

Integrative Metabolomics of Targeted and Non-targeted Analyses in T2D Progression

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Table S1. List of the 104 targeted and 312 non-targeted metabolites used.

No.	Biocrates ID	Biochemical name	Metabolon ID	No.
1	C0	Carnitine	M15500	1
2	C2	Acetylcarnitine	M32198	2
3	C3	Propionylcarnitine	M32452	3
4	C4	Butyrylcarnitine	M32412	4
5	C5	Isovalerylcarnitine	M34407	5
6	C10	Decanoylcarnitine	M33941	6
7	C14:1	2-Tetradecenoylcarnitine	M35472	7
8	C16	Palmitoylcarnitine	M22189	8
9	C18:1	Oleoylcarnitine	M35160	9
10	Arg	Arginine	M01638	10
11	Gly	Glycine	M32338	11
12	Met	Methionine	M01302	12
13	Orn	Ornithine	M01493	13
14	Pro	Proline	M01898	14
15	Ser	Serine	M32315	15
16	Thr	Threonine	M01284	16
17	Tyr	Tyrosine	M01299	17
18	Val	Valine	M01649	18
19	lysoPC a C16:0	2-Palmitoylglycerophosphocholine	M35253	19
20	lysoPC a C18:0	2-Stearoylglycerophosphocholine	M35255	20
21	lysoPC a C18:1	2-Oleoylglycerophosphocholine	M35254	21
22	lysoPC a C18:2	2-Linoleoylglycerophosphocholine	M35257	22
23	SM C16:0	Palmitoylsphingomyelin	M37506	23
24	H1	Hexose (including glucose)	M20489	24
25	C12	Dodecanoylcarnitine		
26	C14:1- OH	Hydroxytetradecenoylcarnitine		
27	C14:2	Tetradecadienylcarnitine		
28	C18	Octadecanoylcarnitine		
29	C18:2	Octadecadienylcarnitine		
30	PC aa C28:1	Phosphatidylcholine Diacyl C28:1		
31	PC aa C30:0	Phosphatidylcholine Diacyl C30:0		
32	PC aa C32:0	Phosphatidylcholine Diacyl C32:0		
33	PC aa C32:1	Phosphatidylcholine Diacyl C32:1		
34	PC aa C32:2	Phosphatidylcholine Diacyl C32:2		
35	PC aa C32:3	Phosphatidylcholine Diacyl C32:3		
36	PC aa C34:1	Phosphatidylcholine Diacyl C34:1		
37	PC aa C34:3	Phosphatidylcholine Diacyl C34:3		
38	PC aa C34:4	Phosphatidylcholine Diacyl C34:4		
39	PC aa C36:1	Phosphatidylcholine Diacyl C36:1		
40	PC aa C36:2	Phosphatidylcholine Diacyl C36:2		
41	PC aa C36:3	Phosphatidylcholine Diacyl C36:3		
42	PC aa C36:4	Phosphatidylcholine Diacyl C36:4		
43	PC aa C36:5	Phosphatidylcholine Diacyl C36:5		
44	PC aa C36:6	Phosphatidylcholine Diacyl C36:6		
45	PC aa C38:0	Phosphatidylcholine Diacyl C38:0		
46	PC aa C38:3	Phosphatidylcholine Diacyl C38:3		
47	PC aa C38:4	Phosphatidylcholine Diacyl C38:4		
48	PC aa C38:5	Phosphatidylcholine Diacyl C38:5		
49	PC aa C38:6	Phosphatidylcholine Diacyl C38:6		

50	PC aa C40:2	Phosphatidylcholine Diacyl C40:2
51	PC aa C40:3	Phosphatidylcholine Diacyl C40:3
52	PC aa C40:4	Phosphatidylcholine Diacyl C40:4
53	PC aa C40:5	Phosphatidylcholine Diacyl C40:5
54	PC aa C42:0	Phosphatidylcholine Diacyl C42:0
55	PC aa C42:1	Phosphatidylcholine Diacyl C42:1
56	PC aa C42:2	Phosphatidylcholine Diacyl C42:2
57	PC aa C42:4	Phosphatidylcholine Diacyl C42:4
58	PC aa C42:5	Phosphatidylcholine Diacyl C42:5
59	PC aa C42:6	Phosphatidylcholine Diacyl C42:6
60	PC ae C32:1	Phosphatidylcholine Acyl-Alkyl C32:1
61	PC ae C32:2	Phosphatidylcholine Acyl-Alkyl C32:2
62	PC ae C34:0	Phosphatidylcholine Acyl-Alkyl C34:0
63	PC ae C34:1	Phosphatidylcholine Acyl-Alkyl C34:1
64	PC ae C34:2	Phosphatidylcholine Acyl-Alkyl C34:2
65	PC ae C34:3	Phosphatidylcholine Acyl-Alkyl C34:3
66	PC ae C36:1	Phosphatidylcholine Acyl-Alkyl C36:1
67	PC ae C36:2	Phosphatidylcholine Acyl-Alkyl C36:2
68	PC ae C36:3	Phosphatidylcholine Acyl-Alkyl C36:3
69	PC ae C36:4	Phosphatidylcholine Acyl-Alkyl C36:4
70	PC ae C36:5	Phosphatidylcholine Acyl-Alkyl C36:5
71	PC ae C38:0	Phosphatidylcholine Acyl-Alkyl C38:0
72	PC ae C38:2	Phosphatidylcholine Acyl-Alkyl C38:2
73	PC ae C38:3	Phosphatidylcholine Acyl-Alkyl C38:3
74	PC ae C38:4	Phosphatidylcholine Acyl-Alkyl C38:4
75	PC ae C38:5	Phosphatidylcholine Acyl-Alkyl C38:5
76	PC ae C38:6	Phosphatidylcholine Acyl-Alkyl C38:6
77	PC ae C40:1	Phosphatidylcholine Acyl-Alkyl C40:1
78	PC ae C40:2	Phosphatidylcholine Acyl-Alkyl C40:2
79	PC ae C40:3	Phosphatidylcholine Acyl-Alkyl C40:3
80	PC ae C40:4	Phosphatidylcholine Acyl-Alkyl C40:4
81	PC ae C40:5	Phosphatidylcholine Acyl-Alkyl C40:5
82	PC ae C40:6	Phosphatidylcholine Acyl-Alkyl C40:6
83	PC ae C42:1	Phosphatidylcholine Acyl-Alkyl C42:1
84	PC ae C42:2	Phosphatidylcholine Acyl-Alkyl C42:2
85	PC ae C42:3	Phosphatidylcholine Acyl-Alkyl C42:3
86	PC ae C42:4	Phosphatidylcholine Acyl-Alkyl C42:4
87	PC ae C42:5	Phosphatidylcholine Acyl-Alkyl C42:5
88	PC ae C44:4	Phosphatidylcholine Acyl-Alkyl C44:4
89	PC ae C44:5	Phosphatidylcholine Acyl-Alkyl C44:5
90	PC ae C44:6	Phosphatidylcholine Acyl-Alkyl C44:6
91	lysoPC a C16:1	Lysophosphatidylcholine Acyl C16:1
92	lysoPC.a.C17:0	Lysophosphatidylcholine Acyl C17:0
93	lysoPC a C20:3	Lysophosphatidylcholine Acyl C20:3
94	lysoPC a C20:4	Lysophosphatidylcholine Acyl C20:4
95	SM (OH)	Hydroxysphingomyeline C14:1
96	SM (OH)	Hydroxysphingomyeline C16:1
97	SM (OH)	Hydroxysphingomyeline C22:1
98	SM (OH)	Hydroxysphingomyeline C22:2
99	SM (OH)C24:1	Hydroxysphingomyeline C24:1
100	SM C16:1	Sphingomyeline C16:1

101	SM C18:0	Sphingomyeline C18:0		
102	SM C18:1	Sphingomyeline C18:1		
103	SM C20:2	Sphingomyeline C20:2		
104	SM C24:1	Sphingomyeline C24:1		
		Glutamine	M00053	25
		Tryptophan	M00054	26
		Histidine	M00059	27
		Leucine	M00060	28
		Cholesterol	M00063	29
		Phenylalanine	M00064	30
		Creatinine	M00513	31
		Lactate	M00527	32
		3-Hydroxybutyrate (BHBA)	M00542	33
		Caffeine	M00569	34
		Fructose	M00577	35
		Mannose	M00584	36
		Pyruvate	M00599	37
		Uridine	M00606	38
		Linoleate (18:2n6)	M01105	39
		Arachidonate (20:4n6)	M01110	40
		Deoxycholate	M01114	41
		Margarate (17:0)	M01121	42
		Isoleucine	M01125	43
		Lysine	M01301	44
		Malate	M01303	45
		Palmitate (16:0)	M01336	46
		Nonadecanoate (19:0)	M01356	47
		Stearate (18:0)	M01358	48
		Oleate (18:1n9)	M01359	49
		Pentadecanoate (15:0)	M01361	50
		Myristate (14:0)	M01365	51
		Pipecolate	M01444	52
		5-Oxoproline	M01494	53
		Pantothenate	M01508	54
		4-Acetamidobutanoate	M01558	55
		Alpha-Tocopherol	M01561	56
		Citrate	M01564	57
		Glycerate	M01572	58
		N-Acetylalanine	M01585	59
		Urate	M01604	60
		Caprate (10:0)	M01642	61
		Heptanoate (7:0)	M01644	62
		Laurate (12:0)	M01645	63
		Urea	M01670	64
		Cortisol	M01712	65
		Cortisone	M01769	66
		Citrulline	M02132	67
		Serotonin (5HT)	M02342	68
		γ -Glutamyl-glutamine	M02730	69
		γ -Glutamyl-tyrosine	M02734	70
		Hypoxanthine	M03127	71

Betaine	M03141	72
Xanthine	M03147	73
Phosphate	M11438	74
3-Methoxytyrosine	M12017	75
Pelargonate (9:0)	M12035	76
Undecanoate (11:0)	M12067	77
Beta-Hydroxyisovalerate	M12129	78
X-02973	M12593	79
X-03003	M12626	80
X-03088	M12768	81
X-03094	M12774	82
Glycerol	M15122	83
Kynurenine	M15140	84
Mannitol	M15335	85
Glycerol 3-Phosphate (G3P)	M15365	86
Acetylphosphate	M15488	87
Choline	M15506	88
N-Acetylmethionine	M15630	89
N1-Methyladenosine	M15650	90
3-Methyl-2-Oxovalerate	M15676	91
Hippurate	M15753	92
Benzoate	M15778	93
Glycerophosphorylcholine (GPC)	M15990	94
Aspartate	M15996	95
X-04357	M16634	96
X-04495	M16818	97
X-04498	M16821	98
X-04499 (Retired For 3,4-Dihydroxybutyrate)	M16822	99
Dihomo-Linoleate (20:2n6)	M17805	100
X-18601	M17807	101
2-Hydroxystearate	M17945	102
Paraxanthine	M18254	103
X-05426	M18283	104
Quinate	M18335	105
γ -Glutamyl-leucine	M18369	106
Theobromine	M18392	107
Theophylline	M18394	108
Eicosapentaenoate (EPA; 20:5n3)	M18467	109
X-05907	M18929	110
Docosahexaenoate (DHA; 22:6n3)	M19323	111
1-Stearoylglycerophosphoinositol	M19324	112
X-06226	M19362	113
X-06246	M19364	114
X-06267	M19368	115
X-06307	M19396	116
Myo-Inositol	M19934	117
1,5-Anhydroglucitol (1,5-AG)	M20675	118
Erythritol	M20699	119
2-Hydroxybutyrate (AHB)	M21044	120
3-Methyl-2-Oxobutyrate	M21047	121
1-Palmitoylglycerol (1-Monopalmitin)	M21127	122

1-Oleoylethanolamine (1-Monoolein)	M21184	123
X-08402	M21630	124
2-Hydroxyisobutyrate	M22030	125
4-Methyl-2-Oxopentanoate	M22116	126
Aspartylphenylalanine	M22175	127
X-08988	M22481	128
X-09026	M22548	129
X-09108	M22649	130
X-09706	M24074	131
X-10395	M25459	132
X-10500	M27256	133
X-10506	M27273	134
X-10510	M27278	135
Indoleacetate	M27513	136
3-Indoxyl Sulfate	M27672	137
N-Acetylglycine	M27710	138
Bilirubin (Z,Z)	M27716	139
Creatine	M27718	140
Erythrose	M27722	141
Threonate	M27738	142
X-10810	M30805	143
Cysteine	M31453	144
Dsgegdfxaeggvr*	M31548	145
Pyridoxate	M31555	146
Androsterone Sulfate	M31591	147
3-Carboxy-4-Methyl-5-Propyl-2-Furanpropanoate (CMPF)	M31787	148
3-(4-Hydroxyphenyl) Lactate	M32197	149
Trans-4-Hydroxyproline	M32319	150
Glutamate	M32322	151
Hexanoylcarnitine	M32328	152
Alanine	M32339	153
Glycochenodeoxycholate	M32346	154
2-Aminobutyrate	M32348	155
Scyllo-Inositol	M32379	156
γ -Glutamyl-valine	M32393	157
Indolepropionate	M32405	158
Myristoleate (14:1n5)	M32418	159
Dehydroisoandrosterone Sulfate (DHEA-S)	M32425	160
Caproate (6:0)	M32489	161
Caprylate (8:0)	M32492	162
10-Undecenoate (11:1n1)	M32497	163
Docosapentaenoate (N3 DPA; 22:5n3)	M32504	164
X-11204	M32518	165
X-02269	M32549	166
Phenol Sulfate	M32553	167
X-06126	M32557	168
X-11247	M32564	169
X-11261	M32578	170
Bilirubin (E, E)*	M32586	171
X-02249	M32587	172
Heme*	M32593	173

X-11299	M32616	174
X-11315	M32632	175
X-11317	M32634	176
1-Linoleoylglycerophosphoethanolamine*	M32635	177
X-11327	M32644	178
X-11334	M32651	179
X-21365 (3-Dehydrocarnitine*)	M32654	180
Pyroglutamine*	M32672	181
C-Glycosyltryptophan*	M32675	182
X-11381	M32698	183
X-03056 (Retired For N-[3-(2-Oxopyrrolidin-1-Yl) Propyl]	M32709	184
X-01911	M32735	185
X-11422 (Retired For Xanthine)	M32739	186
X-11423 (Retired For O-Sulfo-L-Tyrosine)	M32740	187
X-09789	M32753	188
X-11438	M32755	189
X-11440	M32757	190
X-11441	M32758	191
X-11442	M32759	192
X-11444	M32761	193
X-11452	M32769	194
X-11469	M32786	195
X-11470	M32787	196
X-11497	M32814	197
Hwesasxx*	M32836	198
X-11530	M32847	199
X-11538	M32855	200
X-11550	M32867	201
X-11593 (Retired For O-Methylascorbate*)	M32910	202
Adrenate (22:4n6)	M32980	203
Homostachydrine*	M33009	204
Adsggdfxaegggrv*	M33084	205
X-11787	M33132	206
X-11793 (Retired for Oxidized Bilirubin*)	M33138	207
X-11795	M33140	208
X-11818	M33163	209
X-11820	M33165	210
X-11847	M33192	211
1-Arachidonoylglycerophosphocholine*	M33228	212
1-Palmitoleoylglycerophosphocholine*	M33230	213
X-12038	M33389	214
X-12039	M33390	215
X-12063	M33415	216
γ -Glutamyl-phenylalanine	M33422	217
Isobutyrylcarnitine	M33441	218
Pseudouridine	M33442	219
Valerate	M33443	220
Palmitoleate (16:1n7)	M33447	221
Erythronate*	M33477	222
X-12092	M33507	223
X-12094	M33509	224

X-12095 (Retired for N1-Methyl-3-Pyridone-4-Carboxamide)	M33510	225
X-12100 (Retired for Hydroxytryptophan*)	M33515	226
Eicosenoate (20:1n9 or 11)	M33587	227
X-12217	M33638	228
X-12231	M33653	229
X-12244 (Retired For N-Acetylcarnosine)	M33666	230
X-12253	M33675	231
Adpsgegdffaeggvr*	M33801	232
1-Eicosatrienoylglycerophosphocholine*	M33821	233
1-Docosahexaenoylglycerophosphocholine*	M33822	234
X-12405	M33833	235
1-Eicosadienoylglycerophosphocholine*	M33871	236
X-12442 (Retired For 5,8-Tetradecadienoate)	M33884	237
Piperine	M33935	238
Octanoylcarnitine	M33936	239
Alpha-Hydroxyisovalerate	M33937	240
1-Palmitoylglycerophosphocholine	M33955	241
1-Heptadecanoylglycerophosphocholine	M33957	242
1-Oleoylglycerophosphocholine	M33960	243
1-Stearoylglycerophosphocholine	M33961	244
5-Dodecenoate (12:1n7)	M33968	245
Stearidonate (18:4n3)	M33969	246
10-Heptadecenoate (17:1n7)	M33971	247
10-Nonadecenoate (19:1n9)	M33972	248
Epiandrosterone Sulfate	M33973	249
Linolenate [Alpha Or Gamma; (18:3n3 Or 6)]	M34035	250
X-12510 (Retired For 2-Aminooctanoic Acid)	M34040	251
X-12524	M34062	252
Bilirubin (E,Z Or Z,E)*	M34106	253
X-12556	M34123	254
1-Arachidonoylglycerophosphoinositol*	M34214	255
X-12627	M34221	256
X-12644	M34244	257
Asparagine	M34283	258
X-12696	M34306	259
X-12749	M34359	260
Stachydrine	M34384	261
Stearoylcarnitine	M34409	262
1-Stearoylglycerophosphoethanolamine	M34416	263
1-Linoleoylglycerophosphocholine	M34419	264
X-12776	M34453	265
X-12786	M34469	266
X-12798	M34481	267
X-12844	M34527	268
Laurylcarnitine	M34534	269
Isovalerate	M34732	270
X-13069	M34761	271
7-Methylguanine	M35114	272
Phenylacetylglutamine	M35126	273
Pro-Hydroxy-Pro	M35127	274
1-Arachidonoylglycerophosphoethanolamine*	M35186	275

X-13431 (Retired For Nonanoylcarnitine*)	M35189	276
X-13435	M35193	277
X-13477	M35240	278
X-13496	M35270	279
1-Palmitoylglycerophosphoinositol*	M35305	280
Catechol Sulfate	M35320	281
X-13549	M35327	282
X-13619	M35397	283
2-Methylbutyrylcarnitine	M35431	284
Glutaroyl Carnitine	M35439	285
X-13671	M35464	286
1-Myristoylglycerophosphocholine	M35626	287
1-Oleoylglycerophosphoethanolamine	M35628	288
1-Palmitoylglycerophosphoethanolamine	M35631	289
2-Hydroxypalmitate	M35675	290
Dihomo-Linolenate (20:3n3 Or N6)	M35718	291
X-13859	M35754	292
Threitol	M35854	293
X-14056	M35977	294
4-Vinylphenol Sulfate	M36098	295
P-Cresol Sulfate	M36103	296
X-14374	M36300	297
X-14473	M36399	298
X-14588	M36515	299
X-14625	M36552	300
Octadecanedioate	M36754	301
7-Alpha-Hydroxy-3-Oxo-4-Cholestenoate (7-Hoca)	M36776	302
Dimethylarginine (SDMA + ADMA)	M36808	303
Taurolithocholate 3-Sulfate	M36850	304
Succinylcarnitine	M37058	305
Tryptophan Betaine	M37097	306
5alpha-Androstan-3beta,17beta-Diol Disulfate	M37190	307
4-Androsten-3beta,17beta-Diol Disulfate 1*	M37202	308
4-Androsten-3beta,17beta-Diol Disulfate 2*	M37203	309
Phenylalanylphenylalanine	M38150	310
Cis-4-Decenoyl Carnitine	M38178	311
15-Methylpalmitate (Isobar With 2-Methylpalmitate)	M38768	312

The Biocrates IDs, biochemical names, and Metabolon IDs are shown.

Table S2. Characteristics of study participants across glycemic states in the non-targeted metabolomics study.

	S4 (N = 1,346)				F4 (N = 1,609)			
	NORM	PreT2D	T2D	<i>P</i>	NORM	PreT2D	T2D	<i>P</i>
N	857	343	146		1143	350	116	
Age, years	63.46 ± 5.58	64.95 ± 5.19	65.02 ± 5.30	<0.001	58.91 ± 8.54	63.22 ± 8.31	65.18 ± 7.14	<0.001
Male sex, %	48.2	59.5	58.9	<0.001	44.6	54.0	61.2	<0.001
BMI, kg/m²	27.60 ± 4.00	29.52 ± 4.08	30.41 ± 4.46	<0.001	26.95 ± 4.26	29.82 ± 4.58	31.01 ± 4.75	<0.001
Waist circumference, cm	93.22 ± 11.13	99.33 ± 10.37	101.52 ± 11.00	<0.001	91.97 ± 12.86	100.60 ± 13.95	106.32 ± 11.32	<0.001
Fasting glucose, mg/dL	95.58 ± 7.09	107.61 ± 9.49	133.86 ± 33.13	<0.001	93.18 ± 7.47	104.01 ± 10.87	126.46 ± 30.38	<0.001
2-h PG, mg/dL	102.08 ± 20.98	146.68 ± 30.29	233.00 ± 67.19	<0.001	100.81 ± 20.61	151.09 ± 27.75	216.43 ± 50.50	<0.001
HbA_{1C}, %	5.56 ± 0.34	5.65 ± 0.38	6.37 ± 1.20	<0.001	5.42 ± 0.29	5.65 ± 0.34	6.25 ± 0.90	<0.001
HbA_{1C}, mmol/mol	37.24 ± 3.66	38.26 ± 4.16	46.07 ± 13.07	<0.001	35.70 ± 3.22	38.26 ± 3.71	44.84 ± 9.85	<0.001
HDL cholesterol, mg/dL	60.41 ± 16.48	55.37 ± 15.18	50.98 ± 15.31	<0.001	58.93 ± 14.80	53.44 ± 13.80	49.55 ± 11.50	<0.001
Systolic BP, mmHg	131.64 ± 18.96	140.30 ± 19.25	146.85 ± 21.48	<0.001	121.60 ± 17.72	129.39 ± 19.06	134.36 ± 19.12	<0.001
Physical activity, %				0.012				<0.001
Low	52.9	61.1	65.8		37.5	48.3	52.6	
Medium	27.7	22.2	21.2		34.4	30.6	25.0	
High	19.5	16.7	13.0		28.1	21.1	22.4	
Smoking, %				0.231				<0.001
Non-smoker	48.0	47.2	41.1		41.2	46.9	40.5	
Ex-smoker	37.5	41.7	43.8		41.2	45.1	47.4	
Current smoker	14.5	11.1	15.1		17.6	8.0	12.1	
Alcohol intake, g/day	15.10 ± 18.65	19.67 ± 25.42	15.71 ± 21.59	0.003	15.20 ± 19.59	15.88 ± 19.62	21.43 ± 27.83	0.007
GGT, U/l					37.78 ± 37.70	61.90 ± 158.66	62.78 ± 63.72	<0.001

Data are means ± SD for continuous variables and % for categorical variables. *P*-values were calculated using one-way ANOVA for continuous variables and chi-square test for categorical variables, comparing across the three groups (NORM, PreT2D, T2D). **Abbreviations:** BP, blood pressure; BMI, body mass index; GGT, γ -glutamyl-transferase; HDL, high density lipoprotein; NORM, normal glucose metabolism; PG, post-OGTT glucose values; PreT2D, prediabetes; T2D, type 2 diabetes.

Table S3. Characteristics of participants with targeted metabolomics data at S4 and FF4 across T2D trajectory groups.

	NORM		Incident PreT2D		PreT2D		Incident T2D		T2D	
	S4	FF4	S4	FF4	S4	FF4	S4	FF4	S4	FF4
	NORM	NORM	NORM	PreT2D	PreT2D	PreT2D	NORM/PreT2D	T2D	T2D	T2D
N	225	225	114	114	38	38	68	68	11	11
Age, years	61.66 ± 4.92	75.16 ± 4.97	61.54 ± 4.91	75.11 ± 4.88	63.39 ± 5.00	76.97 ± 4.91	62.47 ± 4.92	76.09 ± 4.96	63.27 ± 5.35	76.64 ± 5.41
Male sex, %	47.6	47.6	57.9	57.9	50.0	50.0	58.8	58.8	72.7	72.7
BMI, kg/m²	26.68 ± 3.60	26.84 ± 4.14	27.65 ± 3.79	28.21 ± 3.94	29.41 ± 3.63	29.20 ± 3.18	29.42 ± 4.55	30.27 ± 5.08	27.65 ± 1.90	27.35 ± 2.19
Waist circumference, cm	90.51 ± 10.99	95.61 ± 11.89	93.45 ± 11.09	99.77 ± 11.15	96.50 ± 10.40	102.34 ± 9.46	99.36 ± 10.22	106.72 ± 11.92	91.80 ± 6.62	99.35 ± 8.03
HbA_{1c}, %	5.52 ± 0.33	5.47 ± 0.30	5.55 ± 0.29	5.62 ± 0.30	5.59 ± 0.30	5.67 ± 0.37	5.70 ± 0.35	6.09 ± 0.82	5.58 ± 0.29	6.07 ± 0.40
HbA_{1c}, mmol/mol	36.85 ± 3.65	36.24 ± 3.23	37.18 ± 3.18	37.96 ± 3.32	37.56 ± 3.27	38.48 ± 4.01	38.85 ± 3.82	43.05 ± 8.94	37.51 ± 3.12	42.81 ± 4.38
Fasting glucose, mg/dL	93.95 ± 6.54	95.75 ± 7.05	97.61 ± 6.66	104.82 ± 9.31	105.24 ± 8.72	108.39 ± 8.99	104.85 ± 9.97	123.45 ± 31.97	111.00 ± 15.47	125.36 ± 19.63
HDL cholesterol, mg/dL	61.06 ± 15.67	70.52 ± 18.74	60.10 ± 19.04	66.36 ± 19.86	56.78 ± 17.89	64.96 ± 18.29	54.80 ± 13.43	60.07 ± 14.84	49.87 ± 13.76	54.41 ± 9.82
Systolic BP, mmHg	126.63 ± 17.63	119.73 ± 18.18	133.70 ± 19.04	124.97 ± 19.28	136.47 ± 17.70	126.75 ± 21.58	134.48 ± 20.74	122.90 ± 17.76	142.36 ± 15.91	124.95 ± 25.41
Smoking, %										
Non-smoker	47.1	47.1	49.1	49.1	63.2	63.2	57.4	57.4	63.6	63.6
Ex-smoker	40.4	47.1	35.1	41.2	31.6	34.2	36.8	42.6	36.4	36.4
Current smoker	12.4	5.8	15.8	9.6	5.3	2.6	5.9	0.0	0.0	0.0
Physical activity, %										
Low	40.9	40.9	50.4	48.2	44.7	60.5	58.8	61.8	54.5	63.6
Medium	34.2	29.8	26.5	32.5	34.2	10.5	25.0	20.6	36.4	9.1
High	24.9	29.3	23.0	19.3	21.1	28.9	16.2	17.6	9.1	27.3
Alcohol intake, g/day	14.90 ± 18.78	13.64 ± 17.34	16.38 ± 17.64	16.34 ± 18.54	16.52 ± 20.26	12.77 ± 16.03	20.74 ± 25.26	15.28 ± 22.01	15.00 ± 18.84	15.49 ± 36.95
GGT, U/l		31.70 ± 34.00		34.84 ± 22.56		37.34 ± 24.17		46.12 ± 61.16		74.33 ± 116.04

Data are means ± SD for continuous variables and % for categorical variables.

Abbreviations: NORM: Normal glucose metabolism at both S4 and FF4; Incident PreT2D: Normal glucose metabolism at S4, progressed to prediabetes by FF4; PreT2D: Prediabetes at both time points; Incident T2D: Prediabetes or NORM at S4, progressed to T2D by FF4; T2D: T2D at both time points. GGT: γ -glutamyl transferase; Systolic BP: Systolic blood pressure.

Table S4. Characteristics of participants with non-targeted metabolomics data at S4 and F4 across T2D trajectory groups.

	NORM		Incident PreT2D		PreT2D		Incident T2D		T2D	
	S4	F4	S4	F4	S4	F4	S4	F4	S4	F4
	NORM	NORM	NORM	PreT2D	PreT2D	PreT2D	NORM/PreT2D	T2D	T2D	T2D
N	351	351	97	97	80	80	44	44	22	22
Age, years	60.91 ± 4.24	67.97 ± 4.22	61.75 ± 4.31	68.86 ± 4.35	62.59 ± 3.90	69.61 ± 3.91	63.05 ± 4.24	70.09 ± 4.25	61.68 ± 4.42	68.77 ± 4.52
Male sex, %	47.6	47.6	43.3	43.3	66.2	66.2	70.5	70.5	77.3	77.3
BMI, kg/m ²	27.07 ± 3.84	27.31 ± 4.02	28.28 ± 3.86	28.94 ± 4.07	29.28 ± 3.55	29.80 ± 3.85	29.80 ± 3.25	30.90 ± 4.14	28.38 ± 3.08	28.41 ± 3.84
Waist circumference, cm	91.42 ± 10.86	94.07 ± 11.64	94.19 ± 10.93	97.11 ± 11.34	99.22 ± 9.11	102.83 ± 10.12	101.04 ± 8.94	106.39 ± 10.97	99.04 ± 8.78	99.97 ± 10.39
HbA _{1C} , %	5.54 ± 0.33	5.47 ± 0.28	5.60 ± 0.33	5.66 ± 0.31	5.64 ± 0.28	5.72 ± 0.34	5.75 ± 0.36	6.17 ± 0.46	5.83 ± 0.41	6.83 ± 1.73
HbA _{1C} , mmol/mol	37.04 ± 3.60	36.28 ± 3.06	37.69 ± 3.59	38.41 ± 3.39	38.17 ± 3.07	38.98 ± 3.75	39.29 ± 3.90	43.96 ± 4.98	40.19 ± 4.53	51.12 ± 18.95
Fasting glucose, mg/dL	94.87 ± 6.89	93.93 ± 7.10	98.39 ± 7.41	102.05 ± 11.01	108.51 ± 8.38	107.25 ± 10.36	105.70 ± 11.09	118.11 ± 16.41	124.29 ± 14.60	147.91 ± 56.25
HDL cholesterol, mg/dL	61.46 ± 16.76	59.09 ± 14.31	57.31 ± 16.15	55.51 ± 13.61	55.01 ± 14.59	52.51 ± 13.14	51.85 ± 13.61	49.14 ± 11.73	50.14 ± 10.62	48.73 ± 8.10
Systolic BP, mmHg	128.30 ± 17.04	124.96 ± 18.57	133.03 ± 19.58	127.70 ± 20.34	138.79 ± 17.83	134.46 ± 18.48	134.62 ± 19.73	131.41 ± 17.97	148.41 ± 21.29	148.68 ± 22.90
Physical activity, %										
Low	22.3	16.1	35.4	16.4	28.6	3.0	30.8	14.3	23.1	15.4
Medium	45.5	45.3	36.9	50.7	42.9	54.3	46.2	47.6	46.2	23.1
High	32.2	38.6	27.7	32.8	28.6	32.6	23.1	38.1	30.8	61.5
Smoking, %										
Non-smoker	68.9	79.3	76.3	92.1	86.8	92.1	77.8	85.2	83.3	83.3
Ex-smoker	4.7	3.1	2.6	2.6	5.3	2.6	7.4	7.4	0.0	0.0
Current smoker	26.4	17.6	21.1	5.3	7.9	5.3	14.8	7.4	16.7	16.7
Alcohol intake, g/day	37.04 ± 3.61	13.91 ± 16.81	14.11 ± 21.97	15.19 ± 21.33	21.51 ± 24.00	15.37 ± 16.75	22.99 ± 27.93	18.44 ± 20.56	17.47 ± 23.43	14.80 ± 17.79
GGT, U/l		36.56 ± 29.15		43.51 ± 35.11		48.33 ± 41.87		46.27 ± 28.93		79.00 ± 70.06

Data are means ± SD for continuous variables and % for categorical variables.

Abbreviations: NORM: Normal glucose metabolism at both S4 and F4; Incident PreT2D: Normal glucose metabolism at S4, progressed to prediabetes by F4; PreT2D: Prediabetes at both time points; Incident T2D: Prediabetes or NORM at S4, progressed to T2D by F4; T2D: T2D at both time points. GGT: γ -glutamyl-transferase; Systolic BP: Systolic blood pressure.

Table S5. Bonferroni-significant metabolites identified in targeted metabolomics.

Sample size per group: NORM, N = 3867; PreT2D, N = 1037; T2D, N = 381.

Metabolite	Basic model						Sensitivity model					
	PreT2D vs. NORM		T2D vs. NORM		T2D vs. PreT2D		PreT2D vs. NORM		T2D vs. NORM		T2D vs. PreT2D	
	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P
Persistent												
<i>H1</i>	0.349 ± 0.022	<0.001*	1.281 ± 0.034	<0.001*	0.943 ± 0.055	<0.001*	0.009 ± 0.014	0.519	0.024 ± 0.026	0.355	-0.007 ± 0.033	0.825
<i>Val</i>	0.113 ± 0.031	<0.001*	0.311 ± 0.048	<0.001*	0.228 ± 0.053	<0.001*	0.025 ± 0.033	0.44	0.023 ± 0.060	0.696	0.072 ± 0.062	0.245
<i>SM (OH)</i> <i>C22:2</i>	-0.179 ± 0.028	<0.001*	-0.372 ± 0.045	<0.001*	-0.173 ± 0.045	<0.001*	-0.132 ± 0.029	<0.001*	-0.314 ± 0.053	<0.001*	-0.123 ± 0.050	0.014
Early												
<i>C2</i>	0.172 ± 0.033	<0.001*	0.324 ± 0.052	<0.001*	0.138 ± 0.060	0.021	0.198 ± 0.035	<0.001*	0.423 ± 0.064	<0.001*	0.224 ± 0.070	0.001
<i>C16</i>	0.174 ± 0.032	<0.001*	0.235 ± 0.050	<0.001*	0.065 ± 0.058	0.258	0.171 ± 0.034	<0.001*	0.257 ± 0.062	<0.001*	0.081 ± 0.067	0.228
<i>C18:1</i>	0.135 ± 0.032	<0.001*	0.259 ± 0.050	<0.001*	0.111 ± 0.058	0.055	0.159 ± 0.034	<0.001*	0.391 ± 0.062	<0.001*	0.190 ± 0.067	0.005
<i>Gly</i>	-0.218 ± 0.030	<0.001*	-0.351 ± 0.048	<0.001*	-0.147 ± 0.046	0.001	-0.211 ± 0.031	<0.001*	-0.325 ± 0.058	<0.001*	-0.100 ± 0.053	0.062
<i>PC aa C28:1</i>	-0.111 ± 0.031	<0.001*	-0.199 ± 0.049	<0.001*	-0.073 ± 0.051	0.155	-0.100 ± 0.032	0.001	-0.236 ± 0.058	<0.001*	-0.094 ± 0.058	0.105
<i>PC aa C32:1</i>	0.175 ± 0.031	<0.001*	0.264 ± 0.049	<0.001*	0.110 ± 0.055	0.047	0.153 ± 0.032	<0.001*	0.178 ± 0.059	0.003	0.055 ± 0.063	0.381
<i>PC aa C32:3</i>	-0.149 ± 0.033	<0.001*	-0.260 ± 0.051	<0.001*	-0.063 ± 0.052	0.227	-0.133 ± 0.034	<0.001*	-0.293 ± 0.062	<0.001*	-0.071 ± 0.058	0.222
<i>PC aa C36:4</i>	0.127 ± 0.033	<0.001*	0.207 ± 0.052	<0.001*	0.149 ± 0.060	0.013	0.097 ± 0.034	0.004	0.059 ± 0.062	0.345	0.070 ± 0.069	0.307
<i>PC ae C32:2</i>	-0.149 ± 0.031	<0.001*	-0.262 ± 0.048	<0.001*	-0.109 ± 0.051	0.032	-0.072 ± 0.030	0.017	-0.089 ± 0.055	0.104	-0.022 ± 0.054	0.680
<i>PC ae C34:2</i>	-0.213 ± 0.033	<0.001*	-0.330 ± 0.051	<0.001*	-0.109 ± 0.051	0.033	-0.166 ± 0.033	<0.001*	-0.259 ± 0.060	<0.001*	-0.093 ± 0.057	0.101
<i>PC ae C34:3</i>	-0.243 ± 0.031	<0.001*	-0.393 ± 0.049	<0.001*	-0.161 ± 0.048	0.001	-0.159 ± 0.030	<0.001*	-0.229 ± 0.055	<0.001*	-0.092 ± 0.050	0.067
<i>PC ae C36:2</i>	-0.194 ± 0.030	<0.001*	-0.265 ± 0.047	<0.001*	-0.069 ± 0.050	0.162	-0.166 ± 0.031	<0.001*	-0.252 ± 0.057	<0.001*	-0.098 ± 0.057	0.085
<i>PC ae C36:3</i>	-0.175 ± 0.034	<0.001*	-0.275 ± 0.053	<0.001*	-0.092 ± 0.054	0.088	-0.129 ± 0.034	<0.001*	-0.197 ± 0.062	0.002	-0.064 ± 0.060	0.288
<i>PC ae C38:2</i>	-0.144 ± 0.032	<0.001*	-0.230 ± 0.049	<0.001*	-0.076 ± 0.051	0.135	-0.114 ± 0.033	0.001*	-0.193 ± 0.061	0.001	-0.084 ± 0.059	0.154
<i>PC ae C40:2</i>	-0.132 ± 0.033	<0.001*	-0.257 ± 0.051	<0.001*	-0.104 ± 0.055	0.061	-0.100 ± 0.034	0.003	-0.232 ± 0.062	<0.001*	-0.065 ± 0.063	0.300
<i>PC ae C40:3</i>	-0.135 ± 0.029	<0.001*	-0.254 ± 0.045	<0.001*	-0.117 ± 0.048	0.014	-0.073 ± 0.029	0.013	-0.110 ± 0.054	0.041	-0.042 ± 0.054	0.439
<i>PC ae C42:3</i>	-0.131 ± 0.033	<0.001*	-0.241 ± 0.052	<0.001*	-0.115 ± 0.053	0.030	-0.052 ± 0.034	0.125	-0.042 ± 0.062	0.496	-0.021 ± 0.060	0.722
<i>PC ae C42:5</i>	-0.111 ± 0.031	<0.001*	-0.205 ± 0.050	<0.001*	-0.096 ± 0.052	0.068	-0.052 ± 0.032	0.111	-0.035 ± 0.060	0.566	0.006 ± 0.059	0.914
<i>SM (OH)</i> <i>C14:1</i>	-0.153 ± 0.028	<0.001*	-0.293 ± 0.044	<0.001*	-0.134 ± 0.046	0.004	-0.117 ± 0.028	<0.001*	-0.242 ± 0.053	<0.001*	-0.116 ± 0.052	0.026

