

**Supplementary Table 1** Quality control metrics (CV% and missing rate) for each metabolite.

Metabolite	CV%	Missing rate (%)
Acylcarnitines	C2	3.83
	C3	6.37
	C4	7.50
	C4-DC	8.20
	C4-OH <sup>1</sup>	20.20
	C5 <sup>1</sup>	10.72
	C5:1	11.80
	C5-DC	6.85
	C5-OH/C3-DC	8.19
	C6	6.71
	C7-DC	8.17
	C8	10.36
	C8:1	11.95
	C8:1-DC <sup>1</sup>	16.41
	C8:1-OH/C6-DC <sup>1</sup>	17.00
	C8-DC	12.19
	C8-OH/C6-DC	10.77
	C10	7.90
	C10:1	11.22
	C10:2	16.52
	C10:3	13.35
	C12	10.17
	C12:1	9.28
	C12-OH/C10-DC <sup>1</sup>	80.39
	C14	10.58
	C14:1	10.29
	C14:1-OH	14.14
	C14:2	11.55
	C14-OH/C12-DC	16.05
	C16	5.99
	C16:1	9.80
	C16:1-OH/C14:1-DC	17.84
	C16:2	17.30
C16-OH	18.58	
C18	8.59	
C18:1	5.72	
C18:1-DC	17.21	
C18:1-OH/C16:1-DC <sup>1</sup>	21.44	
C18:2	7.02	
C18:2-OH	18.92	
C18-DC/C20-OH	16.96	
C18-OH/C16-DC <sup>1</sup>	22.76	
C20	19.45	
C20:4	16.43	
C22 <sup>1</sup>	29.85	
Amino acids	Alanine	4.23
	Arginine	7.54
	Citrulline	8.64
	Glutamate/Glutamine	6.04
	Glycine	5.06
	Histidine	5.33
	Isoleucine/Leucine	4.74
	Methionine	7.24
	Ornithine	6.79
	Phenylalanine	4.48
	Proline	5.17
	Serine	4.50
	Tyrosine	5.61
Valine	3.95	

<sup>1</sup> Metabolites subsequently removed from analysis during quality control.

**Supplementary Table 2** Full panel of metabolites measured for this study and summary of functional groups.

	Abbreviation	Biochemical name	Functional group	
Acylcarnitines	C2	Acetylcarnitine	short chain acylcarnitines	
	C3	Propionylcarnitine		
	C4 <sup>1</sup>	Butyrylcarnitine/Isobutyrylcarnitine <sup>1</sup>		
	C4-DC	Succinylcarnitine		
	C4-OH <sup>2</sup>	3-Hydroxybutyrylcarnitine/Hydroxybutyrylcarnitine <sup>2</sup>		
	C5 <sup>2</sup>	Isovalerylcarnitine <sup>2</sup>		
	C5:1	Tiglylcarnitine		
	C5-DC	Glutaryl carnitine		
	C5-OH/C3-DC <sup>1</sup>	3-Hydroxyvalerylcarnitine/Malonylcarnitine <sup>1</sup>		
	C6	Hexanoylcarnitine		
	C7-DC	Pimelylcarnitine		
	C8	Octanoylcarnitine		
	C8:1	Octenoylcarnitine		
	C8:1-DC <sup>2</sup>	Octenedioylcarnitine <sup>2</sup>		
	C8:1-OH/C6-DC <sup>1,2</sup>	3-Hydroxyoctenoylcarnitine/Adipoylcarnitine <sup>1,2</sup>		
	C8-DC	Suberylcarnitine		
	C8-OH/C6-DC <sup>1</sup>	3-Hydroxyoctanoylcarnitine/Adipoylcarnitine <sup>1</sup>		
	C10	Decanoylcarnitine		medium chain acylcarnitines
	C10:1	Decenoylcarnitine		
	C10:2	Decadienoylcarnitine		
	C10:3	Decatrienoylcarnitine		
	C12	Dodecanoylcarnitine		
	C12:1	Dodecenoylcarnitine		
C12-OH/C10-DC <sup>1,2</sup>	3-Hydroxydodecanoylcarnitine/Sebacoylcarnitine <sup>1,2</sup>			
C14	Tetradecanoylcarnitine			
C14:1	Tetradecenoylcarnitine			
C14:1-OH	Hydroxytetradecenoylcarnitine			
C14:2	Tetradecadienoylcarnitine			
C14-OH/C12-DC <sup>1</sup>	3-Hydroxytetradecanoylcarnitine/Dodecanedioylcarnitine <sup>1</sup>			
C16	Hexadecanoylcarnitine	long chain acylcarnitines		
C16:1	Hexadecenoylcarnitine			
C16:1-OH/C14:1-DC <sup>1</sup>	3-Hydroxyhexadecenoylcarnitine/Tetradecenedioylcarnitine <sup>1</sup>			
C16:2	Hexadecadienoylcarnitine			
C16-OH	3-Hydroxyhexadecanoylcarnitine			
C18	Octadecanoylcarnitine			
C18:1	Octadecenoylcarnitine			
C18:1-DC	Octadecenoylcarnitine-dicarboxylic			
C18:1-OH/C16:1-DC <sup>1,2</sup>	3-Hydroxyoctadecenoylcarnitine/Hexadecenedioylcarnitine <sup>1,2</sup>			
C18:2	Octadecadienoylcarnitine			
C18:2-OH	3-Hydroxyoctadecadienoylcarnitine			
C18-DC/C20-OH <sup>1</sup>	Octadecanoylcarnitine-dicarboxylic/3-Hydroxyarachidoylcarnitine <sup>1</sup>			
C18-OH/C16-DC <sup>1,2</sup>	3-Hydroxyoctadecanoylcarnitine/Hexadecanoylcarnitine-dicarboxylic <sup>1,2</sup>			
C20	Arachidoylcarnitine			
C20:4	Arachidonoylcarnitine			
C22 <sup>1</sup>	Docosanoylcarnitine <sup>1</sup>			
Amino acids	Phe	Phenylalanine	aromatic amino acids <sup>3</sup>	
	Tyr	Tyrosine	branched-chain amino acids	
	Ile/Leu <sup>1</sup>	Isoleucine/Leucine <sup>1</sup>		
	Val	Valine	none	
	Ala	Alanine		
	Arg	Arginine		
	Cit	Citrulline		
	Glu/Gln <sup>1</sup>	Glutamate/Glutamine <sup>1</sup>		
	Gly	Glycine		
	His	Histidine		
	Met	Methionine		
	Orn	Ornithine		
	Pro	Proline		
	Ser	Serine		
(Ile/Leu + Val):(Tyr + Phe)	Fischer ratio			
Ala:Gly	Alanine-Glycine ratio			

