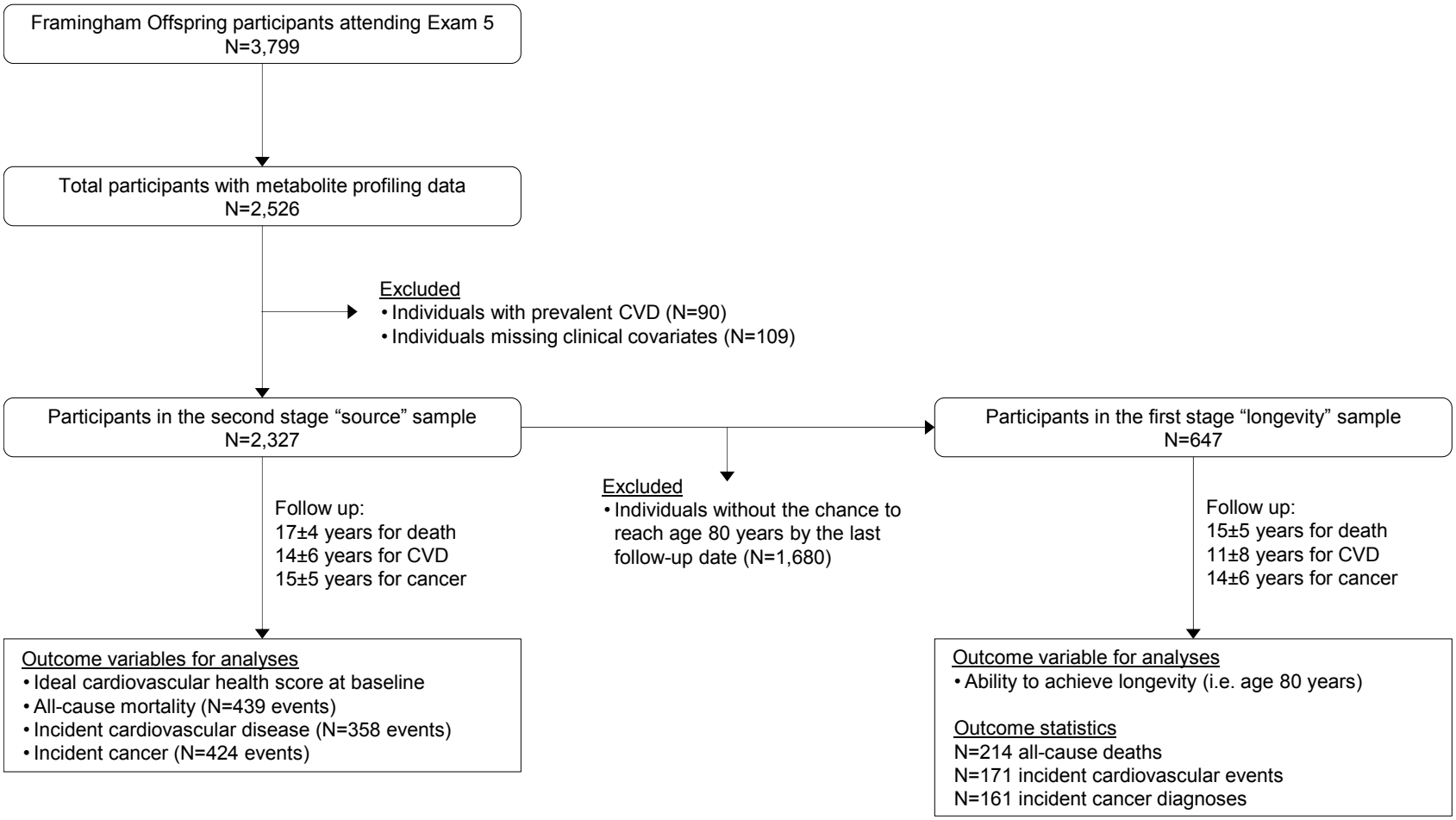
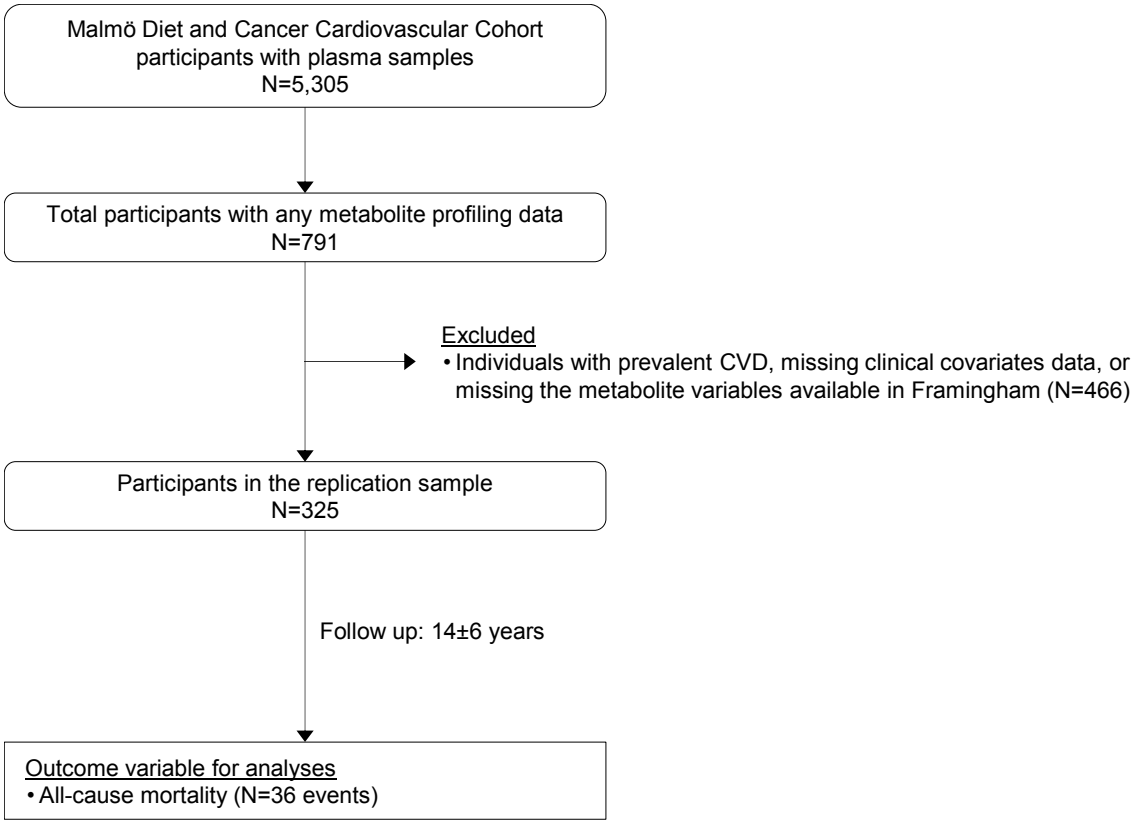
SUPPLEMENTARY FIGURES