<i>SM (OH) C16:1</i>	-0.130 ± 0.029	<0.001*	-0.257 ± 0.046	<0.001*	-0.114 ± 0.049	0.021	-0.098 ± 0.030	0.001	-0.222 ± 0.056	<0.001*	-0.089 ± 0.056	0.114
<i>SM (OH) C24:1</i>	-0.150 ± 0.033	<0.001*	-0.331 ± 0.052	<0.001*	-0.147 ± 0.054	0.006	-0.120 ± 0.034	<0.001*	-0.307 ± 0.062	<0.001*	-0.110 ± 0.061	0.074
<i>SM C16:0</i>	-0.167 ± 0.032	<0.001*	-0.326 ± 0.049	<0.001*	-0.138 ± 0.052	0.008	-0.108 ± 0.032	0.001*	-0.218 ± 0.060	<0.001*	-0.082 ± 0.058	0.155
<i>SM C16:1</i>	-0.144 ± 0.029	<0.001*	-0.311 ± 0.046	<0.001*	-0.131 ± 0.048	0.007	-0.091 ± 0.030	0.002	-0.203 ± 0.055	<0.001*	-0.053 ± 0.054	0.326
<i>SM C20:2</i>	-0.168 ± 0.033	<0.001*	-0.273 ± 0.051	<0.001*	-0.057 ± 0.053	0.284	-0.108 ± 0.035	0.002	-0.130 ± 0.063	0.040	0.054 ± 0.061	0.378
<i>LPC a C16:0</i>	-0.141 ± 0.034	<0.001*	-0.254 ± 0.052	<0.001*	-0.102 ± 0.056	0.066	-0.161 ± 0.036	<0.001*	-0.271 ± 0.065	<0.001*	-0.129 ± 0.065	0.048
<i>LPC a C17:0</i>	-0.267 ± 0.032	<0.001*	-0.421 ± 0.050	<0.001*	-0.176 ± 0.051	0.001	-0.253 ± 0.034	<0.001*	-0.349 ± 0.063	<0.001*	-0.150 ± 0.060	0.012
<i>LPC a C18:0</i>	-0.186 ± 0.034	<0.001*	-0.379 ± 0.053	<0.001*	-0.182 ± 0.056	0.001	-0.196 ± 0.036	<0.001*	-0.393 ± 0.066	<0.001*	-0.182 ± 0.065	0.005
<i>LPC a C18:1</i>	-0.217 ± 0.032	<0.001*	-0.322 ± 0.050	<0.001*	-0.120 ± 0.049	0.015	-0.198 ± 0.034	<0.001*	-0.268 ± 0.062	<0.001*	-0.100 ± 0.056	0.077
<i>LPC a C18:2</i>	-0.270 ± 0.032	<0.001*	-0.346 ± 0.050	<0.001*	-0.104 ± 0.045	0.021	-0.251 ± 0.033	<0.001*	-0.332 ± 0.061	<0.001*	-0.134 ± 0.051	0.009
Non-stage specific												
<i>C5</i>	0.105 ± 0.031	0.001	0.233 ± 0.047	<0.001*	0.141 ± 0.058	0.015	0.079 ± 0.032	0.015	0.146 ± 0.059	0.013	0.049 ± 0.068	0.471
<i>C14:1</i>	0.117 ± 0.034	0.001	0.185 ± 0.052	<0.001*	0.086 ± 0.065	0.187	0.170 ± 0.036	<0.001*	0.369 ± 0.066	<0.001*	0.204 ± 0.076	0.007
<i>Tyr</i>	0.092 ± 0.031	0.003	0.183 ± 0.048	<0.001*	0.130 ± 0.056	0.022	0.018 ± 0.032	0.574	-0.079 ± 0.059	0.183	-0.001 ± 0.064	0.993
<i>PC aa C34:1</i>	0.102 ± 0.032	0.002	0.180 ± 0.050	<0.001*	0.102 ± 0.053	0.055	0.072 ± 0.033	0.031	0.054 ± 0.061	0.374	0.028 ± 0.061	0.647
<i>PC ae C40:1</i>	-0.091 ± 0.034	0.008	-0.189 ± 0.054	<0.001*	-0.077 ± 0.056	0.175	-0.084 ± 0.035	0.017	-0.232 ± 0.065	<0.001*	-0.096 ± 0.064	0.134
<i>PC ae C40:4</i>	-0.090 ± 0.033	0.006	-0.191 ± 0.051	<0.001*	-0.111 ± 0.053	0.039	-0.045 ± 0.034	0.183	-0.092 ± 0.062	0.136	-0.058 ± 0.060	0.338
<i>PC ae C40:5</i>	-0.105 ± 0.033	0.001	-0.214 ± 0.052	<0.001*	-0.106 ± 0.054	0.049	-0.059 ± 0.033	0.076	-0.113 ± 0.062	0.067	-0.044 ± 0.060	0.468
<i>PC ae C42:2</i>	-0.099 ± 0.035	0.005	-0.251 ± 0.054	<0.001*	-0.142 ± 0.057	0.014	-0.064 ± 0.036	0.078	-0.197 ± 0.066	0.003	-0.107 ± 0.066	0.104
<i>PC ae C42:4</i>	-0.096 ± 0.033	0.003	-0.198 ± 0.052	<0.001*	-0.137 ± 0.053	0.010	-0.021 ± 0.034	0.542	0.011 ± 0.062	0.853	-0.034 ± 0.059	0.567
<i>PC ae C44:4</i>	-0.072 ± 0.033	0.027	-0.189 ± 0.052	<0.001*	-0.141 ± 0.054	0.009	0.000 ± 0.034	0.993	0.015 ± 0.062	0.807	-0.035 ± 0.061	0.574
<i>PC ae C44:6</i>	-0.106 ± 0.031	0.001	-0.186 ± 0.050	<0.001*	-0.081 ± 0.052	0.115	-0.031 ± 0.032	0.333	0.030 ± 0.060	0.616	0.039 ± 0.058	0.505
<i>SM (OH) C22:1</i>	-0.105 ± 0.031	0.001	-0.273 ± 0.049	<0.001*	-0.134 ± 0.050	0.007	-0.094 ± 0.032	0.003	-0.333 ± 0.059	<0.001*	-0.160 ± 0.056	0.004
<i>SM C24:1</i>	-0.095 ± 0.033	0.004	-0.263 ± 0.052	<0.001*	-0.109 ± 0.056	0.054	-0.035 ± 0.034	0.304	-0.133 ± 0.063	0.034	0.010 ± 0.063	0.874

This table displays the results (estimate and *P* values) for metabolites that were Bonferroni-significant in at least one of the three pairwise comparisons (PreT2D vs. NORM, T2D vs. NORM, and T2D vs. PreT2D). The analyses were conducted using a linear mixed-effects model under two models: the basic model, adjusted for age, sex, BMI, physical activity, smoking, and alcohol intake, and the sensitivity model, additionally adjusted for fasting glucose, HbA_{1C}, HDL, and systolic blood pressure. *Indicates Bonferroni-corrected *P* values less than 0.05. **Abbreviations:** C2, Acetylcarnitine; C5, Valerylcarnitine; C16, Hexadecanoylcarnitine; C18:1, Octadecenoylcarnitine; LPC, lysoPC. SE, standard error. NORM, normal glucose metabolism; PreT2D, Prediabetes; T2D, type 2 diabetes.

Table S6. Results for Bonferroni-significant metabolites that differed in at least one of the three pairwise comparisons identified from non-targeted metabolomics.

Sample size per group: NORM, N = 2000; PreT2D, N = 693; T2D, N = 262.

Metabolite ID	Basic model						Sensitivity model					
	PreT2D vs. NORM		T2D vs. NORM		T2D vs. PreT2D		PreT2D vs. NORM		T2D vs. NORM		T2D vs. PreT2D	
	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P	Estimate ± SE	P
<i>Persistent</i>												
M00584	0.242 ± 0.038	<0.001*	0.810 ± 0.057	<0.001*	0.565 ± 0.067	<0.001*	0.028 ± 0.038	0.46	0.038 ± 0.068	0.574	0.054 ± 0.070	0.442
M15676	0.277 ± 0.038	<0.001*	0.557 ± 0.057	<0.001*	0.289 ± 0.064	<0.001*	0.204 ± 0.040	<0.001*	0.292 ± 0.072	<0.001*	0.130 ± 0.073	0.076
M16634	0.303 ± 0.044	<0.001*	0.598 ± 0.066	<0.001*	0.302 ± 0.068	<0.001*	0.231 ± 0.047	<0.001*	0.379 ± 0.084	<0.001*	0.207 ± 0.079	0.009
M20489	0.432 ± 0.033	<0.001*	1.233 ± 0.050	<0.001*	0.797 ± 0.065	<0.001*	0.126 ± 0.029	<0.001*	0.133 ± 0.053	0.012	0.096 ± 0.059	0.104
M21044	0.518 ± 0.041	<0.001*	0.890 ± 0.061	<0.001*	0.390 ± 0.066	<0.001*	0.448 ± 0.043	<0.001*	0.636 ± 0.077	<0.001*	0.261 ± 0.076	0.001
M22116	0.241 ± 0.039	<0.001*	0.502 ± 0.059	<0.001*	0.266 ± 0.067	<0.001*	0.168 ± 0.041	<0.001*	0.248 ± 0.074	0.001	0.107 ± 0.077	0.164
M32322	0.279 ± 0.040	<0.001*	0.490 ± 0.060	<0.001*	0.235 ± 0.061	<0.001*	0.208 ± 0.042	<0.001*	0.262 ± 0.075	0.001	0.145 ± 0.071	0.04
M32338	-0.273 ± 0.041	<0.001*	-0.629 ± 0.062	<0.001*	-0.342 ± 0.064	<0.001*	-0.244 ± 0.043	<0.001*	-0.500 ± 0.078	<0.001*	-0.212 ± 0.074	0.004
M33084	0.235 ± 0.042	<0.001*	0.532 ± 0.063	<0.001*	0.285 ± 0.070	<0.001*	0.154 ± 0.044	0.001	0.190 ± 0.080	0.018	0.027 ± 0.080	0.731
M34221	0.293 ± 0.045	<0.001*	0.606 ± 0.067	<0.001*	0.302 ± 0.076	<0.001*	0.282 ± 0.047	<0.001*	0.551 ± 0.085	<0.001*	0.277 ± 0.088	0.002
M36552	0.173 ± 0.044	<0.001*	0.452 ± 0.065	<0.001*	0.276 ± 0.071	<0.001*	0.021 ± 0.045	0.641	-0.150 ± 0.081	0.064	-0.164 ± 0.078	0.035
<i>Early</i>												
M00527	0.364 ± 0.043	<0.001*	0.554 ± 0.064	<0.001*	0.194 ± 0.070	0.005	0.298 ± 0.045	<0.001*	0.366 ± 0.080	<0.001*	0.134 ± 0.081	0.098
M00542	0.208 ± 0.046	<0.001*	0.369 ± 0.069	<0.001*	0.145 ± 0.073	0.047	0.237 ± 0.048	<0.001*	0.451 ± 0.087	<0.001*	0.170 ± 0.086	0.048
M00599	0.232 ± 0.045	<0.001*	0.352 ± 0.067	<0.001*	0.130 ± 0.071	0.069	0.173 ± 0.048	<0.001*	0.159 ± 0.086	0.064	0.035 ± 0.084	0.672
M01105	0.189 ± 0.044	<0.001*	0.388 ± 0.065	<0.001*	0.198 ± 0.069	0.004	0.201 ± 0.046	<0.001*	0.445 ± 0.083	<0.001*	0.265 ± 0.081	0.001
M01121	0.240 ± 0.044	<0.001*	0.453 ± 0.066	<0.001*	0.201 ± 0.069	0.004	0.206 ± 0.046	<0.001*	0.341 ± 0.083	<0.001*	0.153 ± 0.081	0.06
M01336	0.297 ± 0.044	<0.001*	0.544 ± 0.066	<0.001*	0.248 ± 0.070	<0.001	0.274 ± 0.046	<0.001*	0.497 ± 0.083	<0.001*	0.267 ± 0.082	0.001
M01358	0.344 ± 0.044	<0.001*	0.586 ± 0.066	<0.001*	0.237 ± 0.069	0.001	0.296 ± 0.046	<0.001*	0.452 ± 0.084	<0.001*	0.205 ± 0.081	0.012
M01359	0.269 ± 0.044	<0.001*	0.471 ± 0.066	<0.001*	0.198 ± 0.070	0.004	0.253 ± 0.046	<0.001*	0.447 ± 0.084	<0.001*	0.229 ± 0.082	0.005
M01365	0.183 ± 0.044	<0.001*	0.394 ± 0.066	<0.001*	0.190 ± 0.068	0.006	0.173 ± 0.046	<0.001*	0.374 ± 0.083	<0.001*	0.199 ± 0.080	0.013
M01508	0.200 ± 0.044	<0.001*	0.329 ± 0.066	<0.001*	0.131 ± 0.071	0.067	0.186 ± 0.047	<0.001*	0.283 ± 0.084	0.001	0.122 ± 0.083	0.144
M01712	0.178 ± 0.043	<0.001*	0.331 ± 0.064	<0.001*	0.163 ± 0.071	0.021	0.083 ± 0.044	0.062	0.083 ± 0.080	0.297	0.025 ± 0.081	0.755
M15122	0.202 ± 0.041	<0.001*	0.400 ± 0.061	<0.001*	0.188 ± 0.065	0.004	0.197 ± 0.043	<0.001*	0.393 ± 0.077	<0.001*	0.237 ± 0.076	0.002
M15753	-0.224 ± 0.044	<0.001*	-0.277 ± 0.066	<0.001*	-0.070 ± 0.070	0.323	-0.234 ± 0.047	<0.001*	-0.334 ± 0.084	<0.001*	-0.168 ± 0.082	0.041
M17805	0.274 ± 0.044	<0.001*	0.502 ± 0.065	<0.001*	0.218 ± 0.071	0.002	0.266 ± 0.046	<0.001*	0.498 ± 0.082	<0.001*	0.273 ± 0.082	0.001
M18335	-0.178 ± 0.043	<0.001*	-0.338 ± 0.064	<0.001*	-0.146 ± 0.072	0.043	-0.179 ± 0.045	<0.001*	-0.393 ± 0.081	<0.001*	-0.212 ± 0.083	0.011

