

Supplemental Material, table of contents:

Page 2. Supplemental Table 1. Summary statistics and associations between 24hr urine chemistries and stone former status among 218 stone formers with calcium stones only. P-values are derived using log base 2-transformed 24hr urine chemistries, corrected for FDR and adjusted for age, age² and sex.

Page 3-6. Supplemental Table 2. Summary statistics and associations between 24hr concentrations of NMR-quantified metabolites and stone former status among 218 stone formers with calcium stones only. P-values are derived using log base 2-transformed 24hr urine chemistries, corrected for FDR and adjusted for age, age² and sex.

Page 7. Supplemental Table 3. Fold changes and P-values for associations between NMR-quantified metabolites and stone former status. P-values were derived using log base 2-transformed NMR metabolites, corrected for FDR, and adjusted for age, age², sex, cystatin C and 24hr urine protein.

Page 8. Supplemental Table 4. Unadjusted associations between the top 7 significant NMR-quantified metabolites from the ANCOVA analysis and time to stone recurrence.

Page 9. Supplemental Figure 1. Heatmap of Pearson correlations between the statistically significant 24hr-adjusted NMR-quantified metabolites and 24hr-adjusted urine chemistries that contribute to the difference between stone formers and controls.

Page 10. Supplemental Figure 2. Heatmaps of the urine chemistries and NMR-quantified urine metabolites by stone composition type. The lack of clustering observed in the dendrograms provides little evidence for stone compositions exhibiting a urine or metabolite profile.

Supplemental Table 1. Summary statistics and associations between 24hr urine chemistries and stone former status among 218 stone formers with calcium stones only. P-values are derived using log base 2-transformed 24hr urine chemistries, corrected for FDR and adjusted for age, age² and sex.

24hr urine chemistries	Controls (N=440)	Stone formers (N=218)	P-value
Calcium, mg/24hr			<0.001
Median (Q1, Q3)	134 (89.5, 194)	175 (114, 269)	
Range	12.3 - 659	13.3 - 694	
Oxalate, mg/24hr			<0.001
Median (Q1, Q3)	22.2 (16.6, 28.6)	19.2 (13.1, 27.0)	
Range	4.2 - 78.7	4.5 - 121.7	
Phosphate, mg/24hr			0.10
Median (Q1, Q3)	562 (412, 812)	666 (462, 906)	
Range	84.9 - 2426	85.0 - 2265	
Potassium, meq/24hr			0.10
Median (Q1, Q3)	46.0 (34.1, 65.1)	46.0 (31.4, 60.0)	
Range	9.6 - 337	7.9 - 130	
Magnesium, mg/24hr			0.20
Median (Q1, Q3)	82.1 (57.8, 113)	96.7 (64.1, 130)	
Range	4.7 - 483	7.5 - 356	
Creatinine, mg/24hr			0.30
Median (Q1, Q3)	929 (702, 1264)	1031 (742, 1361)	
Range	310 - 3848	329 - 2662	
Sodium, meq/24hr			0.70
Median (Q1, Q3)	114 (76.0, 159)	118 (81.0, 155)	
Range	22.6 - 579	26.5 - 447	
Urine Volume, L			0.70
Median (Q1, Q3)	1.72 (1.19, 2.37)	1.74 (1.28, 2.34)	
Range	0.44 - 4.42	0.28 - 5.18	
Citrate, mg/24hr			0.70
Median (Q1, Q3)	517 (350, 729)	559 (363, 738)	
Range	1.89 - 2155	37.1 - 2176	
Uric Acid, mg/24hr			0.70
Median (Q1, Q3)	389 (294, 542)	407 (297, 557)	
Range	79.7 - 1174	94.2 - 1284	
Urine pH			0.70
Median (Q1, Q3)	6.00 (6.00, 6.85)	6.05 (5.90, 6.50)	
Range	4.00 - 8.00	4.83 - 7.66	
Chloride, meq/24hr			>0.99
Median (Q1, Q3)	104 (70.9, 150)	104 (73.9, 140)	
Range	19.9 - 534	21.8 - 456	

P-values in bold denote statistical significance at the 0.05 level.

Median (Q1, Q3) are presented on the original scales.

Table is ordered by FDR-adjusted p-value based on ANCOVA model with main effects.

FDR, false discovery rate.

Supplemental Table 2. Summary statistics and associations between 24hr concentrations of NMR-quantified metabolites and stone former status among 218 stone formers with calcium stones only. P-values are derived using log base 2-transformed 24hr NMR-quantified metabolites, corrected for FDR and adjusted for age, age² and sex.

24hr NMR-quantified metabolites	Controls (N=440)	Stone formers (N=218)	P-value
Alanine, mmol/24hr			0.004
Median (Q1, Q3)	0.305 (0.204, 0.458)	0.359 (0.247, 0.560)	
Range	0.052 - 2.253	0.072 - 4.967	
2-Furoylglycine, mmol/24hr			0.005
Median (Q1, Q3)	0.085 (0.000, 0.190)	0.052 (0.000, 0.161)	
Range	0.000 - 0.944	0.000 - 0.522	
Hippuric acid, mmol/24hr			0.013
Median (Q1, Q3)	2.387 (1.516, 3.645)	2.226 (1.265, 3.105)	
Range	0.000 - 15.530	0.006 - 11.243	
Trimethylamine, mmol/24hr			0.013
Median (Q1, Q3)	0.005 (0.003, 0.009)	0.007 (0.004, 0.011)	
Range	0.000 - 0.675	0.000 - 0.473	
Trigonelline, mmol/24hr			0.022
Median (Q1, Q3)	0.166 (0.073, 0.339)	0.108 (0.054, 0.302)	
Range	0.000 - 2.142	0.006 - 1.169	
Lactic acid, mmol/24hr			0.064
Median (Q1, Q3)	0.222 (0.147, 0.330)	0.265 (0.171, 0.397)	
Range	0.000 - 6.221	0.038 - 11.626	
Glycine, mmol/24hr			0.14
Median (Q1, Q3)	1.297 (0.808, 2.021)	1.335 (0.928, 1.942)	
Range	0.010 - 5.525	0.245 - 11.413	
Creatine, mmol/24hr			0.16
Median (Q1, Q3)	0.155 (0.078, 0.452)	0.216 (0.106, 0.658)	
Range	0.000 - 20.677	0.000 - 18.066	
Imidazole, mmol/24hr			0.27
Median (Q1, Q3)	0.030 (0.000, 0.091)	0.000 (0.000, 0.079)	
Range	0.000 - 0.459	0.000 - 0.690	
4-Aminobutyric acid, mmol/24hr			0.30
Median (Q1, Q3)	0.000 (0.000, 0.050)	0.000 (0.000, 0.074)	
Range	0.000 - 0.608	0.000 - 0.755	
Dimethylamine, mmol/24hr			0.36
Median (Q1, Q3)	0.299 (0.242, 0.374)	0.322 (0.251, 0.420)	
Range	0.112 - 1.660	0.010 - 0.869	
Pyruvic acid, mmol/24hr			0.37
Median (Q1, Q3)	0.053 (0.036, 0.073)	0.055 (0.037, 0.082)	
Range	0.000 - 0.326	0.010 - 0.280	
Proline betaine, mmol/24hr			0.45
Median (Q1, Q3)	0.189 (0.085, 0.576)	0.159 (0.088, 0.403)	
Range	0.000 - 5.405	0.000 - 3.439	
Caffeine, mmol/24hr			0.50
Median (Q1, Q3)	0.252 (0.191, 0.350)	0.286 (0.202, 0.404)	
Range	0.070 - 14.198	0.104 - 32.743	
3-Hydroxybutyric acid, mmol/24hr			0.56

