

# **SUPPLEMENTAL MATERIAL**

**Table S1. Cluster analysis of phenotypes associated with metabolite profiles.**

	Phenotype Cluster*			
	A	B	C	D
	Healthy	Ketone Bodies	Inflammatory	Metabolic Syndrome
<b>Num. of Obs.</b>	<b>N=359</b>	<b>N=65</b>	<b>N=287</b>	<b>N=250</b>
<b>Ketone Bodies</b>	-0.3 (0.4)	2.5 (1.3)	-0.1 (0.5)	-0.3 (0.4)
<b>Pyruvate</b>	-0.1 (0.8)	-0.7 (0.7)	-0.1 (0.9)	0.5 (1.1)
<b>Citrate</b>	-0.2 (0.9)	1.0 (1.0)	0.2 (0.9)	-0.3 (1.0)
<b>HDL</b>	0.7 (0.9)	0.4 (1.0)	-0.3 (0.6)	-0.7 (0.6)
<b>VLDL</b>	-0.6 (0.4)	-0.6 (0.7)	0.0 (0.6)	1.0 (1.0)
<b>LDL</b>	-0.3 (0.8)	-0.3 (0.9)	0.6 (1.0)	-0.1 (0.9)
<b>VLDL Size</b>	0.1 (1.1)	0.2 (1.3)	-0.4 (0.6)	0.2 (0.7)
<b>HDL Size</b>	0.7 (0.7)	0.6 (0.9)	-0.2 (0.6)	-1.0 (0.5)
<b>LDL Size</b>	0.7 (0.5)	0.4 (0.7)	-0.0 (0.7)	-1.2 (0.7)
<b>Triglyceride</b>	-0.5 (0.4)	-0.5 (0.7)	-0.0 (0.5)	0.9 (1.0)
<b>Cholesterol</b>	-0.1 (0.9)	-0.3 (0.9)	0.5 (1.0)	-0.1 (1.0)
<b>Basal Insulin</b>	-0.2 (0.5)	0.4 (2.9)	-0.0 (0.5)	0.2 (1.4)
<b>GlycA</b>	-0.5 (0.7)	-0.2 (0.9)	0.5 (0.9)	-0.0 (0.9)
<b>Glucose</b>	-0.3 (0.5)	0.2 (1.5)	-0.0 (0.7)	0.2 (1.1)
<b>BMI</b>	-0.4 (0.9)	-0.4 (0.8)	0.3 (1.0)	0.3 (0.9)
<b>eGFR</b>	0.4 (0.9)	-0.3 (0.9)	-0.3 (0.9)	-0.1 (0.9)
<b>BNP</b>	-0.1 (0.7)	0.4 (1.2)	-0.0 (0.7)	-0.2 (0.5)
<b>CRP</b>	-0.3 (0.3)	0.0 (1.1)	0.0 (0.7)	-0.2 (0.4)
<b>IL-6</b>	-0.4 (0.7)	0.7 (3.0)	0.3 (1.1)	-0.1 (0.6)
<b>Fibrinogen</b>	-0.5 (0.7)	0.0 (0.9)	0.4 (0.9)	-0.4 (0.8)

Data are presented as Z-score, calculated by the difference between mean divided by the standard deviation (SD). VLDL indicates very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide; CRP, C-reactive protein; IL-6, interleukin 6; GlycA, glycoprotein acetylation; BMI, body mass index; and eGFR, estimated glomerular filtration rate.

\*Four clusters (A-D) were categorized using K-means clustering analysis including very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL) particle concentrations, sizes, levels of triglyceride, total cholesterol, glucose, basal insulin, B-type natriuretic peptide (BNP), C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, glycoprotein acetylation (GlycA), as well as body mass index (BMI) and estimated glomerular filtration rate (eGFR). Data are presented as mean Z-score (SD) of each cluster.

**Table S2. Multivariate Cox Models for Overall Mortality in 20 years for ketone constituents.**

	<b>Model 1*</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 2†</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 3‡</b> <b>HR (95% CI)</b>	<b>P</b>
<b>Log (3-hydroxybutyrate)</b>	1.2 (1.1 – 1.3)	<0.001	1.2 (1.1 – 1.3)	<0.001	1.2 (1.1 – 1.3)	<0.001
<b>Log (Acetoacetate)</b>	1.1 (1.0 – 1.2)	0.006	1.2 (1.1 – 1.3)	0.004	1.1 (1.0 – 1.2)	0.03
<b>Log (Acetone)</b>	1.1 (1.0 – 1.2)	0.04	1.1 (1.0 – 1.2)	0.1	1.1 (1.0 – 1.2)	0.3

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity and clinic site.

† Model 2 is adjusted age, sex, clinic site, ethnicity, education level, kcals physical activity per week, body mass index, body mass index<sup>2</sup>, smoking status, and alcoholic drinks per week, fasting > 8 hours.

‡ Model 3 is adjusted for covariates in Model 2 and for diagnosis of hypertension, cholesterol, triglycerides, diagnosis of diabetes, estimated glomerular filtration rate, hypertension medication use, lipid-lowering medication use, and estrogen use.

**Table S3. Multivariate Cox Models for Overall Mortality in 20 years by Metabolic Phenotype Clusters.**

	<b>Model 1*</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 2†</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 3‡</b> <b>HR (95% CI)</b>	<b>P</b>
<b>Healthy</b>	Ref		Ref		Ref	
<b>High Ketone Bodies</b>	1.9 (1.3 – 2.9)	0.002	1.8 (1.1 – 2.8)	0.01	2.0 (1.3 – 3.1)	0.003
<b>Chronic Inflammation</b>	1.1 (0.8 – 1.4)	0.3	1.0 (0.8 – 1.3)	0.3	1.0 (0.8 – 1.3)	0.9
<b>Metabolic Syndrome</b>	0.9 (0.7 – 1.2)	0.4	0.8 (0.6 – 1.1)	0.07	0.9 (0.6 – 1.2)	0.3

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity, and clinic site.

† Model 2 is adjusted for covariates in Model 1 and for education level, kcals physical activity per week, smoking status, alcoholic drinks per week, and fasting > 8 hours.

‡ Model 3 is adjusted for covariates in Model 2 and dietary components: linoleic acid, oleic acid, saturated fat, carbohydrates, and protein.

**Table S4. Multivariate Cox Model for Overall Mortality in 20 Years with Logarithmic Transformed Metabolites and Metabolite Quintiles.**

		<b>HR (95% CI)*</b>	<b>p</b>
<b>Ketone bodies</b>	<b>Log (Ketone Bodies)</b>	1.2 (1.1 – 1.3)	0.002
	<b>Quintiles: Q1</b>	Ref	
	<b>Q2</b>	1.1 (0.8 – 1.5)	0.3
	<b>Q3</b>	1.2 (0.9 – 1.6)	0.3
	<b>Q4</b>	1.4 (1.0 – 1.9)	0.02
	<b>Q5</b>	1.5 (1.1 – 2.0)	0.01
<b>Pyruvate</b>	<b>Log (Pyruvate)</b>	1.0 (0.9 – 1.1)	0.8
	<b>Quintiles: Q1</b>	Ref	
	<b>Q2</b>	0.9 (0.7 – 1.2)	0.4
	<b>Q3</b>	0.9 (0.7 – 1.2)	0.3
	<b>Q4</b>	1.0 (0.7 – 1.3)	0.8
	<b>Q5</b>	0.9 (0.6 – 1.2)	0.3
<b>Citrate</b>	<b>Log (Citrate)</b>	1.1 (0.9 – 1.2)	0.4
	<b>Quintiles: Q1</b>	Ref	
	<b>Q2</b>	1.5 (1.1 – 2.0)	0.02
	<b>Q3</b>	1.3 (0.9 – 1.7)	0.1
	<b>Q4</b>	1.2 (0.9 – 1.7)	0.2
	<b>Q5</b>	1.3 (1.0 – 1.9)	0.09

HR indicates hazard ratio; and CI, confidence interval.

\* Adjusted for age, sex, clinic site, ethnicity, education level, kcals physical activity per week, body mass index, body mass index<sup>2</sup>, smoking status, alcoholic drinks per week, fasting > 8 hours, diagnosis of hypertension, cholesterol, triglycerides, diagnosis of diabetes, estimated glomerular filtration rate, hypertension medication use, lipid-lowering medication use, and estrogen use.