<sup>1</sup> Metabolites measured in aggregate.<sup>2</sup> Metabolites subsequently removed from analysis during quality control.<sup>3</sup> Aromatic amino acids also include tryptophan, which was not measured in this analysis.

**Supplementary Table 3** Diagnostic and quality control metrics for the analysis of blood samples.**Location:** National University Hospital**Measurement platform:** ADVIA 2400 (Siemens Healthcare Laboratory Diagnostic, USA)

Measurement	Method	Within-day CV%	Between-day CV%
Fasting plasma glucose	Glucose oxidase	< 0.76	< 5.68
Serum triglycerides	GPO, Trinder without serum blank	< 0.95	< 1.30
High-density lipoprotein cholesterol	Elimination/catalase	< 5.78	< 4.14
Fasting insulin	Microparticle enzyme immunoassay	< 4.00	< 6.29

**Location:** Singapore General Hospital**Measurement platform:** Unicel DxC 800 (Beckman Coulter, USA)

Measurement	Method	Within-day CV%	Between-day CV%
Fasting plasma glucose	Oxygen rate	< 1.70	< 3.30
Serum triglycerides	Spectrophotometry, timed-endpoint	< 0.90	< 2.10
High-density lipoprotein cholesterol	Spectrophotometry, timed-endpoint	< 1.80	< 2.50
Fasting insulin	Immunoenzymatic (Sandwich) assay	< 5.10	< 6.40

**Supplementary Table 4** Unadjusted associations between metabolites and incident diabetes. Significant associations following multiple testing are in bold.

Acylcarnitines	HR <sup>1</sup> (95% CI)	P-value	P-value <sup>2</sup>	Amino acids	HR (95% CI)	P-value	P-value <sup>2</sup>
C2	<b>1.134 (1.020, 1.260)</b>	<b>0.019</b>	<b>0.038</b>	Ala	<b>1.418 (1.278, 1.572)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C3	<b>1.128 (1.016, 1.251)</b>	<b>0.023</b>	<b>0.043</b>	Arg	0.922 (0.823, 1.033)	0.163	0.220
C4	<b>1.228 (1.117, 1.350)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	Cit	1.109 (0.997, 1.234)	0.057	0.100
C4-DC	<b>1.252 (1.131, 1.385)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	Glu/Gln	<b>1.423 (1.291, 1.569)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C5:1	<b>1.158 (1.043, 1.286)</b>	<b>0.006</b>	<b>0.017</b>	Gly	<b>0.733 (0.643, 0.836)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C5-DC	<b>1.132 (1.022, 1.253)</b>	<b>0.017</b>	<b>0.037</b>	His	0.924 (0.823, 1.037)	0.178	0.224
C5-OH/C3-DC	1.103 (0.991, 1.229)	0.074	0.123	Ile/Leu	<b>1.368 (1.237, 1.513)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C6	1.076 (0.969, 1.196)	0.172	0.222	Met	1.066 (0.956, 1.187)	0.249	0.295
C7-DC	0.909 (0.809, 1.022)	0.109	0.174	Orn	<b>1.292 (1.168, 1.430)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C8	<b>0.861 (0.759, 0.978)</b>	<b>0.021</b>	<b>0.041</b>	Phe	<b>1.307 (1.182, 1.446)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C8:1	<b>1.193 (1.086, 1.312)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	Pro	<b>1.215 (1.095, 1.349)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C8-DC	0.921 (0.819, 1.036)	0.172	0.222	Ser	<b>0.785 (0.697, 0.884)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C8-OH/C6-DC	0.966 (0.863, 1.081)	0.547	0.586	Tyr	<b>1.404 (1.272, 1.550)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10	<b>0.852 (0.749, 0.971)</b>	<b>0.016</b>	<b>0.036</b>	Val	<b>1.353 (1.222, 1.499)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10:1	0.893 (0.792, 1.007)	0.065	0.111	Aromatic	<b>1.240 (1.121, 1.372)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10:2	1.019 (0.913, 1.137)	0.735	0.735	Branched-chain	<b>1.373 (1.240, 1.520)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10:3	<b>1.184 (1.077, 1.301)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	Fischer ratio	1.078 (0.831, 1.036)	0.184	0.227
C12	0.967 (0.863, 1.082)	0.556	0.586	<b>Ala:Gly</b>	<b>1.578 (1.436, 1.735)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C12:1	0.959 (0.855, 1.075)	0.469	0.523				
C14	1.087 (0.981, 1.205)	0.113	0.174				
C14:1	1.021 (0.915, 1.139)	0.708	0.720				
C14:1-OH	1.082 (0.973, 1.205)	0.147	0.208				
C14:2	0.960 (0.857, 1.076)	0.485	0.531				
C14-OH/C12-DC	<b>1.150 (1.034, 1.277)</b>	<b>0.010</b>	<b>0.028</b>				
C16	<b>1.189 (1.074, 1.316)</b>	<b>0.001</b>	<b>0.003</b>				
C16:1	1.083 (0.975, 1.203)	0.139	0.202				
C16:1-OH/C14:1-DC	<b>1.130 (1.021, 1.252)</b>	<b>0.019</b>	<b>0.038</b>				
C16:2	1.080 (0.971, 1.201)	0.157	0.217				
C16-OH	<b>1.326 (1.203, 1.462)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>				
C18	1.026 (0.921, 1.142)	0.642	0.665				
C18:1	1.086 (0.977, 1.207)	0.127	0.189				
C18:1-DC	<b>1.143 (1.032, 1.267)</b>	<b>0.011</b>	<b>0.029</b>				
C18:2	1.091 (0.979, 1.216)	0.114	0.174				
C18:2-OH	1.072 (0.963, 1.193)	0.203	0.245				
C18-DC/C20-OH	<b>1.140 (1.028, 1.264)</b>	<b>0.013</b>	<b>0.030</b>				

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C20	0.956 (0.853, 1.072)	0.442	0.503
C20:4	<b>1.139 (1.027, 1.263)</b>	<b>0.013</b>	<b>0.030</b>
Short chain	<b>1.145 (1.030, 1.271)</b>	<b>0.012</b>	<b>0.030</b>
Medium chain	0.935 (0.831, 1.051)	0.258	0.299
Long chain	<b>1.128 (1.016, 1.253)</b>	<b>0.024</b>	<b>0.044</b>

<sup>1</sup> As metabolite data were converted to Z-scores, HR are measured in per SD.

<sup>2</sup> Adjusted for multiple testing using the Benjamini-Hochberg false discovery rate.

**Supplementary Table 5** Associations between metabolites and incident diabetes in study participants of Chinese ethnicity, adjusted for age, sex, height, and parental history of diabetes. Significant associations following multiple testing are in bold.

Acylcarnitines	HR <sup>1</sup> (95% CI)	P-value	P-value <sup>2</sup>	Amino acids	HR (95% CI)	P-value	P-value <sup>2</sup>
C2	1.037 (0.907, 1.185)	0.594	0.716	<b>Ala</b>	<b>1.370 (1.201, 1.562)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C3	1.066 (0.933, 1.218)	0.349	0.506	Arg	0.871 (0.752, 1.010)	0.067	0.144
C4	1.153 (1.022, 1.301)	0.021	0.067	Cit	0.964 (0.836, 1.111)	0.609	0.716
C4-DC	1.162 (1.021, 1.323)	0.023	0.067	<b>Glu/Gln</b>	<b>1.498 (1.327, 1.690)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C5:1	1.058 (0.926, 1.210)	0.406	0.574	<b>Gly</b>	<b>0.670 (0.563, 0.797)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C5-DC	1.077 (0.951, 1.220)	0.244	0.363	His	0.956 (0.829, 1.102)	0.534	0.681
C5-OH/C3-DC	1.008 (0.883, 1.151)	0.904	0.971	<b>Ile/Leu</b>	<b>1.538 (1.342, 1.763)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C6	0.998 (0.878, 1.136)	0.981	0.998	Met	1.147 (0.996, 1.322)	0.057	0.132
C7-DC	0.854 (0.738, 0.989)	0.035	0.092	<b>Orn</b>	<b>1.239 (1.092, 1.406)</b>	<b>0.001</b>	0.006
C8	0.843 (0.722, 0.984)	0.031	0.086	<b>Phe</b>	<b>1.275 (1.121, 1.452)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
<b>C8:1</b>	<b>1.208 (1.072, 1.361)</b>	<b>0.002</b>	<b>0.011</b>	Pro	1.138 (0.992, 1.306)	0.065	0.144
C8-DC	0.882 (0.762, 1.021)	0.093	0.163	Ser	0.839 (0.722, 0.974)	0.021	0.067
C8-OH/C6-DC	0.873 (0.752, 1.012)	0.072	0.149	<b>Tyr</b>	<b>1.290 (1.130, 1.473)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10	0.835 (0.716, 0.974)	0.022	0.067	<b>Val</b>	<b>1.481 (1.296, 1.692)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10:1	0.879 (0.759, 1.019)	0.087	0.158	<b>Aromatic</b>	<b>1.191 (1.045, 1.358)</b>	<b>0.009</b>	<b>0.044</b>
C10:2	0.999 (0.872, 1.144)	0.983	0.998	<b>Branched-chain</b>	<b>1.527 (1.334, 1.747)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C10:3	1.156 (1.020, 1.310)	0.023	0.067	Fischer ratio	1.111 (0.964, 1.280)	0.145	0.247
C12	0.874 (0.754, 1.014)	0.076	0.151	<b>Ala:Gly</b>	<b>1.576 (1.404, 1.768)</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
C12:1	0.838 (0.725, 0.970)	0.018	0.067				
C14	0.953 (0.826, 1.098)	0.505	0.681				
C14:1	0.880 (0.763, 1.014)	0.078	0.151				
C14:1-OH	0.920 (0.801, 1.058)	0.242	0.363				
C14:2	0.846 (0.732, 0.977)	0.023	0.067				
C14-OH/C12-DC	1.000 (0.874, 1.144)	0.998	0.998				
C16	1.088 (0.948, 1.249)	0.228	0.363				
C16:1	0.922 (0.804, 1.056)	0.242	0.363				
C16:1-OH/C14:1-DC	0.974 (0.849, 1.117)	0.705	0.802				
C16:2	0.884 (0.768, 1.017)	0.084	0.157				
C16-OH	1.135 (0.997, 1.292)	0.055	0.132				
C18	0.964 (0.836, 1.112)	0.617	0.716				
C18:1	0.965 (0.843, 1.105)	0.605	0.716				
C18:1-DC	0.993 (0.865, 1.140)	0.923	0.973				
C18:2	0.982 (0.857, 1.124)	0.788	0.862				
C18:2-OH	0.958 (0.838, 1.096)	0.532	0.681				

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C18-DC/C20-OH	0.915 (0.793, 1.056)	0.224	0.363
C20	0.842 (0.726, 0.976)	0.022	0.067
C20:4	1.046 (0.916, 1.195)	0.505	0.681
Short chain	1.043 (0.912, 1.191)	0.540	0.681
Medium chain	0.862 (0.746, 0.997)	0.046	0.116
Long chain	0.981 (0.855, 1.124)	0.777	0.862

<sup>1</sup> As metabolite data were converted to Z-scores, HR are measured in per SD.

<sup>2</sup> Adjusted for multiple testing using the Benjamini-Hochberg false discovery rate.

**Supplementary Figure 1** Heatmap of the pairwise correlations between the 13 potential biomarkers.