Median (Q1, Q3)	0.000 (0.000, 0.123)	0.000 (0.000, 0.147)	
Range	0.000 - 1.270	0.000 - 0.666	
Acetone, mmol/24hr			0.64
Median (Q1, Q3)	0.028 (0.020, 0.040)	0.030 (0.021, 0.045)	
Range	0.000 - 0.564	0.002 - 0.111	
Valine, mmol/24hr			0.65
Median (Q1, Q3)	0.037 (0.028, 0.052)	0.041 (0.028, 0.056)	
Range	0.000 - 0.190	0.000 - 0.201	
D-Lactose, mmol/24hr			0.76
Median (Q1, Q3)	0.156 (0.068, 0.263)	0.169 (0.086, 0.290)	
Range	0.000 - 7.760	0.000 - 16.907	
D-Glucose, mmol/24hr			0.77
Median (Q1, Q3)	0.422 (0.316, 0.564)	0.455 (0.336, 0.643)	
Range	0.043 - 288.215	0.101 - 689.483	
Citrate, mmol/24hr			0.77
Median (Q1, Q3)	3.237 (2.183, 4.450)	3.272 (2.147, 4.244)	
Range	0.018 - 12.549	0.026 - 9.115	
Fumaric acid, mmol/24hr			0.77
Median (Q1, Q3)	0.007 (0.005, 0.010)	0.007 (0.005, 0.011)	
Range	0.001 - 0.039	0.001 - 0.049	
Succinic acid, mmol/24hr			0.77
Median (Q1, Q3)	0.092 (0.058, 0.152)	0.091 (0.055, 0.136)	
Range	0.013 - 0.719	0.005 - 0.909	
Acetic acid, mmol/24hr			0.77
Median (Q1, Q3)	0.102 (0.077, 0.144)	0.114 (0.076, 0.173)	
Range	0.018 - 148.259	0.011 - 3.909	
Allantoin, mmol/24hr			0.77
Median (Q1, Q3)	0.164 (0.111, 0.229)	0.170 (0.111, 0.260)	
Range	0.012 - 0.703	0.000 - 0.593	
Formic acid, mmol/24hr			0.77
Median (Q1, Q3)	0.150 (0.105, 0.206)	0.150 (0.099, 0.209)	
Range	0.016 - 1.247	0.013 - 1.105	
D-Galactose, mmol/24hr			0.77
Median (Q1, Q3)	0.000 (0.000, 0.049)	0.000 (0.000, 0.052)	
Range	0.000 - 1.059	0.000 - 1.287	
Sarcosine, mmol/24hr			0.87
Median (Q1, Q3)	0.010 (0.007, 0.015)	0.010 (0.005, 0.017)	
Range	0.000 - 0.056	0.000 - 0.037	
2-Oxoglutaric acid, mmol/24hr			0.87
Median (Q1, Q3)	0.093 (0.047, 0.160)	0.107 (0.044, 0.171)	
Range	0.000 - 0.636	0.000 - 0.884	
D-Mannitol, mmol/24hr			0.87
Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 9.024	0.000 - 9.841	
N, N-Dimethylglycine, mmol/24hr			0.87
Median (Q1, Q3)	0.068 (0.046, 0.093)	0.071 (0.050, 0.096)	
Range	0.013 - 6.244	0.011 - 0.522	
2-Methylsuccinic acid, mmol/24hr			0.87

Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 0.200	0.000 - 0.316	
Tartaric acid, mmol/24hr			0.87
Median (Q1, Q3)	0.037 (0.022, 0.129)	0.036 (0.020, 0.142)	
Range	0.000 - 1.968	0.000 - 1.986	
Creatinine, mmol/24hr			0.95
Median (Q1, Q3)	11.008 (8.484, 14.212)	11.658 (8.898, 16.157)	
Range	0.313 - 47.666	0.140 - 33.728	
Methionine, mmol/24hr			0.95
Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 0.210	0.000 - 0.092	
1-Methylhistidine, mmol/24hr			0.95
Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 0.630	0.000 - 0.984	
Betaine, mmol/24hr			0.99
Median (Q1, Q3)	0.135 (0.081, 0.202)	0.132 (0.082, 0.217)	
Range	0.000 - 7.181	0.000 - 5.663	
Arginine, mmol/24hr			0.99
Median (Q1, Q3)	0.644 (0.471, 0.881)	0.725 (0.519, 0.938)	
Range	0.000 - 39.823	0.000 - 12.346	
Oxaloacetic acid, mmol/24hr			0.99
Median (Q1, Q3)	0.201 (0.120, 0.342)	0.190 (0.122, 0.335)	
Range	0.000 - 2.846	0.022 - 3.854	
Guanidinoacetic acid, mmol/24hr			0.99
Median (Q1, Q3)	0.632 (0.433, 0.873)	0.669 (0.446, 1.003)	
Range	0.089 - 57.722	0.150 - 37.199	
Benzoic acid, mmol/24hr			0.99
Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 1.092	0.000 - 0.953	
Myo Inositol, mmol/24hr			0.99
Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 0.990	0.000 - 1.517	
1-Methylnicotinamide, mmol/24hr			0.99
Median (Q1, Q3)	0.080 (0.059, 0.107)	0.081 (0.058, 0.107)	
Range	0.019 - 5.431	0.014 - 2.831	
Inosine, mmol/24hr			0.99
Median (Q1, Q3)	0.034 (0.024, 0.055)	0.035 (0.021, 0.057)	
Range	0.000 - 1.370	0.000 - 0.649	
Acetoacetic acid, mmol/24hr			0.99
Median (Q1, Q3)	0.116 (0.082, 0.171)	0.116 (0.085, 0.180)	
Range	0.000 - 1.856	0.000 - 0.878	
Allopurinol, mmol/24hr			0.99
Median (Q1, Q3)	0.061 (0.043, 0.085)	0.062 (0.044, 0.090)	
Range	0.018 - 1.222	0.014 - 0.568	
Taurine, mmol/24hr			0.99
Median (Q1, Q3)	0.492 (0.200, 0.902)	0.477 (0.221, 0.892)	
Range	0.000 - 16.217	0.000 - 5.991	
D-Mandelic acid, mmol/24hr			0.99

Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 0.060	0.000 - 0.039	
D-Mannose, mmol/24hr			0.99
Median (Q1, Q3)	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)	
Range	0.000 - 2.093	0.000 - 2.761	

P-values in bold denote statistical significance at the 0.05 level.

Median (Q1, Q3) are presented on the original scales.

Table is ordered by FDR-adjusted p-value based on ANCOVA model with main effects.

FDR, false discovery rate.

Supplemental Table 3. Adjusted mean (SE), fold changes and P-values for associations between NMR-quantified metabolites and stone former status. Estimates were derived using log base 2-transformed NMR metabolites, corrected for FDR, and adjusted for age, age2, sex, cystatin C and 24hr urine protein. Fold change>1 corresponds to a higher level in stone formers.

24hr NMR-quantified metabolites	Controls (N=429)		Stone formers (N=407)		Fold Change	P-value
	Adjusted Mean	Adjusted SE	Adjusted Mean	Adjusted SE		
Hippuric acid, mmol/24hr	1.150	0.055	0.816	0.057	0.793	0.002
Creatine, mmol/24hr	-2.492	0.105	-1.879	0.108	1.529	0.002
Trigonelline, mmol/24hr	-2.719	0.071	-3.114	0.073	0.760	0.002
Alanine, mmol/24hr	-1.720	0.039	-1.505	0.041	1.161	0.002
Imidazole, mmol/24hr	-7.033	0.183	-7.972	0.188	0.522	0.004
2-Furoylglycine, mmol/24hr	-5.384	0.189	-6.351	0.194	0.512	0.004
Glycine, mmol/24hr	0.229	0.051	0.433	0.053	1.152	0.045
Lactic acid, mmol/24hr	-2.181	0.067	-1.966	0.069	1.161	0.17
Trimethylamine, mmol/24hr	-7.563	0.069	-7.346	0.071	1.162	0.17
Proline betaine, mmol/24hr	-2.264	0.101	-2.566	0.103	0.811	0.20
4-Aminobutyric acid, mmol/24hr	-8.702	0.176	-8.287	0.181	1.334	0.47
Citrate, mmol/24hr	1.492	0.055	1.392	0.056	0.933	0.82
Acetic acid, mmol/24hr	-3.133	0.056	-3.039	0.057	1.068	0.82
Betaine, mmol/24hr	-2.977	0.082	-3.111	0.084	0.911	0.82
1-Methylnicotinamide, mmol/24hr	-3.636	0.040	-3.701	0.041	0.956	0.82
Succinic acid, mmol/24hr	-3.454	0.052	-3.534	0.053	0.946	0.82
Allantoin, mmol/24hr	-2.663	0.041	-2.725	0.042	0.958	0.82
Tartaric acid, mmol/24hr	-4.391	0.099	-4.538	0.102	0.903	0.82
Valine, mmol/24hr	-4.791	0.039	-4.735	0.040	1.040	0.82
3-Hydroxybutyric acid, mmol/24hr	-7.615	0.202	-7.335	0.208	1.214	0.82
Pyruvic acid, mmol/24hr	-4.315	0.041	-4.261	0.042	1.039	0.84
Allopurinol, mmol/24hr	-3.988	0.037	-4.033	0.038	0.969	0.88
2-Oxoglutaric acid, mmol/24hr	-4.337	0.145	-4.493	0.149	0.898	0.94
Sarcosine, mmol/24hr	-7.112	0.090	-7.207	0.093	0.936	0.94
Benzoic acid, mmol/24hr	-9.602	0.140	-9.463	0.144	1.101	0.95
Inosine, mmol/24hr	-4.773	0.059	-4.826	0.061	0.963	0.95
D-Mannitol, mmol/24hr	-8.780	0.213	-8.962	0.219	0.882	0.95
D-Mandelic acid, mmol/24hr	-10.566	0.063	-10.613	0.065	0.968	0.95
Fumaric acid, mmol/24hr	-7.198	0.044	-7.166	0.046	1.022	0.95
Caffeine, mmol/24hr	-1.791	0.048	-1.823	0.049	0.979	0.95
Oxaloacetic acid, mmol/24hr	-2.379	0.070	-2.423	0.072	0.970	0.95
D-Mannose, mmol/24hr	-9.357	0.140	-9.437	0.144	0.946	0.95
Acetone, mmol/24hr	-5.152	0.043	-5.128	0.044	1.017	0.95
N, N-Dimethylglycine, mmol/24hr	-3.875	0.038	-3.891	0.039	0.989	0.95
Creatinine, mmol/24hr	3.467	0.028	3.456	0.029	0.992	0.95
2-Methylsuccinic acid, mmol/24hr	-9.878	0.126	-9.834	0.130	1.032	0.95
Formic acid, mmol/24hr	-2.796	0.041	-2.808	0.042	0.991	0.95
Taurine, mmol/24hr	-1.643	0.128	-1.607	0.132	1.025	0.95
D-Glucose, mmol/24hr	-0.886	0.078	-0.908	0.080	0.985	0.95
Guanidinoacetic acid, mmol/24hr	-0.510	0.058	-0.494	0.060	1.011	0.95
Arginine, mmol/24hr	-1.021	0.115	-1.050	0.119	0.980	0.95
D-Galactose, mmol/24hr	-7.877	0.171	-7.836	0.176	1.029	0.95
Methionine, mmol/24hr	-9.938	0.109	-9.963	0.112	0.983	0.95
Acetoacetic acid, mmol/24hr	-3.315	0.081	-3.333	0.084	0.988	0.95
Dimethylamine, mmol/24hr	-1.722	0.027	-1.718	0.028	1.003	0.95
1-Methylhistidine, mmol/24hr	-9.426	0.147	-9.408	0.151	1.013	0.95
D-Lactose, mmol/24hr	-2.892	0.078	-2.884	0.081	1.006	0.95
Myo Inositol, mmol/24hr	-10.537	0.097	-10.545	0.099	0.994	0.95

P-values in bold denote statistical significance at the 0.05 level.

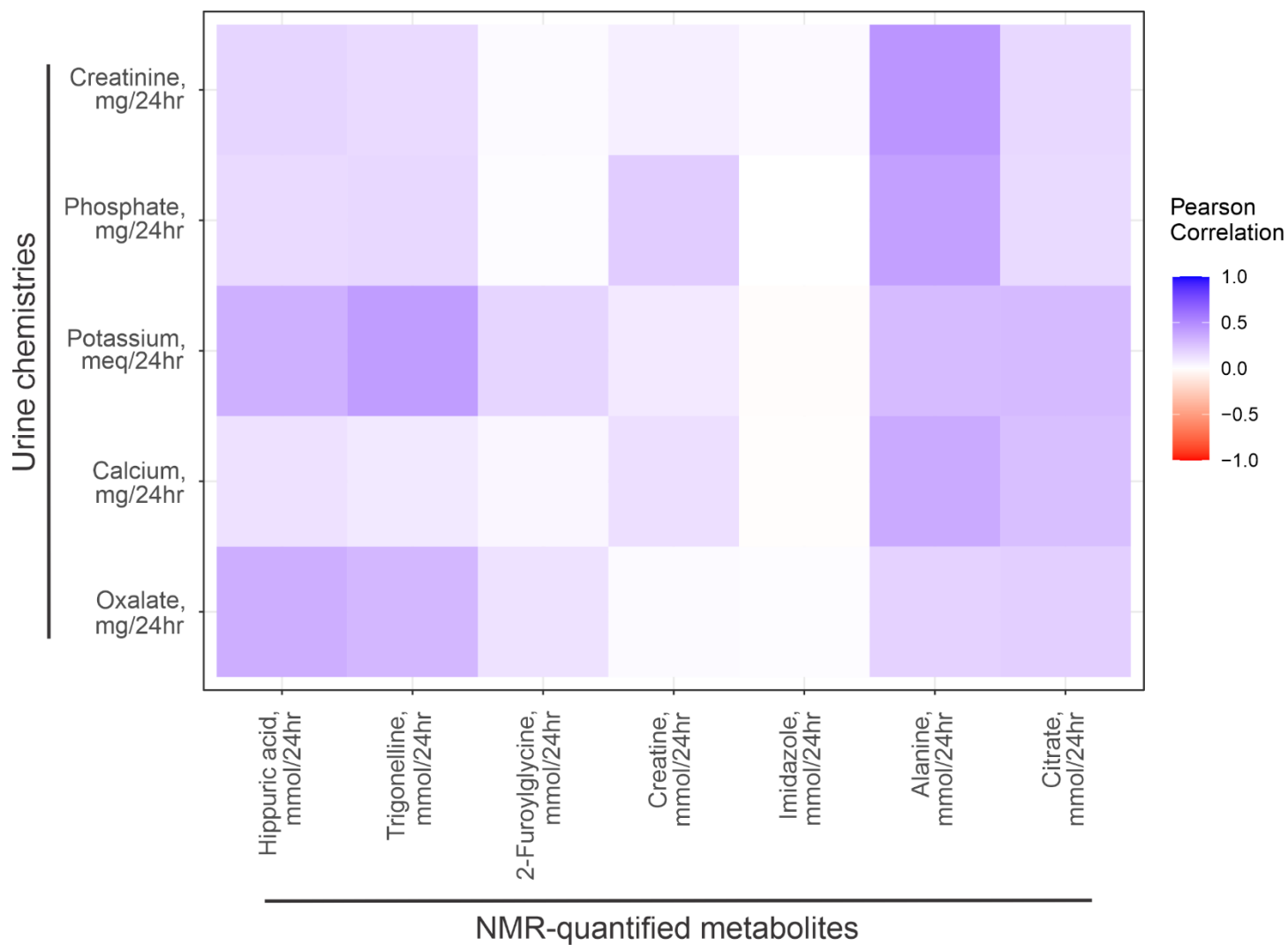
Table is ordered by FDR-adjusted p-value based on ANCOVA model with main effects.

FDR, false discovery rate.