**Table S5. Cause of death prevalence within each metabolic phenotype cluster.**

<b>Cause of death*</b>	<b>Healthy</b>	<b>High Ketone Bodies</b>	<b>Chronic Inflammation</b>	<b>Metabolic Syndrome</b>	<b>Total</b>
<b>Cardiovascular<sup>†</sup></b>	90 (32.5%)	23 (35.9%)	109 (41.4%)	80 (34.6%)	302
<b>Cancer</b>	65 (23.5%)	8 (12.5%)	44 (16.7%)	55 (23.8%)	172
<b>Dementia</b>	42 (15.2%)	8 (12.5%)	45 (17.1%)	38 (16.5%)	133
<b>Infection<sup>‡</sup></b>	15 (5.4%)	6 (9.4%)	23 (8.7%)	22 (9.5%)	66
<b>Respiratory</b>	17 (6.1%)	2 (3.1%)	10 (3.8%)	11 (4.8%)	40
<b>Trauma</b>	15 (5.4%)	5 (7.8%)	8 (3.0%)	7 (3.0%)	35
<b>Others<sup>§</sup></b>	33 (11.9%)	12 (18.8%)	24 (9.1%)	18 (7.8%)	87
<b>Total</b>	277	64	263	231	835

\* Data presented in number of observations (percentage prevalence).

<sup>†</sup> Cardiovascular causes include coronary heart disease, stroke, or any atherosclerotic disease.

<sup>‡</sup> Infection includes pneumonia, sepsis, or any source of proven infection.

<sup>§</sup> Other causes include: Liver disease, gastrointestinal disease, renal failure, amyotrophic lateral sclerosis, Parkinson's disease, bladder disease, metabolic conditions, amyloid, failure to thrive, myelodysplastic syndrome, and musculoskeletal diseases.

**Table S6. Multivariate Cox Models for Incident Heart Failure in 20 Years by Logarithmic Transformed Ketone Bodies and Ketone Body Quintiles.**

		<b>Model 1*</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 2†</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 3‡</b> <b>HR (95% CI)</b>	<b>P</b>
<b>Ketone Bodies</b>	<b>Log Ketone</b>	1.2 (1.0 – 1.3)	0.03	1.2 (1.0 – 1.3)	0.02	1.2 (1.0 - 1.4)	0.08
	<b>Quintiles: Q1</b>	Ref		Ref		Ref	
	<b>Q2</b>	1.0 (0.6 – 1.4)	0.7	0.9 (0.6 – 1.4)	0.7	1.0 (0.6 – 1.5)	0.9
	<b>Q3</b>	1.0 (0.7 – 1.4)	0.8	0.9 (0.6 – 1.4)	0.7	0.9 (0.6 – 1.5)	0.7
	<b>Q4</b>	1.3 (0.9 – 1.8)	0.2	1.2 (0.8 – 1.8)	0.4	1.3 (0.8 – 2.0)	0.3
	<b>Q5</b>	1.3 (0.9 – 1.9)	0.1	1.3 (0.9 – 2.0)	0.1	1.2 (0.7 – 2.0)	0.4
<b>Pyruvate</b>	<b>Log Pyruvate</b>	1.1 (1.0 – 1.3)	0.1	1.0 (0.8 – 1.3)	0.7	0.9 (0.8 – 1.1)	0.5
	<b>Quintiles: Q1</b>	Ref		Ref		Ref	
	<b>Q2</b>	0.9 (0.6 – 1.4)	0.6	0.9 (0.6 – 1.3)	0.4	0.9 (0.5 – 1.4)	0.6
	<b>Q3</b>	1.2 (0.8 – 1.7)	0.4	1.2 (0.8 – 1.8)	0.4	1.1 (0.7 – 1.8)	0.6
	<b>Q4</b>	0.9 (0.6 – 1.3)	0.5	0.8 (0.5 – 1.3)	0.3	0.8 (0.5 – 1.3)	0.2
	<b>Q5</b>	1.2 (0.8 – 1.9)	0.3	1.0 (0.6 – 1.5)	0.9	0.8 (0.5 – 1.3)	0.3
<b>Citrate</b>	<b>Log Citrate</b>	1.0 (0.9 – 1.2)	0.6	1.0 (0.5 – 1.9)	0.9	0.9 (0.4 – 1.9)	0.6
	<b>Quintiles: Q1</b>	Ref		Ref		Ref	
	<b>Q2</b>	1.1 (0.8 – 1.6)	0.5	1.1 (0.7 – 1.7)	0.6	1.1 (0.7 – 1.8)	0.6
	<b>Q3</b>	1.1 (0.7 – 1.6)	0.7	1.1 (0.7 – 1.6)	0.6	1.2 (0.8 – 1.9)	0.4
	<b>Q4</b>	1.0 (0.7 – 1.5)	0.9	1.0 (0.7 – 1.5)	0.9	0.9 (0.6 – 1.4)	0.6
	<b>Q5</b>	1.1 (0.8 – 1.7)	0.5	1.0 (0.7 – 1.6)	0.8	1.0 (0.6 – 1.7)	0.8

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity and clinic site.

† Model 2 is adjusted age, sex, clinic site, ethnicity, education level, kcals physical activity per week, body mass index, body mass index<sup>2</sup>, smoking status, and alcoholic drinks per week, fasting > 8 hours.

‡ Model 3 is adjusted for covariates in Model 2 and for diagnosis of hypertension, cholesterol, triglycerides, diagnosis of diabetes, estimated glomerular filtration rate, hypertension medication use, lipid-lowering medication use, and estrogen use.

**Table S7. Stratified Analysis of Ketone Bodies and Incident Heart Failure by Age.**

	<b>Model 1*</b> HR (95% CI)	<b>P</b>	<b>Model 2†</b> HR (95% CI)	<b>P</b>	<b>Model 3‡</b> HR (95% CI)	<b>P</b>
<b>≤ Median Age</b>						
<b>Log Ketone</b>	1.3 (1.0 – 1.7)	0.05	1.3 (1.0 – 1.8)	0.06	1.4 (1.0 – 2.1)	0.07
<b>Quintiles: Q1</b>	Ref		Ref		Ref	
<b>Q2</b>	0.8 (0.5 – 1.3)	0.3	0.7 (0.4 – 1.3)	0.2	0.8 (0.4 – 1.4)	0.4
<b>Q3</b>	0.9 (0.5 – 1.5)	0.6	0.9 (0.5 – 1.7)	0.8	1.2 (0.7 – 2.2)	0.5
<b>Q4</b>	1.2 (0.7 – 2.0)	0.5	1.3 (0.7 – 2.2)	0.4	1.4 (0.7 – 2.5)	0.3
<b>Q5</b>	1.3 (0.7 – 2.3)	0.3	1.2 (0.7 – 2.3)	0.4	1.3 (0.7 – 2.6)	0.4
<b>&gt; Median Age</b>						
<b>Log Ketone</b>	1.2 (0.9 – 1.6)	0.3	1.2 (0.9 – 1.7)	0.2	1.2 (0.8 - 1.8)	0.4
<b>Quintiles: Q1</b>	Ref		Ref		Ref	
<b>Q2</b>	1.1 (0.7 – 2.0)	0.6	1.2 (0.7 – 2.1)	0.5	1.4 (0.7 – 2.7)	0.3
<b>Q3</b>	1.1 (0.6 – 1.8)	0.8	0.9 (0.5 – 1.7)	0.8	0.8 (0.4 – 1.9)	0.6
<b>Q4</b>	1.3 (0.8 - 2.2)	0.3	1.1 (0.7 - 2.0)	0.6	1.3 (0.7 - 2.6)	0.4
<b>Q5</b>	1.3 (0.8 – 2.3)	0.3	1.4 (0.8 – 2.5)	0.2	1.2 (0.6 – 2.7)	0.5

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity and clinic site.

† Model 2 is adjusted age, sex, clinic site, ethnicity, education level, kcals physical activity per week, body mass index, body mass index<sup>2</sup>, smoking status, and alcoholic drinks per week, fasting > 8 hours.

‡ Model 3 is adjusted for covariates in Model 2 and for diagnosis of hypertension, cholesterol, triglycerides, diagnosis of diabetes, estimated glomerular filtration rate, hypertension medication use, lipid-lowering medication use, and estrogen use.



