-0.04(0.03)	0.156
education	-0.08(0.04)	0.041
BMI	0.05(0.13)	0.701
SBP	0.96(0.46)	0.036
BP med	0.17(0.05)	<0.001
glucose	-0.04(0.05)	0.406
diabetes	-0.02(0.06)	0.767
TC : HDL ratio	0.11(0.03)	<0.001
lipid med	0.02(0.22)	0.913
LVH	0.18(0.10)	0.080
eGFR	-5.87(0.36)	<0.001

X - 11787		
covariate	β (standard error)	p value
age	1.07(0.12)	<0.001
gender	0.24(0.05)	<0.001
CHD	0.49(0.13)	<0.001
smoking	0.05(0.05)	0.255
physical activity	-0.02(0.03)	0.412
education	-0.15(0.04)	<0.001
BMI	0.30(0.13)	0.019
SBP	0.91(0.46)	0.047
BP med	0.13(0.05)	0.003
glucose	0.29(0.05)	<0.001
diabetes	0.29(0.06)	<0.001
TC : HDL ratio	0.15(0.03)	<0.001
lipid med	0.60(0.25)	0.017
LVH	0.35(0.11)	0.001
eGFR	-3.76(0.38)	<0.001

X - 11423		
covariate	β (standard error)	p value
age	0.78(0.12)	<0.001
gender	0.23(0.05)	<0.001
CHD	0.24(0.12)	0.050
smoking	0.09(0.05)	0.053
physical activity	-0.09(0.03)	0.002
education	0.04(0.04)	0.312
BMI	-0.14(0.13)	0.283
SBP	1.74(0.45)	<0.001
BP med	0.20(0.05)	<0.001
glucose	-0.18(0.05)	0.001
diabetes	-0.19(0.06)	0.002
TC : HDL ratio	0.16(0.03)	<0.001
lipid med	-0.07(0.22)	0.737
LVH	0.25(0.10)	0.015
eGFR	-6.20(0.36)	<0.001

Metabolite values are in the form of quartile ordinal scores; continuous variables used liner model (e.g. age= intercept+ β *quartile scores); categorical variables used logistic model (e.g. logit(CHD)= quartile scores).

Abbreviations: CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; BP med, anti-hypertensive medication use; TC : HDL ratio, serum total cholesterol to high-density-cholesterol lipoprotein ratio; lipid med, lipid-lowering medication use; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate.

Regression Coefficients with Established Risk Factors for Quartile-score of Sixteen HF Related Metabolites in Model 3

X – 04499		
covariate	β (standard error)	p value
age	0.39(0.12)	0.001
gender	0.12(0.04)	0.004
CHD	0.07(0.12)	0.531
smoking	0.21(0.05)	<0.001
physical activity	-0.05(0.03)	0.078
education	-0.07(0.04)	0.065
BMI	-0.16(0.12)	0.197
SBP	1.04(0.44)	0.018
BP med	0.16(0.04)	<0.001
glucose	0.12(0.05)	0.020
diabetes	0.06(0.06)	0.285
TC : HDL ratio	0.00(0.03)	0.936
lipid med	-0.03(0.21)	0.894
LVH	0.21(0.10)	0.037
eGFR	-2.82(0.37)	<0.001

X - 11333		
covariate	β (standard error)	p value
age	0.63(0.12)	<0.001
gender	0.32(0.05)	<0.001
CHD	0.27(0.12)	0.027
smoking	0.22(0.05)	<0.001
physical activity	-0.04(0.03)	0.223
education	-0.10(0.04)	0.007
BMI	-0.02(0.13)	0.861
SBP	1.39(0.46)	0.002
BP med	0.23(0.05)	<0.001
glucose	-0.02(0.05)	0.748
diabetes	0.00(0.06)	0.953
TC : HDL ratio	0.16(0.03)	<0.001
lipid med	-0.07(0.22)	0.744
LVH	0.20(0.10)	0.051
eGFR	-4.76(0.37)	<0.001

X - 11308		
covariate	β (standard error)	p value
age	-0.29(0.12)	0.020
gender	0.17(0.04)	<0.001
CHD	-0.09(0.12)	0.434
smoking	-0.13(0.05)	0.007
physical activity	0.18(0.03)	<0.001
education	0.21(0.04)	<0.001
BMI	-0.71(0.13)	<0.001
SBP	-2.02(0.45)	<0.001
BP med	-0.13(0.05)	0.003
glucose	-0.11(0.05)	0.049
diabetes	-0.07(0.06)	0.237
TC : HDL ratio	-0.02(0.03)	0.450
lipid med	-0.02(0.22)	0.913
LVH	-0.01(0.10)	0.960
eGFR	-0.07(0.39)	0.866

