SUPPLEMENTAL MATERIAL

Table S1. In house metabolite library.

Metabolites	% excluded before analysis	mass (m/z)	retention time (min)	HMDB ID	Normalization method
Urea	0.2%	60.032	1.98	HMDB00294	LOESS
Trimethylamine-N-oxide	3.2%	75.068	4.28	HMDB00925	LOESS
Alanine	0.2%	89.048	7.5	HMDB00161	Internal Standard
Sarcosine	11.0%	89.048	7.27	HMDB00271	LOESS
Dimethylglycine	1.0%	103.063	6.59	HMDB00092	Internal Standard
2-Aminoisobutyric acid	0.5%	103.064	6.9	HMDB01906	LOESS
Choline	0.2%	104.108	4.01	HMDB00097	Internal Standard
Serine	0.3%	105.043	8.56	HMDB00187	Internal Standard
Creatinine	0.2%	113.059	4.55	HMDB00562	LOESS
Proline	0.4%	115.063	6.64	HMDB00162	Internal Standard
Guanidineacetate	0.0%	117.054	7.56	HMDB00128	LOESS
Betaine	0.4%	118.087	6.14	HMDB00043	Internal Standard
Valine	0.0%	118.087	6.57	HMDB00883	Internal Standard
Threonine	0.6%	119.058	7.85	HMDB00167	Internal Standard
Nicotinamide	0.6%	122.048	1.36	HMDB01406	Internal Standard
Taurine	0.2%	125.015	6.62	HMDB00251	Internal Standard
Pyroglutamate	0.7%	129.043	2.56	HMDB00267	LOESS
N.Methylproline	6.3%	129.079	6.25	HMDB94696	LOESS
Pipecolate	1.8%	129.079	6.84	HMDB00716	LOESS
Creatine	0.1%	131.07	7.19	HMDB00064	LOESS
Isoleucine	0.3%	131.095	6.09	HMDB00172	Internal Standard
Leucine	0.1%	131.095	5.92	HMDB00687	Internal Standard
Asparagine	0.2%	132.053	8.7	HMDB00168	Internal Standard
Ornithine	0.3%	132.09	11.58	HMDB00214	Internal Standard
Hypoxanthine	0.2%	136.039	3.8	HMDB00157	LOESS
Trigonelline	5.9%	137.048	6.38	HMDB00875	LOESS
Methylnicotinamide	0.8%	137.071	4.96	HMDB03152	Internal Standard
Urocanate	4.7%	138.042	2.38	HMDB00301	LOESS
Proline betaine	0.8%	143.095	6.21	HMDB04827	LOESS
Glutamine	0.1%	146.069	8.48	HMDB00641	Internal Standard
Lysine	0.2%	146.106	11.4	HMDB00182	Internal Standard
4-Trimethylammoniobutanoic acid	0.6%	146.118	4.58	HMDB01161	LOESS
Glutamate	0.2%	147.053	8.14	HMDB00148	Internal Standard
Methionine	0.2%	149.051	6.32	HMDB00696	Internal Standard
N-Methyl-4-pyridone-3-carboxamide	1.1%	152.058	1.92	HMDB04194	LOESS
N-Methyl-2-pyridone-5-carboxamide	1.00%	152.0586	1.72	NA	LOESS
Homostachydrine	2.3%	157.11	6.02	HMDB33433	LOESS
Methyllysine	0.0%	160.121	10.66	HMDB02038	LOESS

Carnitine	1.4%	162.113	6.19	HMDB00062	Internal Standard
Methionine.S.oxide	6.0%	165.046	8.23	HMDB02005	LOESS
7-Methylguanine	0.3%	165.065	4.77	HMDB00897	LOESS
Phenylalanine	0.4%	165.079	5.88	HMDB00159	Internal Standard
1-Methylhistidine	0.4%	169.085	9.72	HMDB00001	LOESS
3-Methylhistidine	2.3%	169.085	10.82	HMDB00479	LOESS
Acetylornithine	0.7%	174.102	7.86	HMDB03357	LOESS
Arginine	0.2%	174.112	10.92	HMDB00517	Internal Standard
Dimethyllysine	0.10%	174.137	9.95	NA	LOESS
Citrulline	0.3%	175.095	9.04	HMDB00904	Internal Standard
Cotinine	71.10%	176.095	1.33	NA	LOESS
Hippurate	2.4%	179.058	1.14	HMDB00714	LOESS
Paraxanthine	2.1%	180.065	1.33	HMDB01860	LOESS
Tyrosine	6.3%	181.074	6.64	HMDB00158	Internal Standard
Acisoga	0.4%	184.121	1.63	HMDB61384	LOESS
Histidine	0.3%	188.127	10.56	HMDB00177	Internal Standard
Homoarginine	0.3%	188.127	10.59	HMDB00670	LOESS
NMMA	0.2%	188.127	10.2	HMDB29416	LOESS
Kynurenate	0.8%	189.043	5.06	HMDB00715	LOESS
Homocitrulline	3.3%	189.111	8.86	HMDB00679	LOESS
Trimethyllysine	1.0%	189.16	10.14	HMDB01325	LOESS
Hydroxycotinine	96.80%	192.09	1.75	NA	LOESS
Caffeine	16.2%	194.08	1	HMDB01847	LOESS
5-Acetylamino-6-amino-3-methyluracil	13.8%	198.075	4.61	HMDB04400	LOESS
DMGV	1.7%	202.119	6.01	HMDB0240212	LOESS
Asymmetric dimethylarginine	1.3%	202.143	9.52	HMDB01539	Internal Standard
Symmetric dimethylarginine	2.0%	202.143	9.51	HMDB03334	LOESS
Tryptophan	0.3%	204.09	5.93	HMDB00929	Internal Standard
Acylcarnitine C2:0	0.3%	204.124	4.45	HMDB00201	Internal Standard
3-Hydroxytrimethyllysine	0.7%	205.155	10.8	HMDB01422	LOESS
Kynurenine	0.3%	208.085	6	HMDB00684	LOESS
Acetylarginine	0.3%	216.122	7.08	HMDB04620	LOESS
Acylcarnitine C3:0	0.4%	218.139	4.06	HMDB00824	Internal Standard
Pantothenate	1.2%	219.111	1.63	HMDB00210	LOESS
Ergothioneine	1.1%	229.088	7.35	HMDB03045	LOESS
Acylcarnitine C4:0	1.2%	232.154	3.63	HMDB02013	Internal Standard
Cystine	0.1%	240.024	13.02	HMDB00192	LOESS
Tiglylcarnitine	2.9%	243.147	3.46	HMDB02366	LOESS
Acylcarnitine C5:0	0.6%	245.163	3.23	HMDB00688	LOESS
Acylcarnitine C4:0-OH	23.90%	247.142	4.7	NA	LOESS
Glycerophosphocholine	0.5%	258.11	8.71	HMDB00086	LOESS
Acylcarnitine C6:0	0.7%	260.186	2.88	HMDB00756	LOESS
Phenylacetylglutamine	0.6%	264.11	1.98	HMDB06344	LOESS
Acetylcarnosine	0.4%	268.117	8.04	HMDB12881	LOESS

1-Methyladenosine	0.2%	281.113	6.46	HMDB03331	LOESS
Piperine	1.50%	285.137	0.85	NA	LOESS
Acylcarnitine C8:1	0.6%	286.202	2.73	HMDB13324	LOESS
Acylcarnitine C8:0	0.9%	288.217	2.49	HMDB00791	Internal Standard
5-Methylthioadenosine	4.1%	297.09	2.08	HMDB01173	LOESS
Acylcarnitine C9:0	0.7%	302.233	2.23	HMDB13288	LOESS
Acylcarnitine C8:0-OH	0.5%	304.212	4.06		LOESS
Acylcarnitine C10:3	0.8%	310.202	2.42		LOESS
N2.N2.Dimethylguanosin e	0.5%	311.123	4.74	HMDB04824	LOESS
Acylcarnitine C10:2	0.6%	312.217	2.44		LOESS
Acylcarnitine C10:1	1.0%	314.232	2.34	HMDB13205	LOESS
Acylcarnitine C10:0	0.7%	316.249	2.18	HMDB00651	LOESS
Acylcarnitine C11:1	0.3%	328.248	2.28		LOESS
Acylcarnitine C11:0	0.6%	330.263	2.14	HMDB13321	LOESS
Acylcarnitine C10:0-OH	1.0%	332.244	3.52		LOESS
Acylcarnitine C12:2	1.0%	340.25	2.23		LOESS
Acylcarnitine C12:1	0.5%	342.263	2.16	HMDB13326	LOESS
Acylcarnitine C12:0	0.4%	344.279	2.13	HMDB02250	LOESS
Acylcarnitine C13:1	0.8%	356.279	2.1		LOESS
Acylcarnitine C13:0	0.8%	358.295	2.03		LOESS
Acylcarnitine C14:2	0.5%	368.28	2.08	HMDB13331	LOESS
Acylcarnitine C14:1	0.4%	370.294	2.03	HMDB0240588	LOESS
Acylcarnitine C14:0	0.4%	372.311	1.94	HMDB05066	Internal Standard
Acylcarnitine C16:1	0.4%	398.326	1.93	HMDB13207	LOESS
25-Hydroxyvitamin D3	0.7%	400.334	0.81	HMDB03550	LOESS
Acylcarnitine C16:0	0.3%	400.343	1.85	HMDB00222	Internal Standard
Acylcarnitine C18:2	0.4%	424.346	1.87		LOESS
Acylcarnitine C18:1	0.3%	426.357	1.86		LOESS
Acylcarnitine C18:0	0.4%	428.372	1.84	HMDB00848	LOESS
Beta-carotene	0.6%	536.438	0.83	HMDB00561	LOESS
In-house metabolite library. Samples with differed more 4SD from the mean after normalization were excluded from analyses.					

Table S2. Cox proportional hazard models associating metabolite levels with risk for incident atrial fibrillation.

Metabolite	P model 1	p_fdr model 1	HR model 1	95% lowint	95% highint	p model 2	HR model 2	95% lowint	95% highint
Caffeine	3E-05	0.003	1.21	1.10	1.32	0.0012	1.17	1.06	1.28
Acylcarnitine C16:1	7E-05	0.004	1.18	1.09	1.28	0.0044	1.13	1.04	1.23
Acylcarnitine C14:0	0.0002	0.009	1.16	1.07	1.26	0.0024	1.14	1.05	1.24
Acylcarnitine C2:0	0.0005	0.01	1.15	1.06	1.25	0.06	1.09	1.00	1.18
Acisoga	0.0005	0.01	1.15	1.06	1.24	0.05	1.08	1.00	1.18
Beta-carotene	0.0006	0.01	0.86	0.79	0.94	0.02	0.90	0.82	0.99
Acylcarnitine C16:0	0.0009	0.01	1.14	1.06	1.23	0.05	1.09	1.00	1.18
Acylcarnitine C14:1	0.0009	0.01	1.15	1.06	1.24	0.007	1.12	1.03	1.22
Acylcarnitine C8:1	0.002	0.02	1.14	1.05	1.23	0.05	1.09	1.00	1.19
Ergothioneine	0.002	0.03	1.15	1.05	1.25	0.1	1.08	0.98	1.19
Acylcarnitine C12:0	0.003	0.03	1.13	1.04	1.22	0.01	1.11	1.03	1.21
Acylcarnitine C18:1	0.003	0.03	1.13	1.04	1.22	0.03	1.10	1.01	1.19
N2.N2.Dimethylguanosine	0.003	0.03	1.12	1.04	1.21	0.8	1.01	0.93	1.10
Acylcarnitine C8:0-OH	0.004	0.03	1.14	1.04	1.24	0.03	1.10	1.01	1.21
Acylcarnitine C12:1	0.006	0.05	1.12	1.03	1.21	0.06	1.08	1.00	1.18
Isoleucine	0.007	0.05	1.12	1.03	1.22				
Trimethylamine-N-oxide	0.009	0.06	1.15	1.04	1.28				
Acylcarnitine C13:0	0.01	0.08	1.11	1.02	1.20				
Acylcarnitine C11:1	0.01	0.09	1.10	1.02	1.20				
Acetylcarnosine	0.02	0.09	0.88	0.79	0.98				
Acylcarnitine C10:0-OH	0.02	0.1	1.10	1.02	1.19				
1-Methyladenosine	0.02	0.1	1.10	1.02	1.19				
Trimethyllysine	0.02	0.1	1.14	1.02	1.27				
Acylcarnitine C13:1	0.02	0.1	1.10	1.02	1.20				
Acylcarnitine C10:3	0.02	0.1	1.11	1.01	1.21				
Acylcarnitine C6:0	0.02	0.1	1.11	1.01	1.21				
Paraxanthine	0.03	0.1	1.10	1.01	1.19				
7-Methylguanine	0.03	0.1	1.09	1.01	1.18				
Glutamate	0.03	0.1	1.09	1.01	1.18				
Acylcarnitine C18:2	0.03	0.1	1.09	1.01	1.18				
1-Methylhistidine	0.03	0.1	1.09	1.01	1.19				
Taurine	0.04	0.1	1.09	1.01	1.18				
Acylcarnitine C8:0	0.04	0.1	1.10	1.01	1.20				
Acylcarnitine C10:2	0.04	0.1	1.10	1.00	1.20				
4-Trimethylammoniobutanoic acid	0.04	0.1	0.91	0.84	1.00				

Kynurenine	0.04	0.1	1.09	1.00	1.18				
25-Hydroxyvitamin D3	0.05	0.1	1.09	1.00	1.19				
Hypoxanthine	0.06	0.2	1.08	1.00	1.17				
Acylcarnitine C10:0	0.07	0.2	1.08	0.99	1.18				
5-Acetylamino-6-amino-3-methyluracil	0.07	0.2	1.09	0.99	1.20				
Guanidineacetate	0.09	0.3	0.93	0.85	1.01				
DMGV	0.09	0.3	1.07	0.99	1.17				
Glutamine	0.1	0.3	0.94	0.87	1.01				
Glycerophosphocholine	0.1	0.3	0.93	0.86	1.02				
Cystine	0.1	0.3	1.06	0.99	1.15				
Methionine.S.oxide	0.1	0.3	1.13	0.97	1.32				
Acylcarnitine C14:2	0.1	0.3	1.07	0.98	1.16				
Acylcarnitine C12:2	0.1	0.3	1.07	0.98	1.15				
Dimethyllysine	0.1	0.3	1.06	0.98	1.15				
2-Aminoisobutyric acid	0.1	0.3	1.07	0.98	1.17				
5-Methylthioadenosine	0.2	0.3	0.94	0.87	1.02				
Acylcarnitine C5:0	0.2	0.3	1.07	0.98	1.16				
Methyllysine	0.2	0.3	1.05	0.98	1.14				
Creatine	0.2	0.3	1.06	0.97	1.16				
Leucine	0.2	0.3	1.06	0.97	1.16				
Choline	0.2	0.3	1.06	0.98	1.15				
Hydroxycotinine	0.2	0.3	0.73	0.46	1.15				
Acetylornithine	0.2	0.3	0.94	0.86	1.03				
Kynurenate	0.2	0.4	1.06	0.97	1.16				
Tyrosine	0.2	0.4	1.06	0.96	1.17				
Homocitrulline	0.2	0.4	1.05	0.97	1.15				
Phenylacetylglutamine	0.2	0.4	0.95	0.87	1.04				
Trigonelline	0.2	0.4	1.06	0.96	1.16				
NMMA	0.3	0.4	1.05	0.97	1.14				
Piperine	0.3	0.4	1.06	0.96	1.16				
Methylnicotinamide	0.3	0.5	0.95	0.86	1.04				
Pipecolate	0.3	0.5	1.07	0.95	1.21				
Proline betaine	0.3	0.5	0.95	0.87	1.04				
N.Methylproline	0.3	0.5	0.95	0.87	1.05				
Acylcarnitine C4:0	0.3	0.5	1.05	0.95	1.15				
Ornithine	0.4	0.6	1.04	0.96	1.13				
Tiglylcarnitine	0.4	0.6	1.04	0.95	1.14				
Asymmetric dimethylarginine	0.4	0.6	1.04	0.96	1.13				
Asparagine	0.4	0.6	0.96	0.89	1.05				

Pyroglutamate	0.4	0.6	0.96	0.89	1.05				
Urocanate	0.4	0.6	0.96	0.87	1.06				
Acylcarnitine C3:0	0.4	0.6	0.97	0.88	1.05				
Threonine	0.5	0.7	0.97	0.88	1.06				
3-Hydroxytrimethyllysine	0.5	0.7	1.03	0.95	1.13				
Nicotinamide	0.5	0.7	1.03	0.94	1.13				
Valine	0.5	0.7	1.03	0.95	1.11				
Tryptophan	0.5	0.7	1.03	0.95	1.11				
Homoarginine	0.5	0.7	0.97	0.89	1.06				
N-Methyl-4-pyridone-3-carboxamide	0.5	0.7	1.03	0.93	1.15				
Phenylalanine	0.6	0.7	1.02	0.94	1.11				
Creatinine	0.6	0.7	0.97	0.89	1.07				
Carnitine	0.6	0.7	0.96	0.84	1.10				
Histidine	0.6	0.7	0.98	0.90	1.06				
Arginine	0.6	0.7	0.98	0.90	1.06				
3-Methylhistidine	0.6	0.8	1.02	0.94	1.12				
Citrulline	0.6	0.8	0.98	0.90	1.07				
Methionine	0.7	0.8	0.98	0.91	1.07				
Homostachydrine	0.7	0.8	1.02	0.93	1.13				
N-Methyl-2-pyridone-5-carboxamide	0.8	0.9	1.02	0.91	1.14				
Alanine	0.8	0.9	1.01	0.93	1.10				
Dimethylglycine	0.8	0.9	1.01	0.92	1.11				
Hippurate	0.8	0.9	0.99	0.91	1.08				
Acylcarnitine C18:0	0.8	0.9	1.01	0.92	1.10				
Symmetric dimethylarginine	0.8	0.9	1.01	0.92	1.11				
Acylcarnitine C10:1	0.9	0.9	1.01	0.92	1.10				
Betaine	0.9	0.9	1.01	0.92	1.10				
Serine	0.9	0.9	1.01	0.93	1.09				
Acylcarnitine C9:0	0.9	0.9	0.99	0.91	1.08				
Proline	0.9	0.9	1.01	0.92	1.10				
Pantothenate	0.9	1.0	1.01	0.91	1.12				
Lysine	0.9	1.0	1.00	0.92	1.08				
Cotinine	0.9	1.0	1.01	0.87	1.16				
Acetylarginine	0.9	1.0	1.00	0.93	1.09				
Urea	0.9	1.0	1.00	0.92	1.09				
Acylcarnitine C11:0	1.0	1.0	1.00	0.92	1.08				
Acylcarnitine C4:0-OH	1.0	1.0	1.00	0.90	1.11				
Sarcosine	1.0	1.0	1.00	0.91	1.10				

Atrial Fibrillation incidence, n = 650

Model 1: Adjusted for sex and age

Model 2: adjusted for sex, age, body mass index (BMI), baseline smoking status, systolic blood pressure, alcohol intake, usage of anti-hypertensive medicine, N-terminal pro b-type natriuretic peptide, prevalent diabetes mellitus, prevalent heart failure and prevalent ischemic heart disease

HR = Hazard Ratio

95% lowint = 95% confidence interval, lower

95% highint = 95% confidence interval, higher

Table S3. Cox proportional hazard models further adjusted.

Metabolites	p	HR	95% lowint	95% highint
Caffeine	0.0014	1.16	1.06	1.28
Acylcarnitine.16:1	0.0021	1.14	1.05	1.24
Acylcarnitine.14:0	0.0018	1.14	1.05	1.24
Acylcarnitine.2:0	0.03	1.10	1.01	1.19
Acisoga	0.07	1.08	0.99	1.17
Beta.carotene	0.02	0.90	0.82	0.98
Acylcarnitine.16:0	0.04	1.09	1.00	1.18
Acylcarnitine.14:1	0.004	1.13	1.04	1.23
Acylcarnitine.8:1	0.06	1.08	1.00	1.18
Ergothioneine	0.05	1.10	1.00	1.20
Acylcarnitine.12:0	0.01	1.12	1.03	1.21
Acylcarnitine.18:1	0.02	1.11	1.02	1.20
N2,N2-Dimethylguanosine	0.54	1.03	0.94	1.12
Acylcarnitine.8:0:OH	0.02	1.11	1.02	1.22
Acylcarnitine.12:1	0.05	1.09	1.00	1.18

Cox proportional hazard models adjusted for sex, age, body mass index (BMI), baseline smoking status, systolic blood pressure, alcohol intake, usage of anti-hypertensive medicine, N-terminal pro b-type natriuretic peptide, prevalent diabetes mellitus, prevalent heart failure, prevalent ischemic heart disease, prevalent cancer, prevalent chronic obstructive pulmonary disease and estimated GFR.

HR = Hazard ratio

95 % lowint = 95% confidence interval, lower

95% highint = 95% confidence interval, higher

Table S4. Cox proportional hazard models for cardioembolic stroke.

Metabolites	p	p_fdr	HR	95% lowint	95% highint	P model 2	HR model 2	95% lowint model 2	95% highint model 2
Caffeine	0.03	0.47	1.30	1.02	1.65	0.05	1.29	1.00	1.67
Beta carotene	0.20	0.47	0.85	0.67	1.08	0.15	0.82	0.62	1.07
Acisoga	0.20	0.47	1.15	0.93	1.42	0.91	1.01	0.80	1.28
Acylcarnitine 8:0:OH	0.20	0.47	1.17	0.92	1.48	0.16	1.19	0.93	1.53
Acylcarnitine 16:1	0.21	0.47	1.15	0.92	1.45	0.27	1.15	0.90	1.47
Acylcarnitine 14:1	0.23	0.47	1.15	0.91	1.44	0.26	1.15	0.90	1.47
Acylcarnitine 12:0	0.30	0.47	1.12	0.90	1.40	0.26	1.15	0.90	1.45
N2,N2-Dimethylguanosine	0.33	0.47	1.11	0.90	1.38	0.73	1.04	0.82	1.32
Acylcarnitine 18:1	0.33	0.47	1.12	0.89	1.39	0.22	1.16	0.91	1.47
Acylcarnitine 2:0	0.33	0.47	1.12	0.89	1.40	0.53	1.08	0.84	1.39
Acylcarnitine 12:1	0.34	0.47	1.12	0.89	1.40	0.43	1.10	0.86	1.41
Acylcarnitine 14:0	0.42	0.50	1.10	0.87	1.38	0.52	1.08	0.85	1.39
Acylcarnitine 8:1	0.43	0.50	1.09	0.87	1.37	0.51	1.08	0.85	1.39
Acylcarnitine 16:0	0.66	0.70	1.05	0.84	1.31	0.90	1.02	0.79	1.31
Ergothioneine	0.82	0.82	1.03	0.80	1.34	0.65	0.93	0.70	1.25

Cardioembolic stroke incidence, n = 83

Model 1: Adjusted for sex and age

Model 2: adjusted for sex, age, body mass index (BMI), baseline smoking status, systolic blood pressure, alcohol intake, usage of anti-hypertensive medicine, LDL cholesterol, HDL cholesterol, prevalent diabetes mellitus, prevalent hear failure and prevalent ischemic heart disease.

HR = Hazard ratio

95% lowint = 95% confidence interval, lower

95% highint = 95% confidence interval, higher