<i>M19323</i>	0.190 ± 0.044	<0.001*	0.324 ± 0.066	<0.001*	0.133 ± 0.071	0.062	0.181 ± 0.046	<0.001*	0.346 ± 0.082	<0.001*	0.206 ± 0.082	0.012
<i>M21047</i>	0.357 ± 0.042	<0.001*	0.620 ± 0.063	<0.001*	0.261 ± 0.069	<0.001	0.276 ± 0.044	<0.001*	0.375 ± 0.079	<0.001*	0.133 ± 0.080	0.098
<i>M21127</i>	0.179 ± 0.043	<0.001*	0.331 ± 0.064	<0.001*	0.154 ± 0.070	0.029	0.112 ± 0.045	0.013	0.111 ± 0.081	0.172	0.017 ± 0.081	0.834
<i>M21184</i>	0.176 ± 0.045	<0.001*	0.384 ± 0.067	<0.001*	0.216 ± 0.075	0.004	0.091 ± 0.046	0.049	0.113 ± 0.083	0.176	0.051 ± 0.086	0.551
<i>M32197</i>	0.146 ± 0.037	<0.001*	0.353 ± 0.057	<0.001*	0.195 ± 0.062	0.002	0.115 ± 0.039	0.004	0.276 ± 0.071	<0.001*	0.205 ± 0.071	0.004
<i>M32198</i>	0.210 ± 0.045	<0.001*	0.329 ± 0.067	<0.001*	0.125 ± 0.072	0.081	0.212 ± 0.047	<0.001*	0.358 ± 0.085	<0.001*	0.205 ± 0.085	0.015
<i>M32504</i>	0.262 ± 0.044	<0.001*	0.366 ± 0.065	<0.001*	0.096 ± 0.072	0.179	0.251 ± 0.046	<0.001*	0.354 ± 0.082	<0.001*	0.155 ± 0.083	0.061
<i>M32757</i>	0.183 ± 0.036	<0.001*	0.282 ± 0.056	<0.001*	0.103 ± 0.063	0.101	0.120 ± 0.037	0.001	0.112 ± 0.067	0.091	0.017 ± 0.070	0.812
<i>M32761</i>	0.171 ± 0.040	<0.001*	0.256 ± 0.061	<0.001*	0.072 ± 0.065	0.264	0.072 ± 0.042	0.084	-0.018 ± 0.075	0.811	-0.024 ± 0.072	0.743
<i>M32980</i>	0.260 ± 0.045	<0.001*	0.506 ± 0.067	<0.001*	0.232 ± 0.070	0.001	0.246 ± 0.047	<0.001*	0.489 ± 0.085	<0.001*	0.281 ± 0.082	0.001
<i>M33009</i>	-0.200 ± 0.045	<0.001*	-0.352 ± 0.067	<0.001*	-0.149 ± 0.072	0.039	-0.163 ± 0.047	0.001	-0.239 ± 0.085	0.005	-0.100 ± 0.084	0.232
<i>M33415</i>	0.210 ± 0.039	<0.001*	0.359 ± 0.060	<0.001*	0.180 ± 0.067	0.007	0.131 ± 0.040	0.001	0.099 ± 0.072	0.169	0.043 ± 0.075	0.568
<i>M33447</i>	0.173 ± 0.043	<0.001*	0.316 ± 0.064	<0.001*	0.127 ± 0.068	0.06	0.194 ± 0.045	<0.001*	0.417 ± 0.081	<0.001*	0.232 ± 0.078	0.003
<i>M33587</i>	0.253 ± 0.044	<0.001*	0.483 ± 0.066	<0.001*	0.217 ± 0.071	0.002	0.244 ± 0.046	<0.001*	0.459 ± 0.083	<0.001*	0.233 ± 0.083	0.005
<i>M33937</i>	0.190 ± 0.038	<0.001*	0.352 ± 0.058	<0.001*	0.159 ± 0.067	0.018	0.173 ± 0.039	<0.001*	0.305 ± 0.071	<0.001*	0.128 ± 0.077	0.099
<i>M33971</i>	0.198 ± 0.044	<0.001*	0.352 ± 0.065	<0.001*	0.143 ± 0.069	0.039	0.193 ± 0.046	<0.001*	0.356 ± 0.083	<0.001*	0.179 ± 0.081	0.027
<i>M33972</i>	0.237 ± 0.044	<0.001*	0.409 ± 0.066	<0.001*	0.156 ± 0.070	0.025	0.212 ± 0.047	<0.001*	0.336 ± 0.084	<0.001*	0.130 ± 0.081	0.112
<i>M34035</i>	0.220 ± 0.044	<0.001*	0.387 ± 0.066	<0.001*	0.169 ± 0.071	0.018	0.228 ± 0.046	<0.001*	0.404 ± 0.083	<0.001*	0.210 ± 0.082	0.011
<i>M34407</i>	0.162 ± 0.041	<0.001*	0.326 ± 0.062	<0.001*	0.194 ± 0.065	0.003	0.150 ± 0.043	0.001	0.252 ± 0.078	0.001	0.140 ± 0.075	0.064
<i>M34469</i>	0.209 ± 0.045	<0.001*	0.481 ± 0.067	<0.001*	0.271 ± 0.073	<0.001	0.158 ± 0.048	0.001	0.337 ± 0.086	<0.001*	0.223 ± 0.085	0.009
<i>M34761</i>	0.185 ± 0.044	<0.001*	0.361 ± 0.066	<0.001*	0.161 ± 0.069	0.021	0.175 ± 0.046	<0.001*	0.370 ± 0.083	<0.001*	0.215 ± 0.081	0.008
<i>M35189</i>	-0.177 ± 0.044	<0.001*	-0.273 ± 0.067	<0.001*	-0.101 ± 0.070	0.152	-0.199 ± 0.046	<0.001*	-0.364 ± 0.083	<0.001*	-0.174 ± 0.082	0.033
<i>M35320</i>	-0.234 ± 0.044	<0.001*	-0.300 ± 0.066	<0.001*	-0.067 ± 0.077	0.382	-0.218 ± 0.046	<0.001*	-0.299 ± 0.083	<0.001*	-0.111 ± 0.089	0.212
<i>M35718</i>	0.198 ± 0.045	<0.001*	0.266 ± 0.068	<0.001*	0.080 ± 0.071	0.26	0.200 ± 0.048	<0.001*	0.320 ± 0.086	<0.001*	0.162 ± 0.083	0.05
<i>M35977</i>	0.229 ± 0.045	<0.001*	0.315 ± 0.067	<0.001*	0.093 ± 0.072	0.199	0.197 ± 0.047	<0.001*	0.244 ± 0.086	0.004	0.096 ± 0.084	0.256
<i>Late</i>												
<i>M00060</i>	0.098 ± 0.037	0.008	0.405 ± 0.056	<0.001*	0.328 ± 0.065	<0.001*	0.050 ± 0.039	0.2	0.197 ± 0.070	0.005	0.180 ± 0.074	0.015
<i>M00577</i>	0.150 ± 0.044	0.001	0.591 ± 0.065	<0.001*	0.447 ± 0.067	<0.001*	0.064 ± 0.046	0.166	0.271 ± 0.083	0.001	0.238 ± 0.079	0.003
<i>M01125</i>	0.108 ± 0.036	0.003	0.423 ± 0.054	<0.001*	0.325 ± 0.060	<0.001*	0.060 ± 0.037	0.107	0.213 ± 0.067	0.001	0.190 ± 0.068	0.005
<i>M01644</i>	-0.055 ± 0.045	0.222	-0.366 ± 0.067	<0.001*	-0.312 ± 0.075	<0.001*	0.026 ± 0.047	0.573	-0.064 ± 0.084	0.445	-0.062 ± 0.085	0.466
<i>M01649</i>	0.115 ± 0.039	0.003	0.426 ± 0.059	<0.001*	0.328 ± 0.066	<0.001*	0.049 ± 0.041	0.235	0.165 ± 0.074	0.025	0.167 ± 0.076	0.028
<i>M02734</i>	0.046 ± 0.042	0.275	0.328 ± 0.063	<0.001*	0.291 ± 0.072	<0.001*	0.002 ± 0.044	0.956	0.194 ± 0.080	0.015	0.276 ± 0.083	0.001
<i>M12035</i>	-0.064 ± 0.044	0.145	-0.421 ± 0.066	<0.001*	-0.353 ± 0.074	<0.001*	0.015 ± 0.046	0.739	-0.109 ± 0.083	0.187	-0.086 ± 0.084	0.303
<i>M18369</i>	0.083 ± 0.039	0.031	0.408 ± 0.058	<0.001*	0.334 ± 0.064	<0.001*	0.023 ± 0.040	0.576	0.192 ± 0.073	0.008	0.236 ± 0.075	0.002

<i>M20675</i>	-0.089 ± 0.038	0.019	-0.543 ± 0.058	<0.001*	-0.451 ± 0.070	<0.001*	-0.006 ± 0.038	0.870	-0.165 ± 0.069	0.017	-0.078 ± 0.072	0.274
<i>M27722</i>	0.153 ± 0.045	0.001	0.487 ± 0.067	<0.001*	0.340 ± 0.071	<0.001*	0.103 ± 0.048	0.031	0.304 ± 0.086	<0.001*	0.241 ± 0.083	0.004
<i>M32346</i>	0.053 ± 0.043	0.223	0.361 ± 0.065	<0.001*	0.313 ± 0.073	<0.001*	0.013 ± 0.046	0.777	0.258 ± 0.082	0.002	0.249 ± 0.084	0.003
<i>M32393</i>	0.114 ± 0.039	0.004	0.384 ± 0.059	<0.001*	0.269 ± 0.063	<0.001*	0.051 ± 0.041	0.22	0.166 ± 0.074	0.026	0.166 ± 0.072	0.022
<i>M32632</i>	-0.067 ± 0.040	0.093	-0.382 ± 0.061	<0.001*	-0.315 ± 0.069	<0.001*	0.024 ± 0.041	0.559	-0.044 ± 0.074	0.554	-0.044 ± 0.076	0.566
<i>M32735</i>	0.081 ± 0.042	0.056	0.397 ± 0.064	<0.001*	0.351 ± 0.067	<0.001*	0.016 ± 0.044	0.711	0.184 ± 0.080	0.021	0.288 ± 0.078	<0.001*
<i>M32814</i>	-0.105 ± 0.043	0.016	-0.443 ± 0.064	<0.001*	-0.353 ± 0.076	<0.001*	-0.001 ± 0.045	0.977	-0.058 ± 0.081	0.471	-0.043 ± 0.085	0.616
<i>M33422</i>	0.053 ± 0.042	0.213	0.322 ± 0.063	<0.001*	0.264 ± 0.069	<0.001*	0.045 ± 0.045	0.318	0.272 ± 0.081	0.001	0.278 ± 0.081	0.001
<i>M33477</i>	0.088 ± 0.040	0.029	0.354 ± 0.061	<0.001*	0.258 ± 0.066	<0.001*	0.080 ± 0.042	0.061	0.321 ± 0.076	<0.001*	0.240 ± 0.076	0.002
<i>M33935</i>	0.060 ± 0.043	0.159	0.334 ± 0.065	<0.001*	0.272 ± 0.066	<0.001*	0.016 ± 0.045	0.728	0.172 ± 0.081	0.035	0.227 ± 0.077	0.003
<i>M34306</i>	-0.066 ± 0.043	0.123	-0.513 ± 0.065	<0.001*	-0.446 ± 0.071	<0.001*	-0.027 ± 0.045	0.542	-0.295 ± 0.081	<0.001*	-0.206 ± 0.079	0.010
<i>M36808</i>	0.085 ± 0.043	0.046	0.490 ± 0.063	<0.001*	0.429 ± 0.071	<0.001*	-0.012 ± 0.045	0.795	0.150 ± 0.081	0.064	0.182 ± 0.082	0.026
<i>Non-stage specific</i>												
<i>M00053</i>	-0.133 ± 0.043	0.002	-0.331 ± 0.065	<0.001*	-0.189 ± 0.074	0.011	-0.115 ± 0.045	0.011	-0.281 ± 0.082	0.001	-0.142 ± 0.086	0.100
<i>M00059</i>	-0.150 ± 0.044	0.001	-0.258 ± 0.066	<0.001*	-0.113 ± 0.073	0.122	-0.118 ± 0.046	0.010	-0.120 ± 0.083	0.149	-0.007 ± 0.086	0.938
<i>M00064</i>	0.104 ± 0.042	0.014	0.343 ± 0.063	<0.001*	0.250 ± 0.071	<0.001	0.079 ± 0.044	0.073	0.247 ± 0.080	0.002	0.198 ± 0.083	0.017
<i>M00569</i>	0.139 ± 0.042	0.001	0.329 ± 0.064	<0.001*	0.174 ± 0.072	0.016	0.079 ± 0.044	0.074	0.119 ± 0.080	0.137	0.047 ± 0.083	0.574
<i>M01114</i>	0.060 ± 0.044	0.172	0.260 ± 0.066	<0.001*	0.201 ± 0.071	0.005	-0.016 ± 0.047	0.733	0.035 ± 0.084	0.677	0.073 ± 0.083	0.383
<i>M01299</i>	0.009 ± 0.041	0.823	0.249 ± 0.062	<0.001*	0.245 ± 0.070	0.001	-0.049 ± 0.043	0.259	0.041 ± 0.078	0.603	0.149 ± 0.080	0.064
<i>M01356</i>	0.134 ± 0.046	0.004	0.333 ± 0.068	<0.001*	0.177 ± 0.071	0.012	0.119 ± 0.048	0.014	0.258 ± 0.087	0.003	0.144 ± 0.082	0.082
<i>M01444</i>	0.075 ± 0.043	0.083	0.250 ± 0.065	<0.001*	0.187 ± 0.071	0.009	0.064 ± 0.046	0.161	0.171 ± 0.082	0.038	0.085 ± 0.083	0.307
<i>M01564</i>	0.162 ± 0.043	<0.001	0.267 ± 0.065	<0.001*	0.087 ± 0.070	0.213	0.173 ± 0.045	<0.001*	0.295 ± 0.082	<0.001*	0.106 ± 0.082	0.192
<i>M01604</i>	0.121 ± 0.037	0.001	0.218 ± 0.057	<0.001*	0.137 ± 0.062	0.028	0.106 ± 0.039	0.007	0.213 ± 0.070	0.002	0.191 ± 0.071	0.008
<i>M01638</i>	-0.116 ± 0.045	0.011	-0.270 ± 0.068	<0.001*	-0.152 ± 0.074	0.040	-0.071 ± 0.048	0.134	-0.136 ± 0.086	0.113	-0.027 ± 0.086	0.753
<i>M01898</i>	0.069 ± 0.040	0.084	0.277 ± 0.062	<0.001*	0.219 ± 0.066	0.001	0.013 ± 0.042	0.755	0.112 ± 0.075	0.136	0.163 ± 0.074	0.028
<i>M02730</i>	-0.161 ± 0.043	<0.001	-0.318 ± 0.064	<0.001*	-0.157 ± 0.076	0.038	-0.111 ± 0.045	0.013	-0.117 ± 0.081	0.148	0.030 ± 0.087	0.726
<i>M12768</i>	-0.122 ± 0.046	0.008	-0.279 ± 0.068	<0.001*	-0.132 ± 0.074	0.076	-0.103 ± 0.048	0.034	-0.228 ± 0.087	0.009	-0.089 ± 0.087	0.309
<i>M15365</i>	-0.134 ± 0.045	0.003	-0.352 ± 0.067	<0.001*	-0.212 ± 0.072	0.003	-0.106 ± 0.048	0.026	-0.234 ± 0.086	0.006	-0.154 ± 0.083	0.064
<i>M15778</i>	-0.095 ± 0.045	0.034	-0.306 ± 0.066	<0.001*	-0.197 ± 0.074	0.008	-0.038 ± 0.047	0.417	-0.068 ± 0.085	0.423	-0.018 ± 0.085	0.835
<i>M15990</i>	-0.106 ± 0.045	0.020	-0.361 ± 0.068	<0.001*	-0.260 ± 0.072	<0.001	-0.083 ± 0.048	0.084	-0.299 ± 0.086	0.001	-0.238 ± 0.085	0.005
<i>M16818</i>	0.129 ± 0.039	0.001	0.281 ± 0.059	<0.001*	0.157 ± 0.063	0.014	0.143 ± 0.041	0.001	0.330 ± 0.074	<0.001*	0.173 ± 0.074	0.019
<i>M19364</i>	0.109 ± 0.045	0.015	0.349 ± 0.067	<0.001*	0.248 ± 0.073	0.001	0.004 ± 0.047	0.926	0.025 ± 0.085	0.77	0.105 ± 0.085	0.22
<i>M20699</i>	0.106 ± 0.042	0.012	0.288 ± 0.063	<0.001*	0.159 ± 0.066	0.016	0.060 ± 0.044	0.175	0.134 ± 0.080	0.093	0.063 ± 0.076	0.407

<i>M27256</i>	-0.051 ± 0.044	0.245	-0.282 ± 0.065	<0.001*	-0.193 ± 0.070	0.006	-0.030 ± 0.045	0.506	-0.225 ± 0.082	0.006	-0.122 ± 0.079	0.125
<i>M27273</i>	0.132 ± 0.045	0.003	0.353 ± 0.066	<0.001*	0.221 ± 0.069	0.001	0.015 ± 0.047	0.75	-0.058 ± 0.084	0.491	-0.067 ± 0.079	0.397
<i>M27278</i>	-0.132 ± 0.041	0.001	-0.303 ± 0.063	<0.001*	-0.165 ± 0.070	0.018	-0.116 ± 0.043	0.007	-0.263 ± 0.078	0.001	-0.146 ± 0.080	0.066
<i>M32315</i>	-0.155 ± 0.044	<0.001	-0.252 ± 0.066	<0.001*	-0.103 ± 0.072	0.154	-0.172 ± 0.047	<0.001*	-0.293 ± 0.085	0.001	-0.135 ± 0.085	0.110
<i>M32405</i>	-0.115 ± 0.045	0.011	-0.263 ± 0.068	<0.001*	-0.168 ± 0.072	0.020	-0.102 ± 0.048	0.032	-0.224 ± 0.086	0.009	-0.170 ± 0.084	0.044
<i>M32489</i>	-0.045 ± 0.045	0.321	-0.297 ± 0.067	<0.001*	-0.259 ± 0.075	0.001	0.019 ± 0.047	0.687	-0.087 ± 0.085	0.306	-0.080 ± 0.086	0.351
<i>M32492</i>	-0.037 ± 0.044	0.395	-0.262 ± 0.065	<0.001*	-0.226 ± 0.074	0.002	0.040 ± 0.046	0.388	-0.005 ± 0.083	0.948	-0.012 ± 0.084	0.887
<i>M32634</i>	-0.066 ± 0.045	0.139	-0.307 ± 0.067	<0.001*	-0.238 ± 0.076	0.002	-0.005 ± 0.047	0.922	-0.092 ± 0.084	0.273	-0.061 ± 0.087	0.482
<i>M32672</i>	-0.036 ± 0.034	0.286	-0.207 ± 0.052	<0.001*	-0.177 ± 0.058	0.003	0.022 ± 0.035	0.537	0.034 ± 0.063	0.597	0.001 ± 0.065	0.987
<i>M32855</i>	0.140 ± 0.043	0.001	0.244 ± 0.065	<0.001*	0.095 ± 0.068	0.163	0.149 ± 0.045	0.001	0.247 ± 0.081	0.002	0.105 ± 0.079	0.183
<i>M32867</i>	-0.057 ± 0.044	0.199	-0.307 ± 0.066	<0.001*	-0.253 ± 0.077	0.001	0.006 ± 0.046	0.895	-0.080 ± 0.083	0.338	-0.052 ± 0.086	0.543
<i>M33390</i>	-0.124 ± 0.038	0.001	-0.247 ± 0.057	<0.001*	-0.109 ± 0.062	0.080	-0.131 ± 0.039	0.001	-0.338 ± 0.071	<0.001*	-0.177 ± 0.071	0.013
<i>M34453</i>	-0.141 ± 0.046	0.002	-0.300 ± 0.068	<0.001*	-0.161 ± 0.075	0.031	-0.088 ± 0.048	0.070	-0.128 ± 0.087	0.141	-0.018 ± 0.088	0.839
<i>M35257</i>	-0.096 ± 0.044	0.030	-0.255 ± 0.066	<0.001*	-0.162 ± 0.073	0.026	-0.082 ± 0.046	0.075	-0.272 ± 0.083	0.001	-0.184 ± 0.085	0.030
<i>M35431</i>	0.020 ± 0.041	0.621	0.252 ± 0.062	<0.001*	0.235 ± 0.065	<0.001	-0.010 ± 0.043	0.816	0.117 ± 0.077	0.13	0.168 ± 0.075	0.025
<i>M35754</i>	0.059 ± 0.046	0.194	0.274 ± 0.068	<0.001*	0.225 ± 0.073	0.002	-0.001 ± 0.048	0.987	0.031 ± 0.087	0.723	0.088 ± 0.085	0.303
<i>M37203</i>	0.109 ± 0.035	0.002	0.246 ± 0.055	<0.001*	0.126 ± 0.062	0.04	0.053 ± 0.036	0.149	0.084 ± 0.065	0.201	0.038 ± 0.069	0.582
<i>M37506</i>	-0.109 ± 0.043	0.012	-0.372 ± 0.065	<0.001*	-0.240 ± 0.070	0.001	-0.052 ± 0.045	0.246	-0.170 ± 0.080	0.035	-0.103 ± 0.079	0.191

This table displays the linear mixed-effects model results (estimate and P values) for the three pairwise comparisons (PreT2D vs. NORM, T2D vs. NORM, and T2D vs. PreT2D) under two models: the basic model, adjusted for age, sex, BMI, physical activity, smoking, and alcohol intake, the and sensitivity model, additionally adjusted for fasting glucose, HbA_{1C}, HDL, and systolic blood pressure. *Indicates Bonferroni-corrected *P* values less than 0.05. **Abbreviations:** SE, standard error. NORM, normal glucose metabolism; PreT2D, Prediabetes; T2D, type 2 diabetes.

Table S7. Sensitivity Analyses for Horizontal Pleiotropy and Instrument Heterogeneity in Mendelian Randomization.

<i>Metabolite</i>	<i>MR-PRESSO outlier test</i>		<i>MR-Egger intercept test</i>			<i>Cochran's Q test</i>		
	RSSobs	P	Intercept	SE	P	Q value	DF	P
C2	21.94	0.291	0.002	0.005	0.734	20.28	17	0.260
BCAA	27.44	0.041	0.009	0.007	0.266	24.55	12	0.017
<i>γ-GluVal</i>	22.43	0.111	0.001	0.010	0.930	19.77	13	0.101
BCAA (IR-predominated T2D)	20.72	0.168	0.021	0.046	0.655	18.09	12	0.113

This table presents results from three sensitivity analyses assessing the robustness of Mendelian randomization (MR) assumptions for three primary exposure–outcome pairs (acetylcarnitine [C2], branched-chain amino acids [BCAA: leucine, isoleucine, valine], and γ -glutamyl-valine in relation to T2D), as well as an additional analysis of BCAA in relation to insulin resistance–predominated T2D. The MR-PRESSO global test was used to detect horizontal pleiotropic outliers (RSSobs and P value reported; $P < 0.05$ indicates potential bias). The MR-Egger intercept test evaluates directional pleiotropy (intercept, SE, and P value), with $P > 0.05$ suggesting no evidence of bias. Cochran's Q test assesses heterogeneity among instruments (Q, DF, and P value), where $P < 0.05$ may reflect violations of MR assumptions.

Table S8. Summary of GWAS datasets included in Mendelian randomization analyses.

<i>Study Identifier</i>	<i>Phenotype</i>	<i>Sample Size</i>	<i>Population</i>	<i>URL</i>
<i>ebi-a-GCST90018926</i>	Type 2 diabetes	490,089	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018926/
<i>ebi-a-GCST90026414</i>	Severe insulin-resistant type 2 diabetes	3874	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90026414/
<i>met-a-463</i>	Acetylcarnitine	7,805	European	https://gwas.mrcieu.ac.uk/datasets/met-a-463/
<i>met-d-Total_BCAA</i>	BCAA (Leu + Ile + Val)	115,047	European	https://gwas.mrcieu.ac.uk/datasets/met-d-Total_BCAA/
<i>met-a-474</i>	Gamma-glutamyl-valine	7,753	European	https://gwas.mrcieu.ac.uk/datasets/met-a-474/

This table provides a summary of the GWAS datasets used in MR analyses, including the exposure and outcome traits, study identifiers, sample sizes, population ancestry, and data source URLs. All datasets were obtained from the IEU OpenGWAS database.

Fig. S1. Study design.

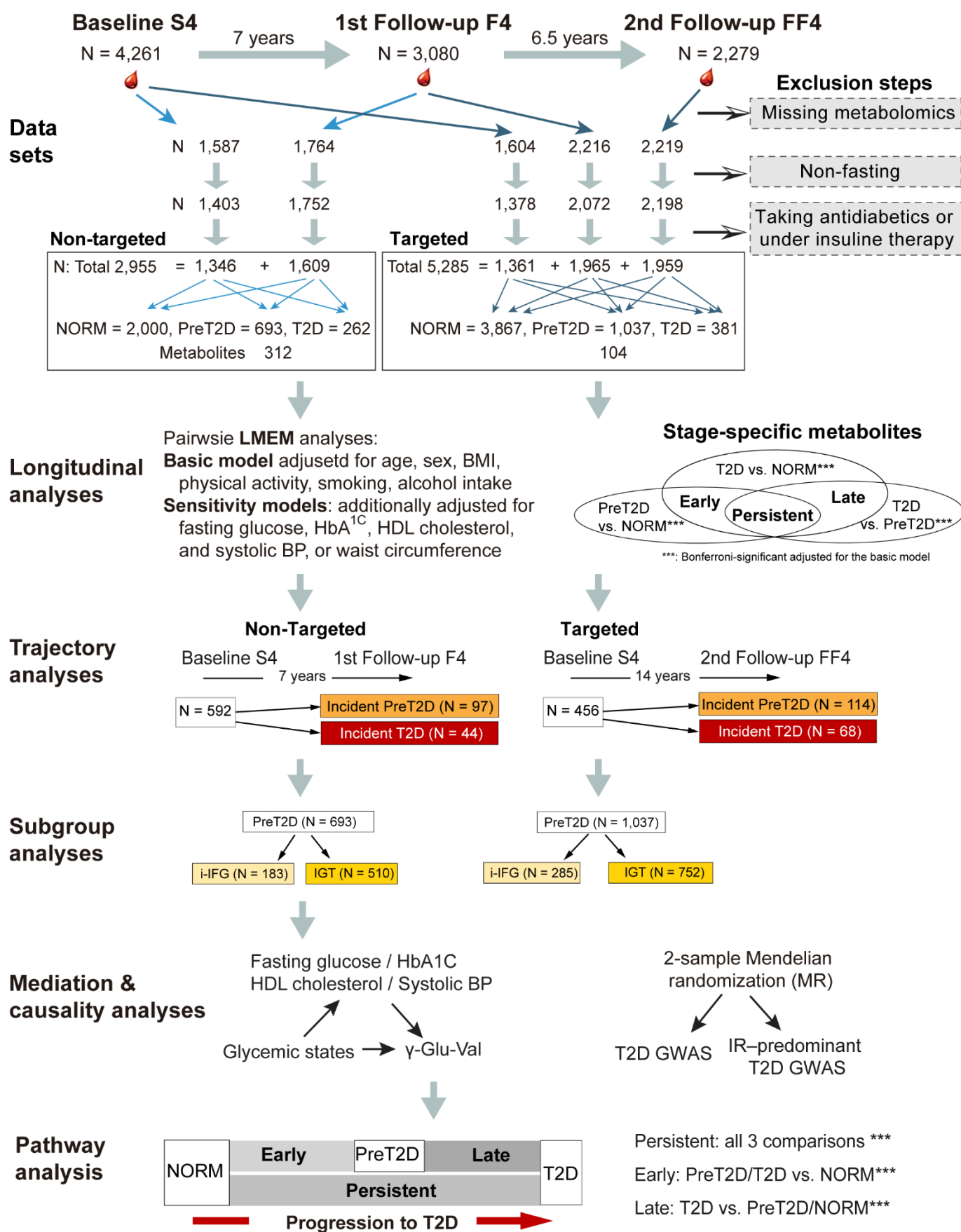
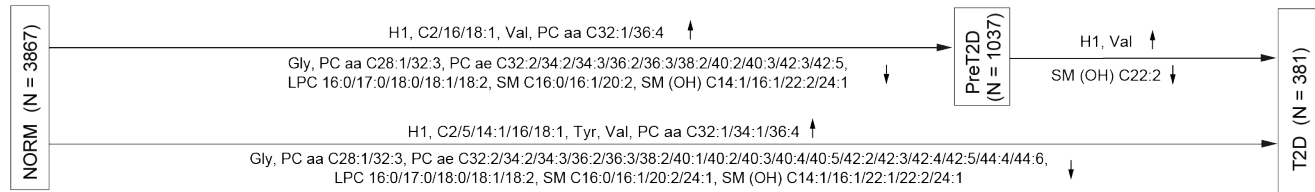
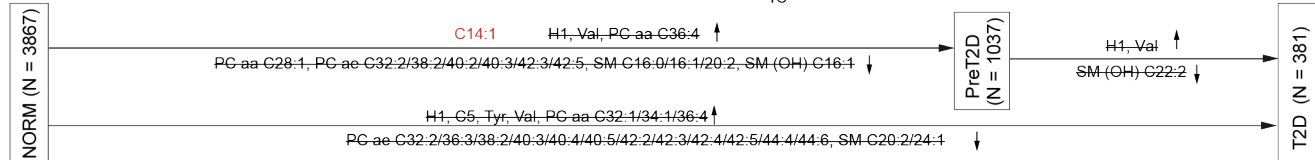


Fig. S2. Glycemic stage-specific metabolite shifts: Targeted metabolomics summary.

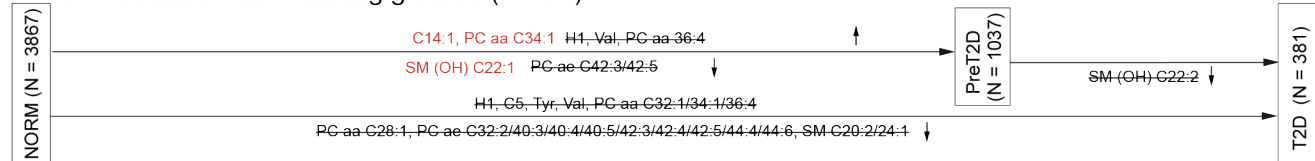
A Basic model: age + sex + bmi + physical activity + smoking + alcohol intake (n = 45 metabolites)



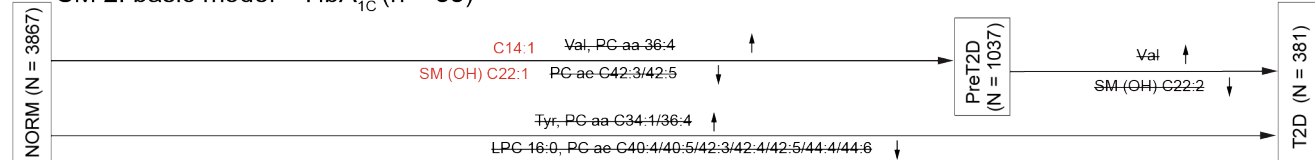
B Sensitivity model (SM): basic model + fasting glucose + HbA_{1c} + HDL cholesterol + systolic BP (n = 26)



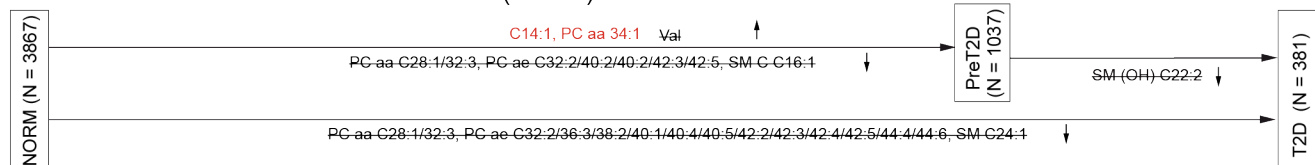
C SM 1: basic model + fasting glucose (n = 31)



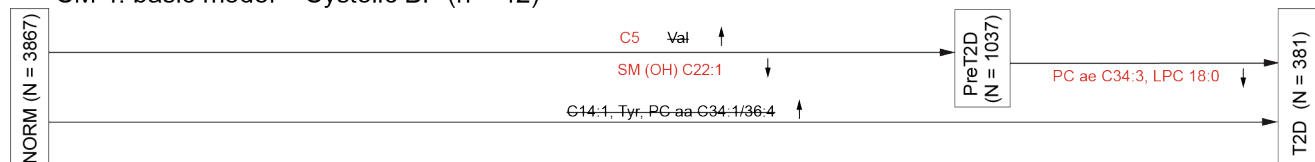
D SM 2: basic model + HbA_{1c} (n = 35)



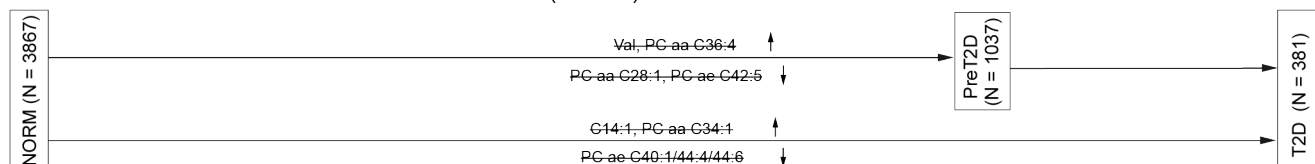
E SM 3: basic model + HDL cholesterol (n = 32)



F SM 4: basic model + Systolic BP (n = 42)

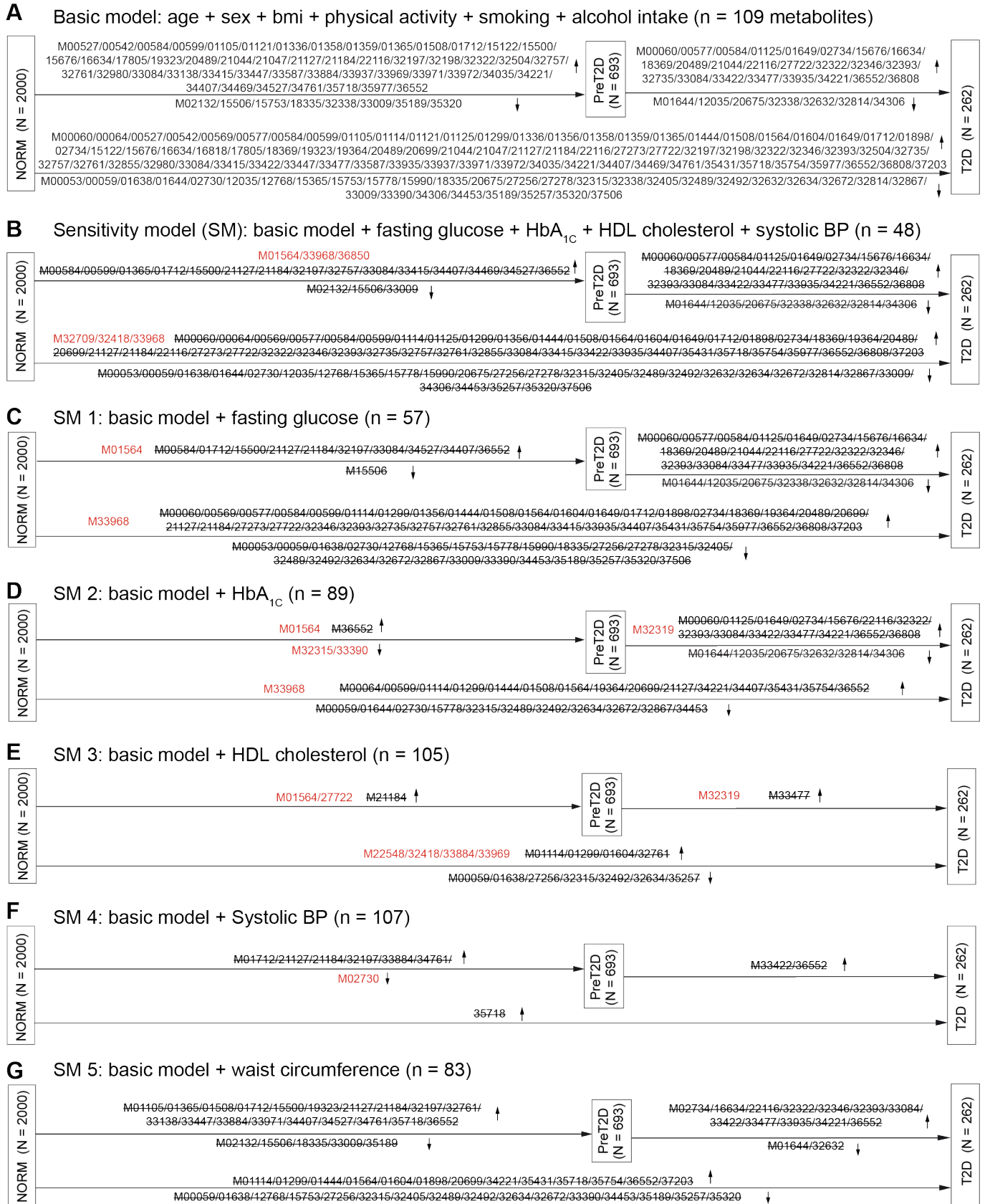


G SM 5: basic model + waist circumference (n = 36)



This figure summarizes the significantly altered metabolites along the glycemic progression from NORM (N = 3.867) to PreT2D (N = 1,037) and T2D (N = 381). The basic model adjusted for age, sex, BMI, physical activity, smoking status, and alcohol intake (A). The sensitivity analyses adjusted the basic model with additional covariates: fasting glucose, HbA_{1c}, HDL cholesterol, and systolic blood pressure (B), fasting glucose only (C), HbA_{1c} only (D), HDL cholesterol only (E), systolic blood pressure only (F), and waist circumference (G). Plots B-G compared to plot A: Metabolites that remained significant in the basic model are not shown in plots B-G. Metabolites with newly identified significant changes (not observed in the basic model) are highlighted in red. Metabolites that are non longer significant in the sensitivity analyses are shown with a strikethrough. Note: All results are Bonferroni-adjusted for multiple comparisons.

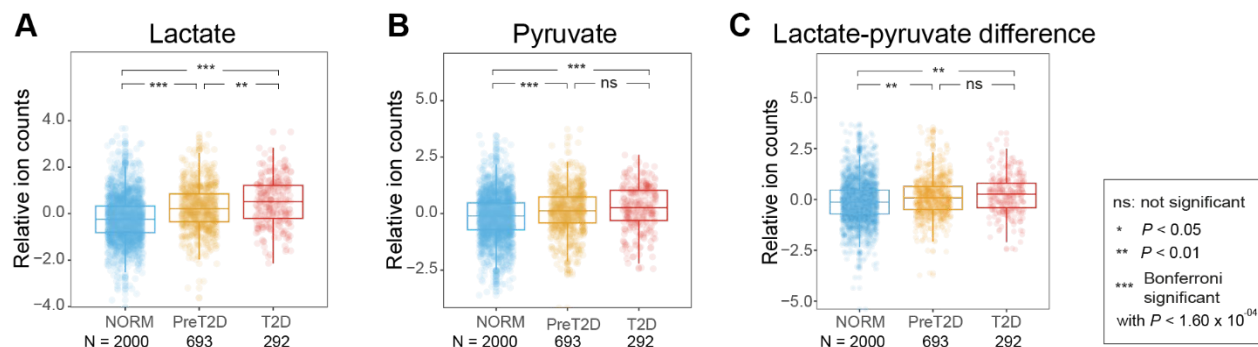
Fig. S3. Glycemic stage-specific metabolite shifts: Non-targeted metabolomics summary.



This figure summarizes the significantly altered metabolites along the glycemic progression from NORM (N = 2000) to PreT2D (N = 693) and T2D (N = 262) from non-targeted metabolomics data, as identified under the basic model and five sensitivity models. Basic model adjusted for age, sex, BMI, physical activity, smoking status, and alcohol intake (A). Sensitivity analyses further adjusting the basic model with additional covariates: fasting glucose, HbA_{1c}, HDL cholesterol, and systolic blood pressure (B), fasting glucose only (C), HbA_{1c} only (D), HDL cholesterol only (E), systolic blood pressure

only (F), and waist circumference (G). Plots B-G compared to plot A: Metabolites that remained significant in the basic model are not shown in plots B-G. Metabolites with newly identified significant changes (not observed in the basic model) are highlighted in red. Metabolites that are non longer significant in the sensitivity analyses are shown with a strikethrough. Note: All results are Bonferroni-adjusted for multiple comparisons.

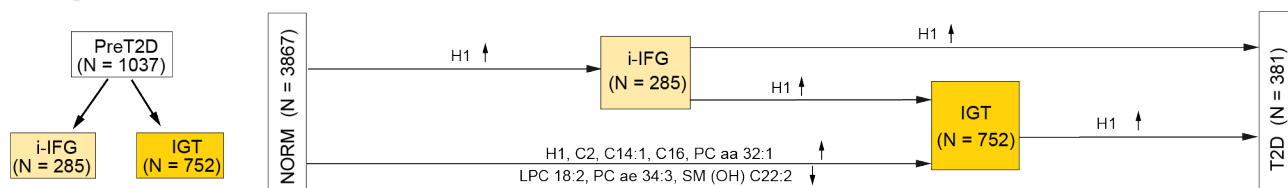
Fig. S4. Lactate, pyruvate, and their normalized difference across glycemic states.



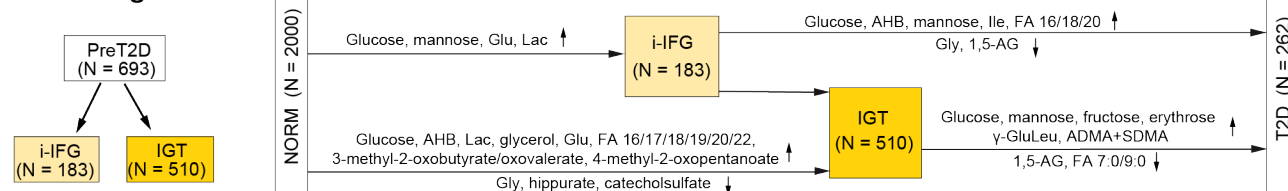
(A) Lactate (normalized, unitless intensity). (B) Pyruvate (normalized, unitless intensity). (C) Normalized difference (lactate – pyruvate). Points are individual participants; boxes show median and interquartile range; sample size in each group indicted with N are shown below group name in the x-axis. *P*-values are nominal from linear mixed effect models of each outcome (lactate, pyruvate, or lactate – pyruvate) on glycemic state, adjusting for age, sex, BMI, smoking status, physical activity, and alcohol intake.

Fig. S5. Subgroup analyses.

A Targeted

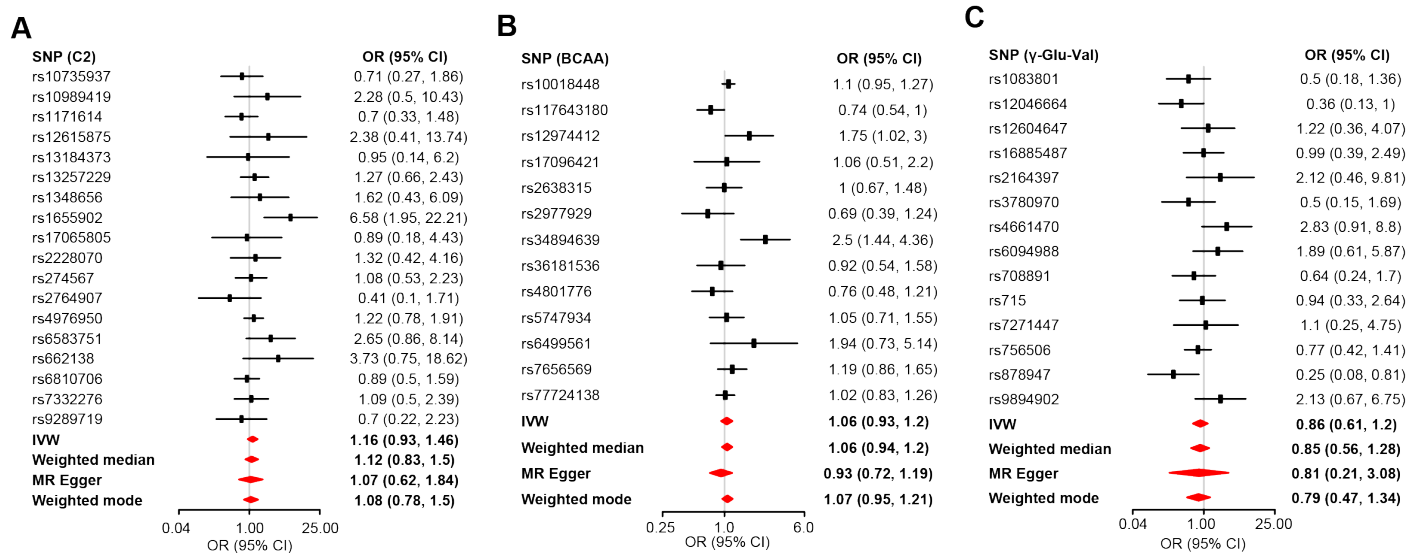


B Non-Targeted



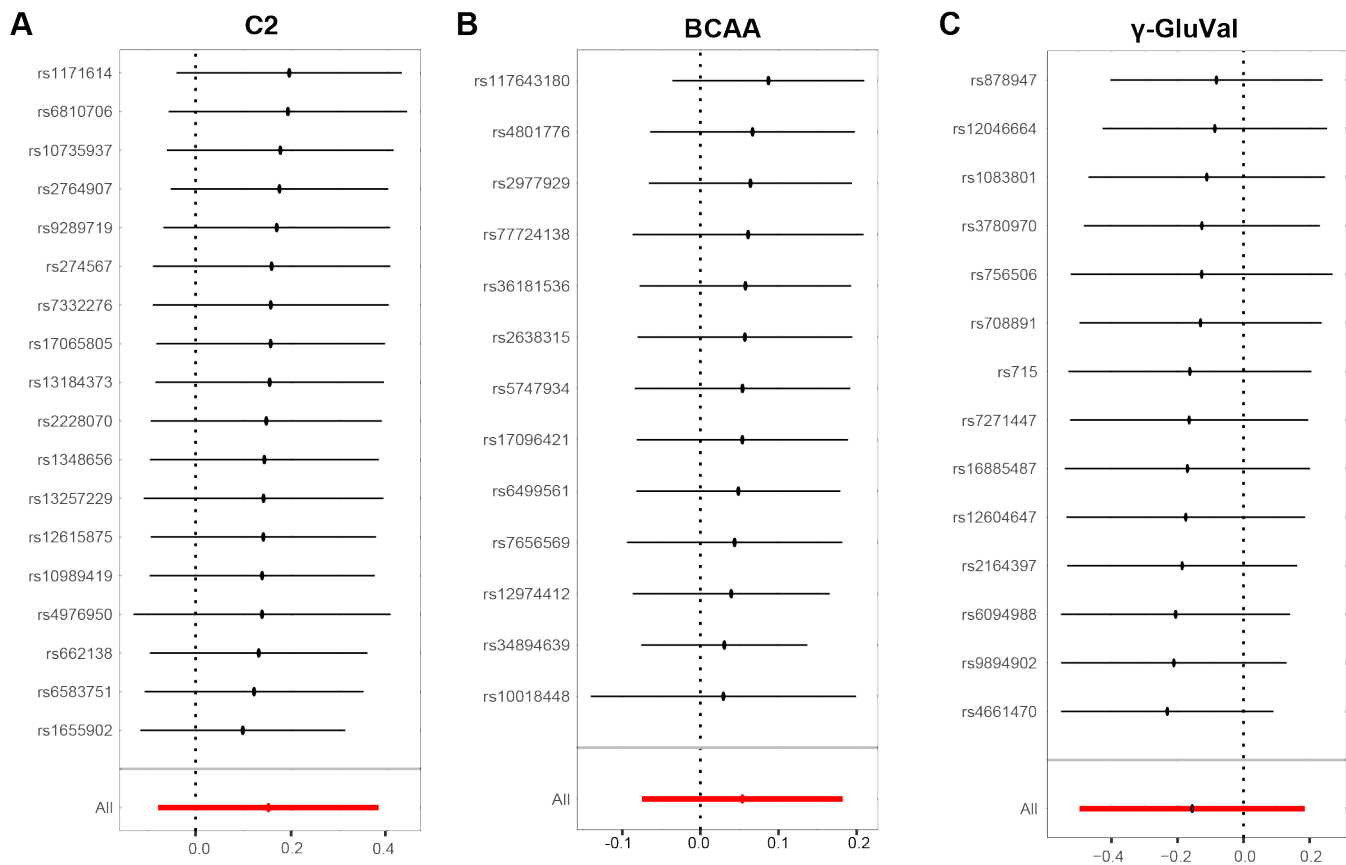
This figure summarizes subgroup analyses across NORM, i-IFG, IGT, and T2D for targeted (A) and non-targeted (B). All analyses were conducted using linear mixed-effects models (LMEM) adjusted for age, sex, BMI, and lifestyle factors (physical activity, smoking status, and alcohol intake). Metabolites with Bonferroni-significant are shown in plots A and B.

Fig. S6. Mendelian randomization analysis of C2, BCAA and γ -Glu-Val on T2D.



The forest plot depicts individual SNP-level estimates and pooled causal effects derived from various MR methods. Summary effects were obtained using IVW (primary method), weighted median, MR-Egger, and weighted mode approaches, to account for potential pleiotropy and heterogeneity. Red diamonds represent combined estimates, while black squares indicate SNP-specific effects. Error bars denote 95% CIs. SNPs are labeled by their rsID.

Fig. S7. Leave-one-out sensitivity analysis for the causal association between C2, BCAA and γ -Glu-Val and T2D.



Forest plot displaying the results of the leave-one-out sensitivity analysis based on the inverse variance weighted (IVW) method in the Mendelian randomization (MR) framework. Each data point represents the overall causal estimate obtained by excluding one single nucleotide polymorphism (SNP) at a time. The horizontal lines correspond to 95% confidence intervals. The consistency of estimates across all iterations indicates that no individual SNP disproportionately influenced the overall MR estimate. The red diamond represents the overall effect estimate including all SNPs. The vertical dashed line indicates the null value ($\beta = 0$).