X - 11564		
covariate	β (standard error)	p value
age	0.94(0.12)	<0.001
gender	0.37(0.05)	<0.001
CHD	0.42(0.13)	0.001
smoking	0.18(0.05)	<0.001
physical activity	-0.15(0.03)	<0.001
education	-0.09(0.04)	0.017
BMI	0.15(0.13)	0.234
SBP	2.36(0.45)	<0.001
BP med	0.26(0.05)	<0.001
glucose	-0.03(0.05)	0.599
diabetes	0.02(0.06)	0.722
TC : HDL ratio	0.09(0.03)	0.006
lipid med	-0.22(0.22)	0.330
LVH	0.27(0.10)	0.008
eGFR	-5.10(0.37)	<0.001

Metabolite values are in the form of quartile ordinal scores; continuous variables used liner model (e.g. age= intercept+ β *quartile scores); categorical variables used logistic model (e.g. logit(CHD)= quartile scores).

Abbreviations: CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; BP med, anti-hypertensive medication use; TC : HDL ratio, serum total cholesterol to high-density-cholesterol lipoprotein ratio; lipid med, lipid-lowering medication use; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate.

The β regression coefficient (standard error as well as the p value testing the association of the ordinal quartile score of each of the 16 metabolites identified in Model 3 and the covariates adjusted in Model 4 are presented in the above tables. Consistently, most of the metabolites were significantly related to eGFR (except for X- 11308), while few of them were related to lipid-lowering medication use (except for X-11787 and X-11429). Their associations with the other established risk factors (covariates) vary among different metabolites.

Figure S1. Cumulative Hazards Curves of Incident Hospitalized Heart Failure across Quartiles of the Three Candidate Metabolites Identified in Model 4 among 1,744 African Americans in Jackson, MS field center of the Atherosclerosis Risk in Communities Study over the Period from 1987 to 2008.

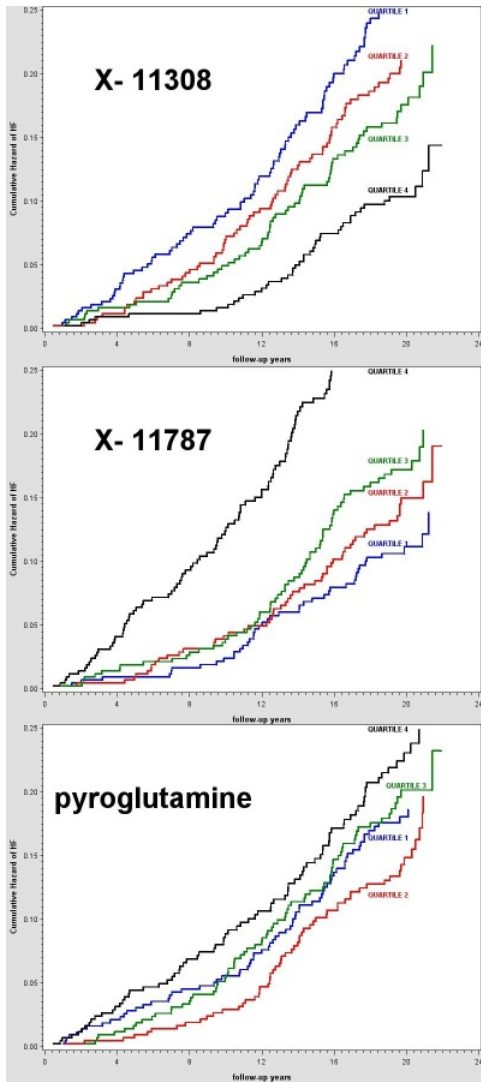


Figure S2. Heat map of Metabolite-Metabolite Correlations among All 187 Metabolites (Treated as Continuous Variables, Figure A) and among the 16 Metabolites Significant in Model 3 (Figure B) collected at 1986-1987 among 1,744 African Americans in Jackson, MS field center of the Atherosclerosis Risk in Communities Study. Metabolites were grouped by pathway and the three metabolites identified in Model 4 are labeled on the diagonal axis in Figure

A.