**Table S8. Stratified Analysis of Ketone Bodies and Incident Heart Failure by Body Mass Index.**

	<b>Model 1*</b> HR (95% CI)	<b>P</b>	<b>Model 2†</b> HR (95% CI)	<b>P</b>	<b>Model 3‡</b> HR (95% CI)	<b>P</b>
<b>≤ Median Body Mass Index</b>						
<b>Log Ketone</b>	1.4 (1.0 – 1.8)	0.02	1.4 (1.1 – 1.9)	0.01	1.6 (1.1 – 2.3)	0.02
<b>Quintiles: Q1</b>	Ref		Ref		Ref	
<b>Q2</b>	1.1 (0.6 – 1.9)	0.7	1.2 (0.7 – 2.1)	0.5	1.2 (0.6 – 2.3)	0.5
<b>Q3</b>	1.2 (0.7 – 2.0)	0.6	1.2 (0.7 – 2.2)	0.5	1.1 (0.5 – 2.3)	0.7
<b>Q4</b>	1.3 (0.7 – 2.5)	0.3	1.4 (0.8 – 2.6)	0.2	1.6 (0.8 - 3.1)	0.1
<b>Q5</b>	1.6 (1.0 – 2.8)	0.07	1.7 (1.0 – 3.0)	0.04	1.8 (0.9 – 3.6)	0.08
<b>&gt; Median Body Mass Index</b>						
<b>Log Ketone</b>	1.1 (0.8 – 1.5)	0.5	1.1 (0.8 – 1.5)	0.6	1.0 (0.7 - 1.5)	0.9
<b>Quintiles: Q1</b>	Ref		Ref		Ref	
<b>Q2</b>	0.8 (0.5 – 1.4)	0.3	0.7 (0.4 – 1.2)	0.2	0.9 (0.5 – 1.5)	0.5
<b>Q3</b>	0.8 (0.5 – 1.4)	0.4	0.7 (0.4 – 1.3)	0.2	0.7 (0.4 – 1.4)	0.3
<b>Q4</b>	1.0 (0.6 - 1.8)	0.8	0.9 (0.5 - 1.6)	0.7	1.0 (0.6 – 1.9)	0.9
<b>Q5</b>	1.0 (0.6 – 1.9)	0.9	0.9 (0.5 – 1.7)	0.7	0.8 (0.4 – 1.6)	0.4

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity and clinic site.

† Model 2 is adjusted age, sex, clinic site, ethnicity, education level, kcals physical activity per week, body mass index, body mass index<sup>2</sup>, smoking status, and alcoholic drinks per week, fasting > 8 hours.

‡ Model 3 is adjusted for covariates in Model 2 and for diagnosis of hypertension, cholesterol, triglycerides, diagnosis of diabetes, estimated glomerular filtration rate, hypertension medication use, lipid-lowering medication use, and estrogen use.

**Table S9. Multivariate Cox Models for Incident Heart Failure in 20 Years by Metabolite Phenotype Cluster.**

	<b>Model 1*</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 2†</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 3‡</b> <b>HR (95% CI)</b>	<b>P</b>
<b>Healthy</b>	Ref		Ref		Ref	
<b>Ketone Bodies</b>	2.4 (1.3 – 4.6)	0.006	2.2 (1.2 – 4.2)	0.01	2.5 (1.3 – 4.8)	0.04
<b>Chronic Inflammation</b>	1.4 (0.9 – 2.1)	0.1	1.3 (0.8 – 2.0)	0.2	1.5 (0.9 – 2.3)	0.1
<b>Metabolic Syndrome</b>	1.3 (0.8 – 2.0)	0.2	1.2 (0.8 – 1.8)	0.4	1.1 (0.7 – 1.8)	0.6

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity, and clinic site.

† Model 2 is adjusted for covariates in Model 1 and for education level, kcals physical activity per week, smoking status, alcoholic drinks per week, and fasting > 8 hours.

‡ Model 3 is adjusted for covariates in Model 2 and dietary components: linoleic acid, oleic acid, saturated fat, carbohydrates, and protein.