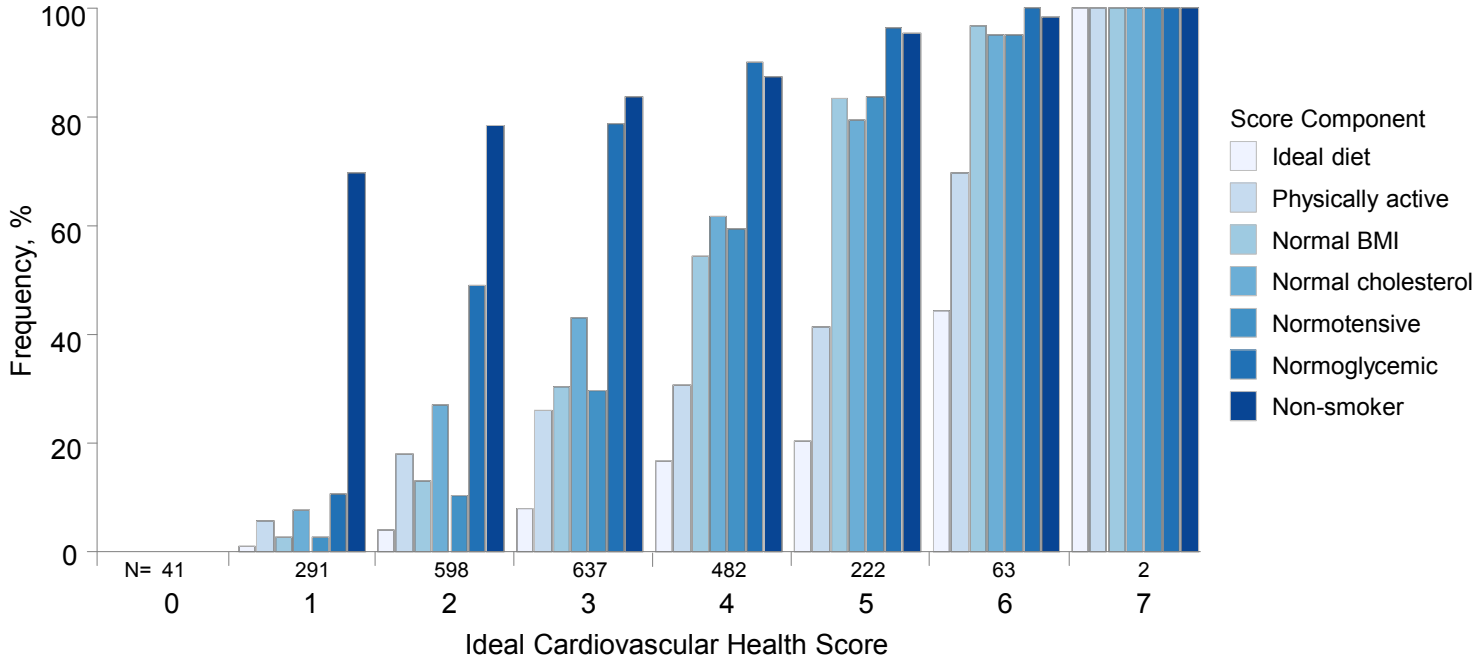
a



b

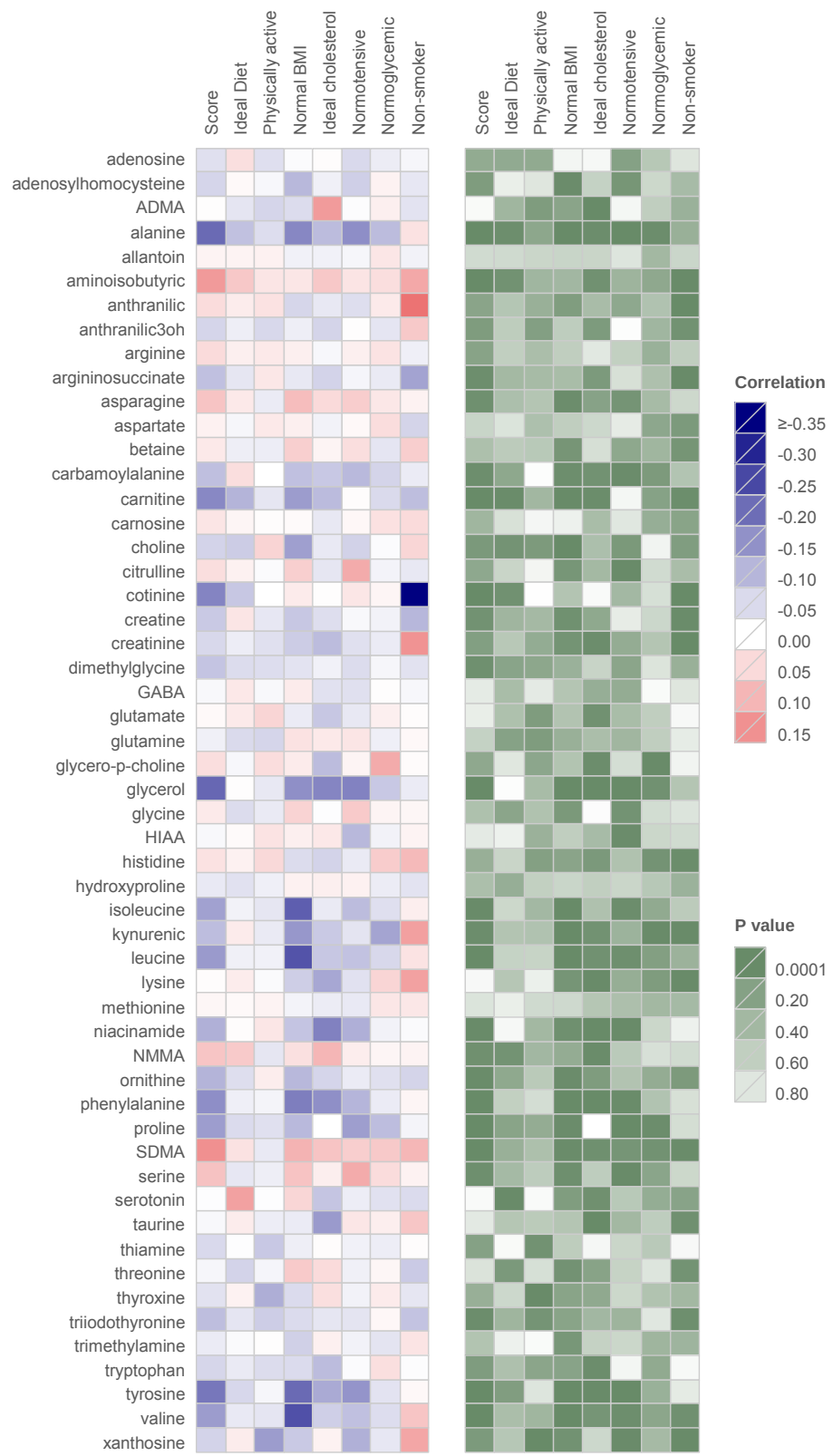


Supplementary Figure 1. Sampling strategy for the longevity analyses. The approach to sampling individuals for longevity analyses from both the Framingham Heart Study (**a**) and Malmö Diet and Cancer study (**b**) cohorts is shown.

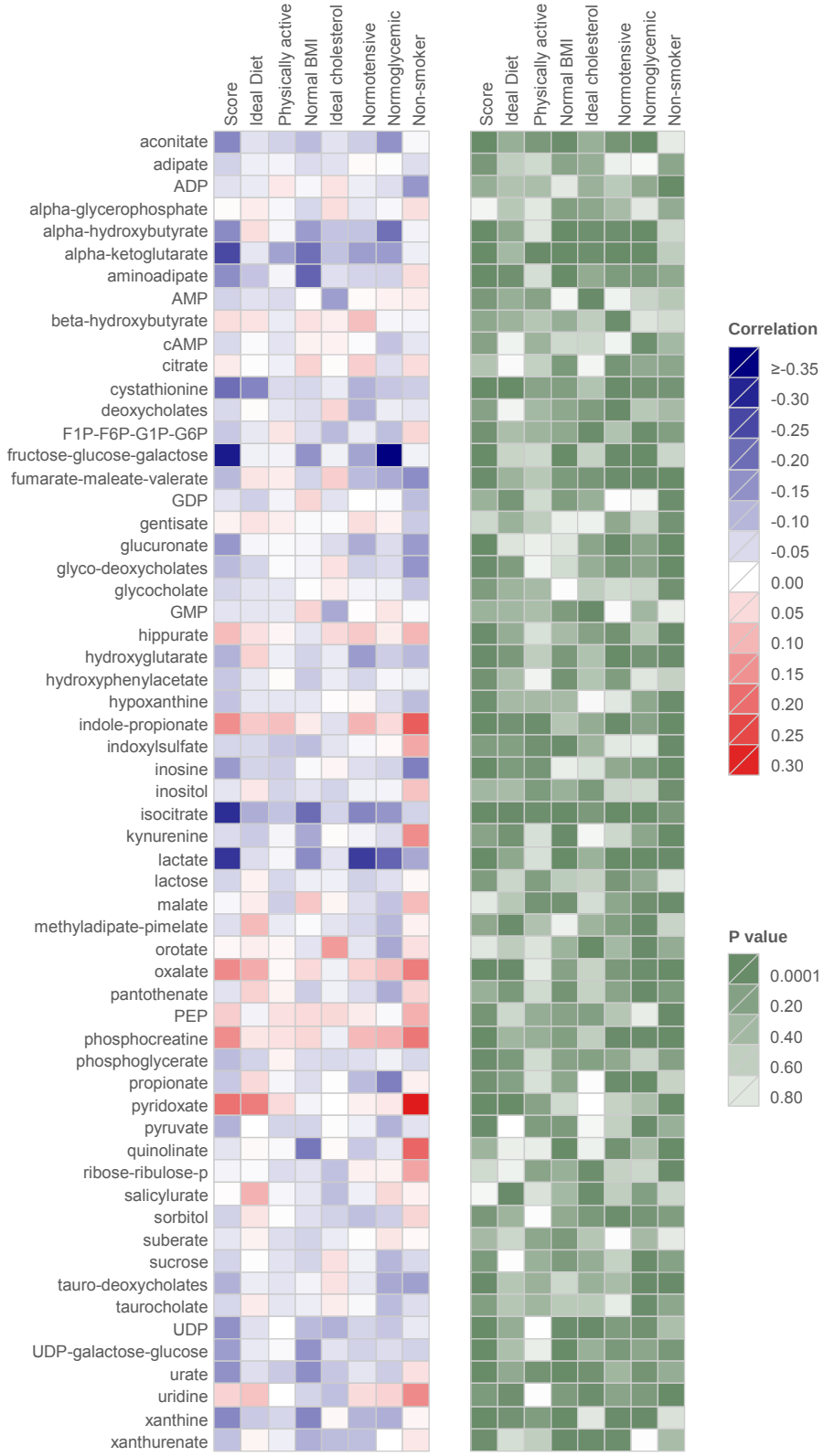


Supplementary Figure 2. Distribution of cardiovascular health score components. Frequency of cardiovascular health components contributing to increasing 'ideal cardiovascular health score' is shown for the total study sample (N=2327).

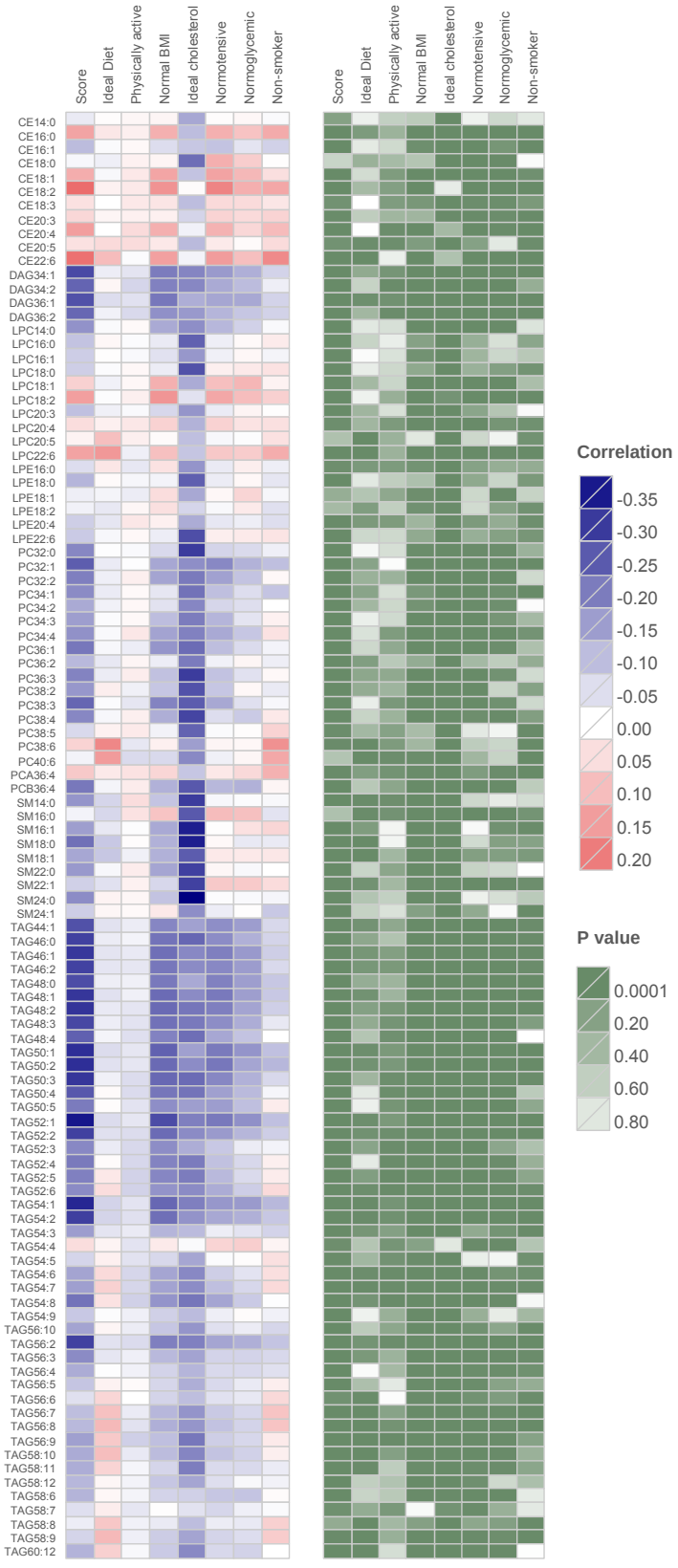
a


Score
Ideal Diet
Physically active
Normal BMI
Ideal cholesterol
Normotensive
Normoglycemic
Non-smoker
adenosine
adenosylhomocysteine
ADMA
alanine
allantoin
aminoisobutyric
anthranilic
anthranilic3oh
arginine
argininosuccinate
asparagine
aspartate
betaine
carbamoylalanine
carnitine
carnosine
choline
citrulline
cotinine
creatine
creatinine
dimethylglycine
GABA
glutamate
glutamine
glycero-p-choline
glycerol
glycine
HIAA
histidine
hydroxyproline
isoleucine
kynurenic
leucine
lysine
methionine
niacinamide
NMMA
ornithine
phenylalanine
proline
SDMA
serine
serotonin
taurine
thiamine
threonine
thyroxine
triiodothyronine
trimethylamine
tryptophan
tyrosine
valine
xanthosine
Correlation
≥-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
P value
0.0001
0.20
0.40
0.60
0.80

b


Score
Ideal Diet
Physically active
Normal BMI
Ideal cholesterol
Normotensive
Normoglycemic
Non-smoker
aconitate
adipate
ADP
alpha-glycerophosphate
alpha-hydroxybutyrate
alpha-ketoglutarate
aminoadipate
AMP
beta-hydroxybutyrate
cAMP
citrate
cystathionine
deoxycholates
F1P-F6P-G1P-G6P
fructose-glucose-galactose
fumarate-maleate-valerate
GDP
gentisate
glucuronate
glyco-deoxycholates
glycocholate
GMP
hippurate
hydroxyglutarate
hydroxyphenylacetate
hypoxanthine
indole-propionate
indoxylsulfate
inosine
inositol
isocitrate
kynurenine
lactate
lactose
malate
methyladipate-pimelate
orotate
oxalate
pantothenate
PEP
phosphocreatine
phosphoglycerate
propionate
pyridoxate
pyruvate
quinolinate
ribose-ribulose-p
salicylurate
sorbitol
suberate
sucrose
tauro-deoxycholates
taurocholate
UDP
UDP-galactose-glucose
urate
uridine
xanthine
xanthurenate
Correlation
≥-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
0.20
0.25
0.30
P value
0.0001
0.20
0.40
0.60
0.80

c


Score
Ideal Diet
Physically active
Normal BMI
Ideal cholesterol
Normotensive
Normoglycemic
Non-smoker
CE14:0
CE16:0
CE16:1
CE18:0
CE18:1
CE18:2
CE18:3
CE20:3
CE20:4
CE20:5
CE22:6
DAG34:1
DAG34:2
DAG36:1
DAG36:2
LPC14:0
LPC16:0
LPC16:1
LPC18:0
LPC18:1
LPC18:2
LPC20:3
LPC20:4
LPC20:5
LPC22:6
LPE16:0
LPE18:0
LPE18:1
LPE18:2
LPE20:4
LPE22:6
PC32:0
PC32:1
PC32:2
PC34:1
PC34:2
PC34:3
PC34:4
PC36:1
PC36:2
PC36:3
PC38:2
PC38:3
PC38:4
PC38:5
PC38:6
PC40:6
PCA36:4
PCB36:4
SM14:0
SM16:0
SM16:1
SM18:0
SM18:1
SM22:0
SM22:1
SM24:0
SM24:1
TAG44:1
TAG46:0
TAG46:1
TAG46:2
TAG48:0
TAG48:1
TAG48:2
TAG48:3
TAG48:4
TAG50:1
TAG50:2
TAG50:3
TAG50:4
TAG50:5
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TAG56:8
TAG56:9
TAG58:10
TAG58:11
TAG58:12
TAG58:6
TAG58:7
TAG58:8
TAG58:9
TAG60:12
Correlation
-0.35
-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
0.20
P value
0.0001
0.20
0.40
0.60
0.80

Supplementary Figure 3. Associations between metabolites and components of the ideal cardiovascular health score. Age- and sex-adjusted Spearman correlation coefficients are shown with corresponding P values for polar positively charged metabolites (**a**), polar negatively charge metabolites (**b**), and lipid metabolites (**c**).

SUPPLMENTARY TABLES

Supplementary Table 1. Morbidity Profiles for Individuals in the Longevity Sample by Sex*

Characteristics	Total N=682	Men N=332	Women N=350
Achieved longevity (age 80 years), %	79	71	86
Cardiovascular profile, %			
Survivor	2	3	1
Delayer	19	18	21
Escaper	58	51	65
Cancer profile, %			
Survivor	7	7	7
Delayer	14	16	11
Escaper	58	48	67
Combined cardiovascular and cancer profile, %			
Survivor	9	9	8
Delayer	28	29	27
Escaper	42	33	51

*Survivors developed the outcome(s) before age 70; delayers developed the outcome(s) at age 70 or after; and, escapers never developed the outcome(s).

Supplementary Table 2. Metabolites Associated with Attaining Longevity Defined as 85 Years of Age (Sample: N=329)

Profiling Method	Metabolite	Age- and Sex-Adjusted OR (95% CI)	P value	Multivariable-Adjusted† OR (95% CI)	P value
Polar, positively charged	cotinine	0.62 (0.46-0.83)	0.001	0.59 (0.36-0.96)	0.03
	histidine	1.20 (0.95-1.53)	0.13	1.16 (0.90-1.51)	0.26
	lysine	1.30 (1.00-1.69)	0.05	1.28 (0.97-1.70)	0.08
	threonine	1.07 (0.83-1.38)	0.58	0.98 (0.75-1.29)	0.90
Polar, negatively charged	aconitate	0.69 (0.52-0.91)	0.01	0.76 (0.57-1.03)	0.08
	beta-hydroxybutyrate	0.75 (0.57-0.99)	0.04	0.79 (0.59-1.07)	0.12
	isocitrate	0.60 (0.43-0.82)	0.001	0.70 (0.49-0.99)	0.04
	malate	0.81 (0.63-1.02)	0.08	0.87 (0.68-1.12)	0.29
	taurocholate	0.88 (0.67-1.15)	0.34	0.90 (0.67-1.21)	0.48
	uridine	2.19 (1.60-3.00)	9.0E-07	2.07 (1.49-2.88)	1.6E-05
Lipid	LPC 22:6	1.24 (0.96-1.60)	0.10	1.08 (0.81-1.42)	0.61
	PC 38:6	1.24 (0.95-1.62)	0.12	1.19 (0.88-1.62)	0.25

LPC, lysophosphatidylcholine; PC, phosphatidylcholine.
*Metabolites were natural log transformed and standardized (mean=0, sd=1).
†All logistic regression analyses adjusted for age and sex; multivariable-adjusted models additionally adjusted for body mass index, systolic blood pressure, anti-hypertensive treatment, diabetes, smoking status, total cholesterol, HDL cholesterol, and log triglycerides.

Supplementary Table 3. Metabolites Associated with Attaining Longevity Defined as 75 Years of Age (Sample: N=996)

Profiling Method	Metabolite	Age- and Sex-Adjusted OR (95% CI)	P value	Multivariable-Adjusted† OR (95% CI)	P value
Polar, positively charged	cotinine	0.84 (0.69-1.03)	0.09	1.08 (0.76-1.54)	0.68
	histidine	1.13 (0.93-1.37)	0.21	1.11 (0.91-1.36)	0.30
	lysine	1.17 (0.95-1.43)	0.14	1.19 (0.96-1.47)	0.11
	threonine	1.32 (1.07-1.64)	0.01	1.28 (1.02-1.59)	0.03
Polar, negatively charged	aconitate	0.87 (0.69-1.10)	0.25	0.93 (0.73-1.19)	0.55
	beta-hydroxybutyrate	0.77 (0.62-0.95)	0.01	0.75 (0.60-0.95)	0.01
	isocitrate	0.76 (0.60-0.96)	0.02	0.81 (0.63-1.05)	0.11
	malate	0.79 (0.64-0.97)	0.03	0.83 (0.67-1.02)	0.08
	taurocholate	0.69 (0.54-0.90)	0.006	0.70 (0.54-0.92)	0.01
	uridine	1.07 (0.86-1.34)	0.56	1.02 (0.81-1.29)	0.87
Lipid	LPC 22:6	1.14 (0.91-1.44)	0.26	1.11 (0.87-1.41)	0.40
	PC 38:6	1.21 (0.96-1.53)	0.11	1.22 (0.95-1.57)	0.11

LPC, lysophosphatidylcholine; PC, phosphatidylcholine.
*Metabolites were natural log transformed and standardized (mean=0, sd=1).
†All logistic regression analyses adjusted for age and sex; multivariable-adjusted models additionally adjusted for body mass index, systolic blood pressure, anti-hypertensive treatment, diabetes, smoking status, total cholesterol, HDL cholesterol, and log triglycerides.

Supplementary Table 4. Metabolites Associated with Attaining Longevity Defined as 70 Years of Age (Sample: N=1248)

		Age- and Sex-Adjusted		Multivariable-Adjusted†	
Profiling Method	**Metabolite**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Polar, positively charged	cotinine	0.85 (0.68-1.06)	0.14	0.84 (0.57-1.25)	0.39
	histidine	1.21 (0.98-1.50)	0.07	1.19 (0.96-1.48)	0.11
	lysine	1.02 (0.81-1.27)	0.88	1.05 (0.84-1.33)	0.66
	threonine	1.33 (1.04-1.69)	0.02	1.29 (1.01-1.65)	0.05
Polar, negatively charged	aconitate	0.78 (0.59-1.03)	0.08	0.88 (0.65-1.19)	0.40
	beta-hydroxybutyrate	0.77 (0.62-0.97)	0.02	0.78 (0.61-1.00)	0.05
	isocitrate	0.69 (0.53-0.90)	0.006	0.77 (0.57-1.03)	0.07
	malate	0.79 (0.62-1.01)	0.06	0.83 (0.64-1.07)	0.15
	taurocholate	0.85 (0.63-1.13)	0.25	0.86 (0.64-1.16)	0.33
	uridine	0.96 (0.75-1.22)	0.74	0.95 (0.74-1.23)	0.70
Lipid	LPC 22:6	1.31 (1.01-1.68)	0.04	1.27 (0.97-1.66)	0.08
	PC 38:6	1.29 (1.01-1.66)	0.05	1.34 (1.02-1.77)	0.03

LPC, lysophosphatidylcholine; PC, phosphatidylcholine.
*Metabolites were natural log transformed and standardized (mean=0, sd=1).
†All logistic regression analyses adjusted for age and sex; multivariable-adjusted models additionally adjusted for body mass index, systolic blood pressure, anti-hypertensive treatment, diabetes, smoking status, total cholesterol, HDL cholesterol, and log triglycerides.

Supplementary Table 5. Characteristics of the Malmö Diet and Cancer Study Replication Sample

Clinical Characteristics	Malmo Sample N=325
Age, years	57.5±5.8
Female, %	55
Body mass index, kg/m^2	28.3±4.9
Systolic blood pressure, mmHg	145±18
Diastolic blood pressure, mmHg	89±10
Hypertension, %	65
Treatment for hypertension, %	23
Total cholesterol, mg/dL	244±42
HDL cholesterol, mg/dL	49±12
Total/HDL cholesterol	5.3±1.6
Triglycerides, mg/dL*	144±67
Fasting glucose, mg/dL	97±8
Treatment for diabetes, %	0
Diabetes, %	0
Current smoker, %	27

Supplementary Table 6. Age- and Sex-Adjusted Associations of Selected Metabolites with the Ideal Cardiovascular Health Score

Metabolite		Model Adjusting for Age and Sex	Model Adjusting for Age, Sex, and Ideal Cardiovascular Health Score
		Total R2	Total R2
Polar, positively charged	cotinine	0.0112	0.0810
	histidine	0.0174	0.0200
	lysine	0.0346	0.0354
	threonine	0.0233	0.0261
Polar, negatively charged	aconitate	0.1164	0.1374
	β-hydroxybutyrate	0.0115	0.0115
	isocitrate	0.1393	0.1983
	malate	0.0463	0.0491
	taurocholate	0.0164	0.0164
	uridine	0.0054	0.0072
Lipid	LPC22:6	0.0505	0.0673
	PC38:6	0.0566	0.0611

Supplementary Table 7. Results of Metabolomic Pathway Topology Analysis

Pathway	Total No. Analytes*	Exp.	Act.	Analyte Associated with Longevity (KEGG compound name): