SUPPLEMENTAL MATERIAL

Data S1. Sensitivity analyses to determine impact of alternate cohort definitions

We sought to determine whether results would change significantly with implementation of stricter definitions of HFpEF, HFrEF, and no-HF controls. Accordingly, in this sensitivity analysis, we defined our cohorts as described below. Results are shown in Supplemental Tables S4 and S5.

HFpEF cases were defined by left ventricular ejection fraction (LVEF) > 45%, diastolic dysfunction grade ≥ 1, clinical history of HF determined by cardiologists at the time of catheterization, and one of the following objective indicators of HF in the 12 months before sample collection: elevated NT-proBNP (>400 pg/mL), loop diuretic use, or HF ICD-9 code associated with a clinical encounter. HFrEF controls were defined similarly to HFpEF cases, with the exception of having LVEF < 45%. No-HF controls were defined by LVEF > 45%, normal diastolic function, absence of heart failure symptoms, and no elevated NT-proBNP (>400 pg/mL), loop diuretic use, or HF ICD-9 code EVER before sample collection. Additionally, all patients were excluded who had a major adverse cardiac event (myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention) within 1 month of catheterization. Objective indicators of HF history were generated during routine clinical care and extracted by automated search of medical records.

We also sought to determine whether using alternate LVEF thresholds would impact results of our analyses. Accordingly, we regenerated our cohorts using all of the same inclusion criteria as the primary cohorts except that the HFpEF and No-HF groups had LVEF ≥ 50% and HFrEF LVEF < 35%.

Data S2. Approach to diastolic dysfunction classification

Diastolic function assessments were made during routine clinical care. Given temporal variation in diastolic function classification practices, a 10% overread was performed by experienced echocardiographers (S.H.S. and M.G.K.) to ensure accuracy of these assessments. Diastolic classifications made during overreading were based on American Society of

Echocardiography guidelines (Supplemental Table S1, below). Concordance between present overreading and prior assessments was 84%, which was deemed to be an acceptable level of agreement to support using previous clinical assessments. [1]

Data S3. Sensitivity analyses to determine the impact of insulin resistance

As noted in the Discussion, elevations in plasma LCAC may be a cause or consequence of insulin resistance (IR). Although we reported and adjusted for overt diabetes in our analyses, it is possible that IR exerts an incremental mediation effect. To determine the impact of IR on the relationships observed between HFpEF, HFrEF, no-HF, and plasma LCAC, we performed several sensitivity analyses. In addition to repeating the primary analysis with adjustment for IR, we assessed correlations between IR and LCACs directly.

We used the Lipoprotein Insulin Resistance Index (LP-IR), a validated IR measurement derived from nuclear magnetic resonance (NMR)-based lipoprotein subclass particle size and concentration.[2] The LP-IR index has been shown to have strong correlations with glucose disposal rate (GDR) and HOMA-IR. [2]

Correlations between LCAC and IR

To determine the relationship between LCAC and IR directly, we evaluated unadjusted correlations between Factor 4 (LCAC) and LP-IR for the full cohort using Spearman's rho. We found no correlation between LCAC and LP-IR (r =-0.04; P = 0.3).

Impact of IR Adjustment on Primary Analysis Results

To determine whether IR mediates the relationship between HFpEF, HFrEF, no-HF, and plasma LCAC levels, we created two separate general linear models. The first model included all of the covariates used in the primary analysis (age, race, sex, body mass index, number of diseased coronary arteries, history of diabetes, hypertension, dyslipidemia, smoking, glomerular filtration rate, batch), and added LP-IR. The second model included all of the covariates used in the primary

analysis, but replaced 'history of diabetes' with LP-IR levels. We performed multivariate adjusted analysis of covariance (ANCOVA) with post-hoc pairwise comparisons using both models.