**Table S10. Lunn-Macneil Competing-Risk Estimates for Incidence of Heart Failure and All-Cause Mortality.**

	<b>Univariate Model HR (95% CI)</b>	<b>P</b>	<b>Model 1* HR (95% CI)</b>	<b>P</b>
<b>All-Cause Mortality</b>				
<b>Log Ketone</b>	1.2 (1.1 – 1.3)	<0.001	1.1 (1.0 – 1.3)	0.005
<b>Quintiles: Q1</b>	Ref		Ref	
<b>Q2</b>	1.1 (0.9 – 1.5)	0.3	1.1 (0.9 – 1.5)	0.3
<b>Q3</b>	1.3 (1.0 - 1.6)	0.09	1.2 (0.9 – 1.5)	0.2
<b>Q4</b>	1.5 (1.1 – 1.9)	0.003	1.4 (1.1 – 1.7)	0.01
<b>Q5</b>	1.6 (1.2 – 2.0)	0.001	1.3 (1.0 – 1.7)	0.04
<b>Incident Heart Failure</b>				
<b>Log Ketone</b>	1.2 (1.1 – 1.4)	0.002	1.2 (1.0 – 1.3)	0.03
<b>Quintiles: Q1</b>	Ref		Ref	
<b>Q2</b>	1.0 (0.6 – 1.4)	0.7	1.0 (0.6 – 1.4)	0.7
<b>Q3</b>	1.0 (0.7 - 1.5)	0.8	1.0 (0.7 – 1.4)	0.8
<b>Q4</b>	1.3 (0.9 – 1.9)	0.1	1.1 (0.9 – 1.8)	0.2
<b>Q5</b>	1.4 (1.0 – 2.1)	0.04	1.2 (0.9 – 1.9)	0.1

HR indicates hazard ratio; and CI, confidence interval.

\* Model 1 is adjusted for age, sex, ethnicity, and clinic site.

**Table S11. Stratified Analysis of Ketone Bodies and Incident Heart Failure by Ejection Fraction.**

	<b>Model 1*</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 2†</b> <b>HR (95% CI)</b>	<b>P</b>	<b>Model 3‡</b> <b>HR (95% CI)</b>	<b>P</b>
<b>HFrEF</b>						
<b>Log Ketone</b>	1.3 (1.1-1.6)	0.001	1.4 (1.1-1.7)	0.001	1.4 (1.1-1.7)	0.01
<b>Quintiles: Q1</b>	Ref		Ref		Ref	
<b>Q2</b>	1.1 (0.6-1.9)	0.7	1.2 (0.6-2.1)	0.6	1.1 (0.5-2.2)	0.8
<b>Q3</b>	1.0 (0.6-1.7)	0.9	1.0 (0.6-1.8)	0.9	1.0 (0.5-2.1)	0.9
<b>Q4</b>	1.8 (1.1-2.9)	0.02	1.7 (1.0-2.8)	0.054	1.6 (0.9-2.9)	0.1
<b>Q5</b>	1.9 (1.2-3.2)	0.01	2.1 (1.2-3.6)	0.007	1.8 (0.9-3.5)	0.08
<b>HFpEF</b>						
<b>Log Ketone</b>	1.1 (0.8-1.7)	0.6	1.1 (0.7-1.7)	0.6	1.1 (0.7-1.9)	0.6
<b>Quintiles: Q1</b>	Ref		Ref		Ref	
<b>Q2</b>	0.9 (0.4-2.1)	0.8	0.9 (0.4-2.1)	0.8	0.8 (0.4-2.0)	0.6
<b>Q3</b>	1.9 (0.9-4.0)	0.07	1.8 (0.8-3.9)	0.1	1.2 (0.5-2.9)	0.6
<b>Q4</b>	1.4 (0.6-3.2)	0.4	1.3 (0.5-3.1)	0.5	1.1 (0.4-3.3)	0.8
<b>Q5</b>	1.6 (0.7-3.7)	0.2	1.7 (0.8-4.0)	0.1	1.5 (0.6-3.8)	0.3

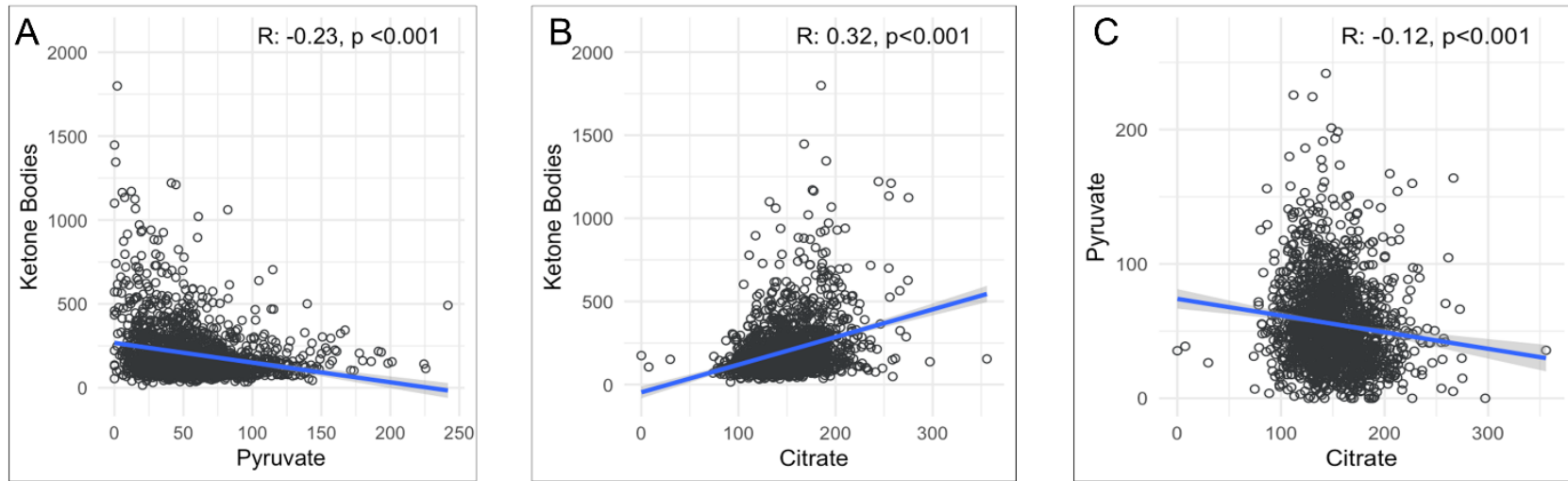
HR indicates hazard ratio; CI, confidence interval; HFrEF, Heart Failure with Reduced Ejection Fraction; and HFpEF, Heart Failure with Preserved Ejection Fraction.

\* Model 1 is adjusted for age, age<sup>2</sup>, sex, ethnicity and clinic site.

† Model 2 is adjusted age, sex, clinic site, ethnicity, education level, kcals physical activity per week, body mass index, body mass index<sup>2</sup>, smoking status, and alcoholic drinks per week, fasting > 8 hours.

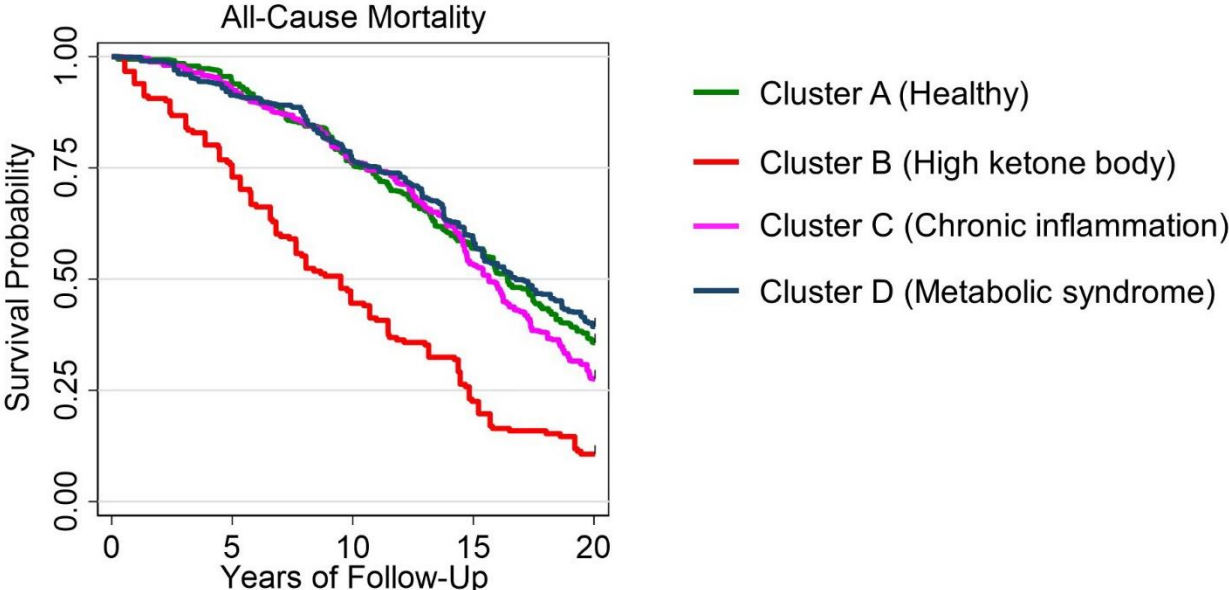
‡ Model 3 is adjusted for covariates in Model 2 and for diagnosis of hypertension, cholesterol, triglycerides, diagnosis of diabetes, estimated glomerular filtration rate, hypertension medication use, lipid-lowering medication use, and estrogen use.

**Figure S1. Cross-sectional relationships of metabolites in the Cardiovascular Health Study cohort at baseline.**



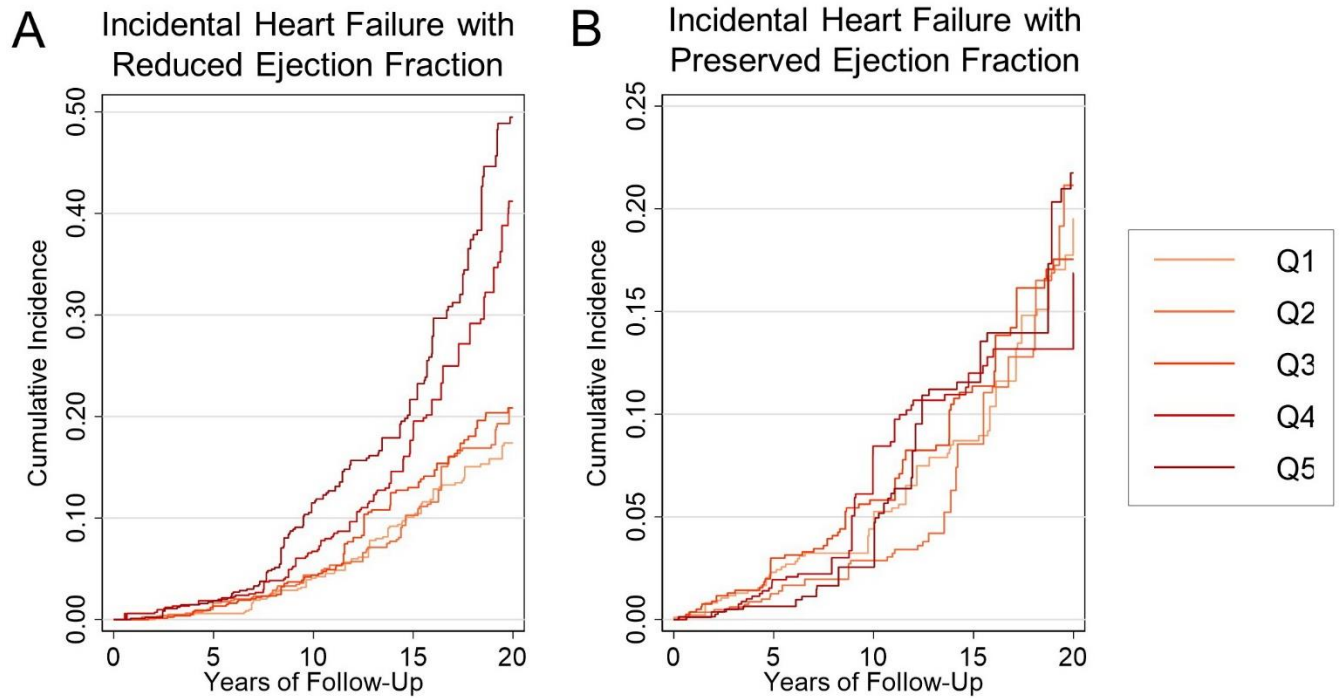
Two-way plots were generated to evaluate the cross-sectional relationship among three metabolites measured by nuclear magnetic resonance (NMR) spectroscopy: A. ketone bodies vs. pyruvate, B. ketone bodies vs. citrate, and C. pyruvate vs. citrate. The Pearson correlation coefficient (R) and p-value are shown in each plot. Each dot represents a participant in the Cardiovascular Health Study cohort.

**Figure S2. Kaplan-Meier Analysis for Overall Mortality by Metabolic Phenotypes.**



Kaplan Meier survival analysis for overall mortality by the metabolic phenotype clusters were plotted over a follow-up of 20 years. Cluster A: Healthy (green); Cluster B, high ketone bodies (red); Cluster C, chronic inflammation (magenta); and cluster D, metabolic syndrome (blue).

**Figure S3. Kaplan-Meier Estimates for 20 years for Incident Heart Failure Phenotypes for Ketone Bodies Quintiles.**



Kaplan Meier analyses are conducted for the incidence of heart failure with reduced ejection fraction (A) and preserved ejection fraction (B) by the quintiles of plasma ketone bodies.