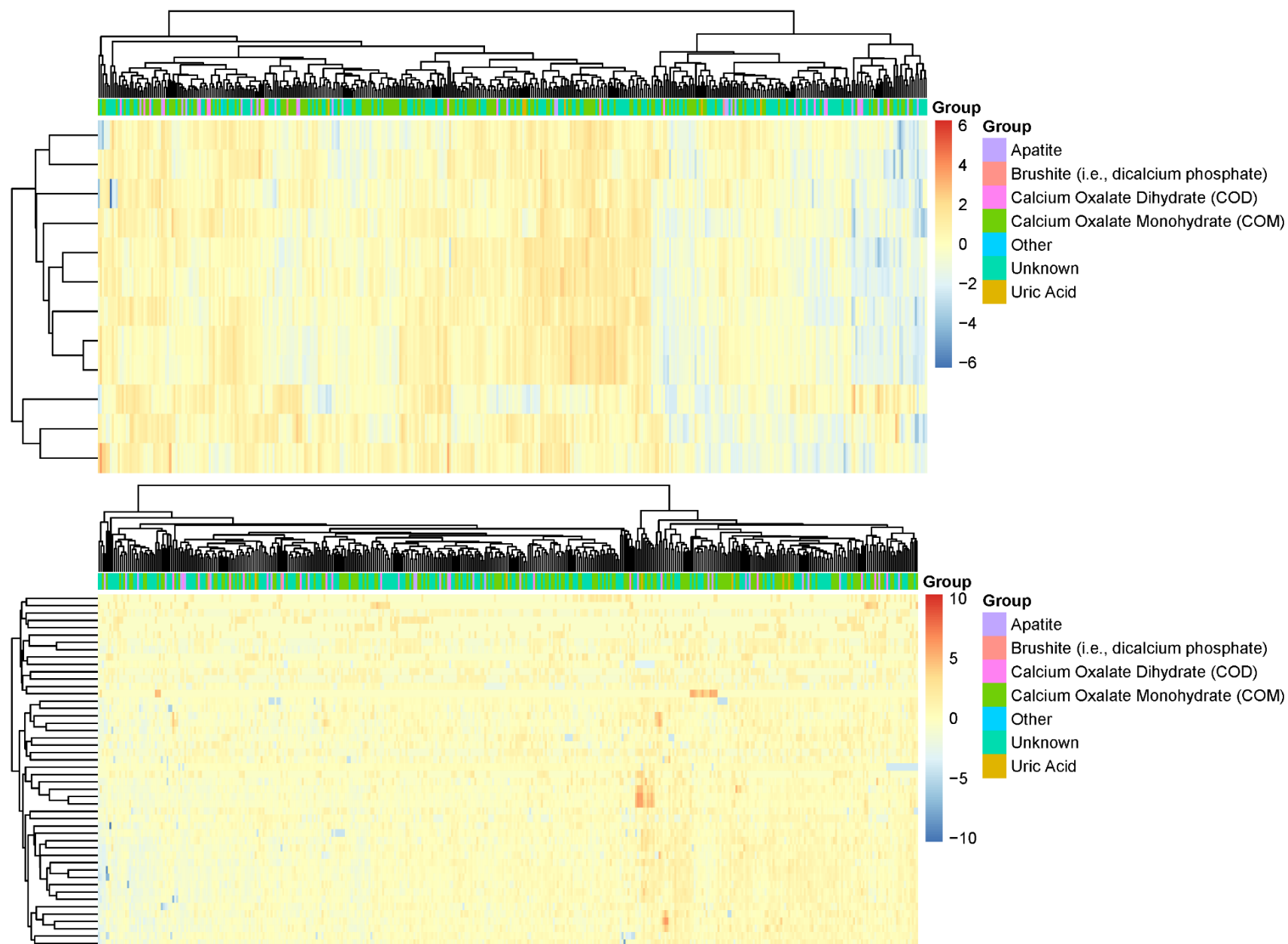
Supplemental Table 4. Unadjusted associations between the top 7 significant NMR-quantified metabolites from the ANCOVA analysis and time to stone recurrence.

24hr NMR-quantified metabolites	HR (95% CI)	P-value
Hippuric acid, mmol/24hr	1.03 (0.91, 1.16)	0.62
Trigonelline, mmol/24hr	0.99 (0.39, 2.55)	0.99
2-Furoylglycine, mmol/24hr	0.43 (0.06, 3.07)	0.39
Creatine, mmol/24hr	0.94 (0.79, 1.13)	0.51
Imidazole, mmol/24hr	1.10 (0.06, 19.55)	0.95
Alanine, mmol/24hr	1.44 (0.85, 2.45)	0.17
Citrate, mmol/24hr	1.05 (0.93, 1.18)	0.45

HR, Hazard ratio; CI, confidence interval.



Supplemental Figure 1. Heatmap of Pearson correlations between the statistically significant 24hr-adjusted NMR-quantified metabolites and 24hr-adjusted urine chemistries that contribute to the difference between stone formers and controls.



Supplemental Figure 2. Heatmaps of the urine chemistries (top panel) and NMR-quantified urine metabolites (bottom panel) by stone composition type. The lack of clustering observed in the dendrograms provides little evidence for stone compositions exhibiting a urine or metabolite profile.