As shown in Supplemental Tables S6 and S7, this adjustment did not change the results. Specifically, LCAC factor levels remained significantly different among groups in the omnibus ANCOVA for both IR sensitivity analyses (both $P<0.0001$). Similarly, all pairwise comparisons of LCAC factor levels remained significantly different in the IR sensitivity analyses. Additionally, the trends in mean LCAC factor concentrations were preserved in the IR sensitivity analyses, with LCAC levels highest in HFrEF, intermediate in HFpEF, and lowest in no-HF patients. Analyses of individual LCAC metabolites in HFpEF, HFrEF, and no-HF patients (Supplemental Tables S8 and S9) confirmed findings from the IR sensitivity analyses and were concordant with those from the primary analysis. Altogether, these results suggest that LCAC factor findings were not driven by IR.

Data S4: Complete list of measured metabolites

See Supplemental Table S2 below for the complete list of metabolites measured in this investigation.

Data S5. Detailed results of principal components analysis

Principal components analysis reduced the full set of 63 metabolites into a smaller number of uncorrelated factors. Fourteen factors exceeded the Eigenvalue threshold of 1.0, and are listed in Supplemental Table S3 below. This threshold is based on the Kaiser Criterion, which allows parsimonious selection of factors explaining a significant amount of inter-subject variation. Component metabolites are listed in order of magnitude of factor load, with only those having a factor load $\geq |0.4|$ listed. Variance refers to the proportion of overall variance explained by a given factor.

Data S6: Plasma LCAC means for additional HFpEF, HFrEF, and control cohorts

To provide insight into how the plasma LCAC values of our cohorts compare with those reported in similar populations, we have provided baseline plasma LCAC means for three additional cohorts: 1) N=161 patients enrolled in the RELAX trial of sildenafil in HFpEF; [3] 2) N=453 patients enrolled in the HF-ACTION trial of exercise in HFrEF; [4] and 3) N=3653 patients without HF enrolled in CATHGEN who were not included in the primary analysis. [5]

As shown in Table S10 below, we found similar levels of individual LCAC metabolites for HFpEF and no-HF controls between the respective cohorts. For HFrEF, there were some metabolites that were higher in CATHGEN as compared with HF-ACTION, likely related to the fact that HF-ACTION participants were outpatients and CATHGEN participants included inpatients with more acute heart failure presentations. Results of these analyses support generalizability of the present findings to broader populations.

TABLE S1: Parameters Used in Diastolic Dysfunction Class Overreading

Grade	Mitral E/A ratio	E/E' ratio	Left Atrial (LA) Size (ml/m^2)	Deceleration Time (ms)	Pulmonary Vein Flow
0 (none)	>0.8	<8	< 34	> 200	D>S
I (mild)	<0.8	<8	≥ 34	> 200	S>D
II (moderate)	≥1	>10	≥ 34	160-200	S>D
III/IV (severe)	≥2	≥13	≥ 34	< 160	S>D

TABLE S2: List of Measured Metabolites	
Short name*	**Trivial names**
C2	Acetyl carnitine
C3	Propionyl carnitine
C4/Ci4	Butyryl carnitine or isobutyryl carnitine
C5:1	Tiglyl carnitine or 3-methyl crotonyl carnitine
C5	Isovaleryl, 3-methylbutyryl carnitine , 2-Methylbutyryl, valeryl or pivaloyl carnitine
C4-OH	D-3-Hydroxy-butyryl carnitine, L-3-hydroxybutyryl carnitine
C6	Hexanoyl carnitine
C5-OH/C3-DC	3-Hydroxy-isovaleryl carnitine or malonyl carnitine
Ci4-DC/C4-DC	Methylmalonyl carnitine or succinyl carnitine
C8:1	Octenoyl carnitine†
C8	Octanoyl carnitine
C5-DC	Glutaryl carnitine, ethylmalonyl carnitine
C8:1-OH/C6:1-DC	3-Hydroxy- octenoyl carnitine or hexenedioyl carnitine
C8-OH/C6-DC	3-hydroxy octanoyl carnitine or adipoyl carnitine, 3-methylglutaryl carnitine
C10:3	Decatrienoyl carnitine†
C10:2	Decadienoyl carnitine†
C10:1	Decenoyl carnitine†
C10	Decanoyl carnitine
C7-DC	Pimeloyl carnitine, heptanedioyl carnitine
C10:1-OH/C8:1-DC	3-Hydroxy-decenoyl carnitine or octadecenedioyl carnitine
C10-OH/C8-DC	3-Hydroxy-decanoyl carnitine or suberoyl carnitine
C12:1	Dodecenoyl carnitine†
C12	Lauroyl carnitine
C12-OH/C10-DC	3-Hydroxy-dodecanoyl carnitine or sebacoyl carnitine
C14:2	Tetradecadienoyl carnitine†
C14:1	Tetradecenoyl carnitine†
C14	Myristoyl carnitine
C14:1-OH/C12:1-DC	3-Hydroxy-tetradecenoyl carnitine or dodecenedioyl carnitine
C14-OH/C12-DC	3-Hydroxy-tetradecanoyl carnitine or dodecanedioyl carnitine
C16:2	Hexadecadienoyl carnitine†
C16:1	Palmitoleoyl carnitine†
C16	Palmitoyl carnitine

C16:1-OH/C14:1-DC	3-Hydroxy-palmitoleoyl carnitine or cis-5-tetradecenedioyl carnitine
C16-OH/C14-DC	3-Hydroxy-hexadecanoyl carnitine or tetradecanedioyl carnitine
C18:2	Linoleyl carnitine
C18:1	Oleyl carnitine
C18	Stearoyl carnitine
C18:2-OH/C16:2-DC	3-Hydroxy-linoleyl carnitine or hexadecadienedioyl carnitine
C18:1-OH/C16:1-DC	3-Hydroxy-octadecenoyl carnitine or hexadecanedioyl carnitine
C18-OH/C16-DC	3-Hydroxy-octadecanoyl carnitine or hexadecanedioyl carnitine, thapsoyl carnitine
C20:4	Arachidonoyl carnitine
C20	Arachidoyl carnitine, eicosanoyl carnitine
C18:1-DC	Octadecenedioyl carnitine
C20-OH/C18-DC/C22:6	3-Hydroxy-eicosanoyl carnitine or octadecanedioyl carnitine or docosahexaenoyl carnitine
C22	Docosanoyl carnitine, Behenoyl carnitine
GLY	Glycine
ALA	Alanine
SER	Serine
PRO	Proline
VAL	Valine
LEU/ILE	Leucine/Isoleucine
MET	Methionine
HIS	Histidine
PHE	Phenylalanine
TYR	Tyrosine
ASX	Aspartic acid/asparagine
GLX	Glutamine/glutamate
ORN	Ornithine
CIT	Citrulline
ARG	Arginine
FFA	Total free fatty acids
HBUT	β-Hydroxybutyrate
KET	Ketones

* Some metabolite isomers and isobars could not be differentiated by flow injection tandem mass spectrometry; potential isomers or isobars are listed where applicable. † Positions of double bond(s) uncertain. Abbreviations: C indicates acylcarnitine carbon chain length; OH, hydroxyl; DC, dicarboxyl.

TABLE S3: Peripheral Blood Metabolite Principal Components

Factor	Description	Component Metabolites	Eigenvalue	Variance
1	Medium-chain acylcarnitines	C8, C10, C12, C14:1, C14, C16:2, C16:1, C14:2, C12:1, C10:1	14.06	7.17
2	Long-chain dicarboxyl-acylcarnitines	C20:1-OH/C18:1-DC, C18-OH/C16-DC, C20-OH/C18-DC, C16-OH/C14-DC, C18:1-OH/C16:1-DC, C20, C12-OH/C10-DC, C14-OH/C12-DC	5.64	5.61
3	Short-chain dicarboxyl-acylcarnitines	C5-DC, C6:1-DC/C8:1-OH, C8:1-DC, C6-DC, Ci4-DC/C4-DC, C10-OH/C8-DC, C12-OH/C10-DC, Citrulline	4.86	5.12
4	Long-chain acylcarnitines	C18:1, C18:2, C18, C16, C20:4, C16:1-OH/C14:1-DC	3.80	4.34
5	Ketones and related metabolites	Ketones, ß-hydroxybutyrate, ß-hydroxybutyryl-carnitine, acetylcarnitine, alanine	2.52	4.19
6	C8-C10 acylcarnitines	C10:3, C8:1, C10:2, C10:1	2.47	3.08
7	BCAA and related metabolites	phenylalanine, tyrosine, leucine/isoleucine, valine, methionine,	2.32	2.88
8	Various amino acids	glycine, methionine, serine, ornithine, arginine, C5:1, proline	1.60	2.79
9	Short-chain acylcarnitines	C4/Ci4, C3, C5's	1.47	2.31
10	3-hydroxyisovaleryl / malonyl carnitine, asparagine, aspartate,	C5-OH/C3-DC, asparagine/aspartate,	1.42	1.65
11	Tigylcarnitine, histidine, 3-hydroxy linoleyl /hexadeca-dienedioylcarnitine, arginine	C5:1, histidine, C18:2-OH/C16:2-DC, arginine	1.22	1.49
12	Glutamine, glutamate, valine	glutamine/glutamate, valine	1.12	1.43
13	Alanine, proline, free fatty acids	alanine, proline, circulating free (non-esterified) fatty acids	1.07	1.35
14	Docosanoylcarnitine	C22	1.01	1.16

TABLE S4: Metabolite Factor Means and Comparisons Between HFpEF, HFrEF, and No-HF Controls Using Strict Cohort Definitions

Factor	Description	ANCOVA*		Pairwise Comparisons§			Metabolite Factor Mean Values¶		
		*Basic**	*Fully Adjusted***	HFrEF vs HFpEF	HFrEF vs No-HF	HFpEF vs No-HF	HFrEF (N=136)	HFpEF (N=117)	No-HF (N=129)
1	Medium-chain acylcarnitines	0.04	0.13						
2	Long-chain dicarboxyl-acylcarnitines	0.008	0.04						
3	Short-chain dicarboxyl-acylcarnitines	0.005	0.07						
4	Long-chain acylcarnitines	<0.0001	<0.0001	0.0004	<0.0001	0.003	0.458 (0.219)	0.007 (0.219)	-0.334 (0.221)
5	Ketones and related metabolites	0.13	0.15						
6	C8-C10 acylcarnitines	0.0001	0.09						
7	BCAA and related metabolites	0.04	0.005	0.03	0.01	1.00	0.264 (0.219)	-0.006 (0.219)	-0.213 (0.221)
8	Various amino acids	0.14	0.07						
9	Short-chain acylcarnitines	0.13	0.95						
10	Asparagine, aspartate, 3-hydroxyisovaleryl / malonyl carnitine	0.17	0.11						
11	Histidine, arginine, tigylcarnitine, 3-hydroxylinoleyl / hexadecadienedioyl carnitine	0.11	0.01	1.00	0.01	0.05	-0.395 (0.175)	-0.390 (0.175)	-0.112 (0.176)
12	Valine, glutamine, glutamate	0.008	0.004	0.03	0.008	1.00	-0.694 (0.229)	-0.291 (0.229)	-0.228 (0.231)
13	Alanine, proline, free fatty acids	0.02	0.03	0.36	0.02	0.61	0.067 (0.213)	-0.190 (0.213)	-0.094 (0.215)
14	Docosanoyl-carnitine	0.004	0.03	1.00	0.03	0.18	-0.258 (0.211)	-0.119 (0.211)	0.101 (0.213)

*Statistical significance in omnibus ANCOVA analyses was $P<0.0036$, reflecting Bonferroni correction for 14 factor comparisons. † P values for basic model, adjusted for age, race and sex. ‡ P values for full model, adjusted for age, race, sex, body mass index, number of diseased coronary arteries, history of diabetes, hypertension, dyslipidemia, smoking, glomerular filtration rate, and batch. § Pairwise comparisons for factors significant at Bonferroni corrected threshold test for significant between-group differences. P values for factors significant at nominal threshold of $P<0.05$ are reported for exploratory purposes. P values reflect between-group pairwise contrasts generated from the fully adjusted ANCOVA procedure. ¶ Values are least square means, adjusted for all 11 covariates. Standard error of the mean is provided beneath each value. Abbreviations: HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ANCOVA, analysis of covariance; BCAA, branched-chain amino acids; C, carbon chain length.

TABLE S5: Metabolite Factor Means and Comparisons Between HFpEF, HFrEF, and No-HF Controls Using Alternate LVEF Thresholds

Factor	Description	ANCOVA*		Pairwise Comparisons§			Metabolite Factor Mean Values¶		
		Basic†	*Fully Adjusted‡*	HFrEF vs HFpEF	HFrEF vs No-HF	HFpEF vs No-HF	HFrEF (N=189)	HFpEF (N=232)	No-HF (N=166)
1	Medium-chain acylcarnitines	0.007	0.04	0.27	0.05	1.00	0.345 (0.142)	0.196 (0.140)	0.109 (0.150)
2	Long-chain dicarboxyl-acylcarnitines	0.003	0.02	0.04	0.09	1.00	0.297 (0.212)	-0.027 (0.208)	-0.016 (0.223)
3	Short-chain dicarboxyl-acylcarnitines	0.009	0.17						
4	Long-chain acylcarnitines	<0.0001	<0.0001	0.0001	<0.0001	0.003	0.611 (0.188)	0.138 (0.185)	-0.277 (0.198)
5	Ketones and related metabolites	0.07	0.16						
6	C8-C10 acylcarnitines	<0.0001	0.02	0.67	0.02	0.25	0.195 (0.146)	0.086 (0.143)	-0.085 (0.154)
7	BCAA and related metabolites	0.01	0.002	0.02	0.003	1.00	0.017 (0.172)	-0.268 (0.169)	-0.376 (0.181)
8	Various amino acids	0.13	0.05	0.05	0.44	1.00	-0.128 (0.148)	0.093 (0.146)	0.018 (0.156)
9	Short-chain acylcarnitines	0.10	0.81						
10	Asparagine, aspartate, 3-hydroxyisovaleryl / malonyl carnitine	0.42	0.23						
11	Histidine, arginine, tigylcarnitine, 3-hydroxylinoleyl / hexadecadienedioyl carnitine	0.34	0.05	1.00	0.05	0.19	-0.286 (0.127)	-0.235 (0.125)	0.076 (0.134)
12	Valine, glutamine, glutamate	0.0007	0.0008	0.01	0.002	1.00	-0.473 (0.168)	-0.172 (0.165)	-0.074 (0.177)
13	Alanine, proline, free fatty acids	0.03	0.02	0.51	0.01	0.27	-0.061 (0.161)	-0.074 (0.158)	-0.257 (0.169)
14	Docosanoyl-carnitine	0.0005	0.004	0.32	0.003	0.19	0.026 (0.153)	0.178 (0.150)	0.369 (0.161)

*Statistical significance in omnibus ANCOVA analyses was $P<0.0036$, reflecting Bonferroni correction for 14 factor comparisons. † *P* values for basic model, adjusted for age, race and sex. ‡ *P* values for full model, adjusted for age, race, sex, body mass index, number of diseased coronary arteries, history of diabetes, hypertension, dyslipidemia, smoking, glomerular filtration rate, and batch. § Pairwise comparisons for factors significant at Bonferroni corrected threshold test for significant between-group differences. *P* values for factors significant at nominal threshold of $P<0.05$ are reported for exploratory purposes. *P* values reflect between-group pairwise contrasts generated from the fully adjusted ANCOVA procedure. ¶ Values are least square means, adjusted for all 11 covariates. Standard error of the mean is provided beneath each value. Abbreviations: HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ANCOVA, analysis of covariance; BCAA, branched-chain amino acids; C, carbon chain length.

TABLE S6: Adjusted Metabolite Factor Means and Comparisons Between HFpEF, HFrEF, and No-HF Controls, Controlling for History of Diabetes and Insulin Resistance*

Factor	Description	ANCOVA	Pairwise Comparisons‡			Metabolite Factor Mean Values§		
		P-value †	HFrEF vs HFpEF	HFrEF vs No-HF	HFpEF vs No-HF	HFrEF (N=263)	HFpEF (N=273)	No-HF (N=183)
1	Medium-chain acylcarnitines	0.16						
2	Long-chain dicarboxyl-acylcarnitines	0.0009	0.002	0.01	1.00	0.317 (0.136)	0.036 (0.137)	0.041 (0.146)
3	Short-chain dicarboxyl-acylcarnitines	0.13						
4	Long-chain acylcarnitines	<0.0001	0.0002	<0.0001	0.003	0.454 (0.155)	0.070 (0.156)	-0.299 (0.167)
5	Ketones and related metabolites	0.36						
6	C8-C10 acylcarnitines	0.06						
7	BCAA and related metabolites	0.007	0.046	0.01	1.00	0.042 (0.151)	-0.182 (0.152)	-0.259 (0.162)
8	Various amino acids	0.03	0.07	0.10	1.00	-0.150 (0.130)	0.032 (0.131)	0.042 (0.140)
9	Short-chain acylcarnitines	0.90						
10	Asparagine, aspartate, 3-hydroxyisovaleryl / malonyl carnitine	0.15						
11	Histidine, arginine, tigylcarnitine, 3-hydroxylinoleyl / hexadecadienedioyl carnitine	0.01	1.00	0.009	0.09	-0.374 (0.112)	-0.316 (0.112)	-0.143 (0.120)
12	Valine, glutamine, glutamate	0.007	0.16	0.007	0.54	-0.372 (0.147)	-0.199 (0.147)	-0.060 (0.158)
13	Alanine, proline, free fatty acids	0.02	0.40	0.02	0.54	0.131 (0.138)	0.005 (0.138)	-0.126 (0.148)
14	Docosanoyl-carnitine	0.06						

* Statistical significance in omnibus ANCOVA analyses was $P<0.0036$, reflecting Bonferroni correction for 14 factor comparisons. † *P* values adjusted for age, race, sex, body mass index, number of diseased coronary arteries, history of diabetes, hypertension, dyslipidemia, smoking, glomerular filtration rate, insulin resistance, and batch. ‡ Pairwise comparisons for factors significant at Bonferroni corrected threshold test for significant between-group differences. *P* values for factors significant at nominal threshold of $P<0.05$ are reported for exploratory purposes. *P* values reflect between-group pairwise contrasts generated from the fully adjusted ANCOVA procedure. § Values are least square means, adjusted for all 12 covariates. Standard error of the mean is provided beneath each value. Abbreviations: HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ANCOVA, analysis of covariance; BCAA, branched-chain amino acids; C, carbon chain length.

TABLE S7: Adjusted Metabolite Factor Means and Comparisons Between HFpEF, HFrEF, and No-HF Controls, Controlling for Insulin Resistance but NOT Diabetes*

Factor	Description	ANCOVA	Pairwise Comparisons‡			Metabolite Factor Mean Values§		
		P-value †	HFrEF vs HFpEF	HFrEF vs No-HF	HFpEF vs No-HF	HFrEF (N=263)	HFpEF (N=273)	No-HF (N=183)
1	Medium-chain acylcarnitines	0.18						
2	Long-chain dicarboxyl-acylcarnitines	0.0008	0.002	0.008	1.00	0.305 (0.136)	0.026 (0.137)	0.020 (0.145)
3	Short-chain dicarboxyl-acylcarnitines	0.12						
4	Long-chain acylcarnitines	<0.0001	0.0001	<0.0001	0.004	0.470 (0.155)	0.083 (0.156)	-0.271 (0.165)
5	Ketones and related metabolites	0.36						
6	C8-C10 acylcarnitines	0.03	1.00	0.02	0.20	0.186 (0.132)	0.112 (0.132)	-0.060 (0.140)
7	BCAA and related metabolites	0.008	0.04	0.02	1.00	0.055 (0.151)	-0.171 (0.151)	-0.235 (0.161)
8	Various amino acids	0.03	0.06	0.11	1.00	-0.155 (0.129)	0.028 (0.130)	0.033 (0.138)
9	Short-chain acylcarnitines	0.91						
10	Asparagine, aspartate, 3-hydroxyisovaleryl / malonyl carnitine	0.17						
11	Histidine, arginine, tigylcarnitine, 3-hydroxylinoleyl / hexadecadienedioyl carnitine	0.01	1.00	0.009	0.09	-0.377 (0.111)	-0.318 (0.112)	-0.148 (0.119)
12	Valine, glutamine, glutamate	0.02	0.13	0.02	1.00	-0.422 (0.148)	-0.241 (0.148)	-0.147 (0.158)
13	Alanine, proline, free fatty acids	0.02	0.40	0.02	0.52	0.130 (0.137)	0.004 (0.138)	-0.128 (0.146)
14	Docosanoyl-carnitine	0.07						

* Statistical significance in omnibus ANCOVA analyses was $P<0.0036$, reflecting Bonferroni correction for 14 factor comparisons. † *P* values adjusted for age, race, sex, body mass index, number of diseased coronary arteries, hypertension, dyslipidemia, smoking, glomerular filtration rate, insulin resistance, and batch. ‡ Pairwise comparisons for factors significant at Bonferroni corrected threshold test for significant between-group differences. *P* values for factors significant at nominal threshold of $P<0.05$ are reported for exploratory purposes. *P* values reflect between-group pairwise contrasts generated from the fully adjusted ANCOVA procedure. § Values are least square means, adjusted for all 11 covariates. Standard error of the mean is provided beneath each value. Abbreviations: HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ANCOVA, analysis of covariance; BCAA, branched-chain amino acids; C, carbon chain length.

TABLE S8: Adjusted Individual Metabolite Means and Comparisons Between HFpEF, HFrEF, and No-HF Controls, Controlling for History of Diabetes and Insulin Resistance

Metabolites		ANCOVA	Pairwise Comparisons†			Mean Concentration in µM‡		
Structure	Trivial Name	*	HFrEF vs HFpEF	HFrEF vs No-HF	HFpEF vs No-HF	HFrEF (N=263)	HFpEF (N=273)	No-HF (N=183)
C16	Palmitoyl-carnitine	<0.0001	0.003	<0.0001	0.0004	0.105 (0.036)	0.097 (0.030)	0.084 (0.026)
C18:2	Linoleyl-carnitine	<0.0001	<0.0001	<0.0001	0.04	0.100 (0.047)	0.083 (0.040)	0.073 (0.028)
C18:1	Oleyl-carnitine	<0.0001	<0.0001	<0.0001	0.006	0.185 (0.077)	0.160 (0.070)	0.137 (0.053)
C18	Stearoyl-carnitine	<0.0001	0.13	<0.0001	0.007	0.049 (0.017)	0.046 (0.015)	0.041 (0.017)
C16:1-OH/ C14:1-DC	3-hydroxy-palmitoleoyl-carnitine or cis-5-tetradecenedioyl-carnitine	<0.0001	0.006	<0.0001	0.06	0.012 (0.006)	0.010 (0.005)	0.009 (0.004)
C20:4	Arachidinoyl-carnitine	<0.0001	0.0003	<0.0001	0.69	0.010 (0.006)	0.008 (0.005)	0.008 (0.004)

* *P* values for multivariate ANCOVA, adjusted for age, race, sex, body mass index, number of diseased coronary arteries, and history of diabetes, hypertension, dyslipidemia, smoking, glomerular filtration rate, batch, and lipoprotein insulin resistance score (LP-IR). † *P* values reflect between-group pairwise contrasts generated from the fully adjusted ANCOVA. ‡ Values are unadjusted mean concentrations. Standard deviation is provided beneath each value. Abbreviations: HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ANCOVA, analysis of covariance; C, carbon chain length.

TABLE S9: Adjusted Individual Metabolite Means and Comparisons Between HFpEF, HFrEF, and No-HF Controls, Controlling for Insulin Resistance but NOT Diabetes

Metabolites		ANCOVA*	Pairwise Comparisons†			Mean Concentration in µM‡		
Structure	Trivial Name		HFrEF vs HFpEF	HFrEF vs No-HF	HFpEF vs No-HF	HFrEF (N=263)	HFpEF (N=273)	No-HF (N=183)
C16	Palmitoyl-carnitine	<0.0001	0.003	<0.0001	0.0005	0.105 (0.036)	0.097 (0.030)	0.084 (0.026)
C18:2	Linoleyl-carnitine	<0.0001	<0.0001	<0.0001	0.04	0.100 (0.047)	0.083 (0.040)	0.073 (0.028)
C18:1	Oleyl-carnitine	<0.0001	<0.0001	<0.0001	0.009	0.185 (0.077)	0.160 (0.070)	0.137 (0.053)
C18	Stearoyl-carnitine	<0.0001	0.13	<0.0001	0.007	0.049 (0.017)	0.046 (0.015)	0.041 (0.017)
C16:1-OH/ C14:1-DC	3-hydroxy-palmitoleoyl-carnitine or cis-5-tetradecenedioyl-carnitine	<0.0001	0.007	<0.0001	0.046	0.012 (0.006)	0.010 (0.005)	0.009 (0.004)
C20:4	Arachidinoyl-carnitine	<0.0001	0.0003	<0.0001	0.85	0.010 (0.006)	0.008 (0.005)	0.008 (0.004)

* *P* values for multivariate ANCOVA, adjusted for age, race, sex, body mass index, number of diseased coronary arteries, hypertension, dyslipidemia, smoking, glomerular filtration rate, batch, and lipoprotein insulin resistance score (LP-IR). † *P* values reflect between-group pairwise contrasts generated from the fully adjusted ANCOVA. ‡ Values are unadjusted mean concentrations. Standard deviation is provided beneath each value. Abbreviations: HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; ANCOVA, analysis of covariance; C, carbon chain length.

Table S10. Plasma LCAC Means for Primary and Additional Cohorts*						
	HFrEF		HFpEF		No-HF	
Metabolite	Primary Analysis (N=273)	HF-ACTION Trial (N=453)	Primary Analysis (N=263)	RELAX Trial (N=161)	No-HF (N=180)	CATHGEN Overall (N=3653)
C16	0.105 (0.04)	0.081 (0.03)	0.097 (0.03)	0.099 (0.030)	0.084 (0.03)	0.082 (0.026)
C18:2	0.099 (0.05)	0.055 (0.03)	0.084 (0.04)	0.080 (0.035)	0.072 (0.03)	0.070 (0.033)
C18:1	0.185 (0.08)	0.120 (0.05)	0.161 (0.07)	0.138 (0.055)	0.137 (0.05)	0.150 (0.066)
C18	0.050 (0.02)	0.044 (0.01)	0.047 (0.02)	0.043 (0.013)	0.041 (0.02)	0.041 (0.018)
C16:1-OH/ C14:1-DC	0.011 (0.01)	0.007 (0.003)	0.010 (0.005)	0.009 (0.004)	0.009 (0.004)	0.008 (0.004)
C20:4	0.010 (0.01)	0.006 (0.004)	0.008 (0.01)	0.008 (0.004)	0.007 (0.004)	0.007 (0.005)
Values are unadjusted means in uM with standard deviation below.						

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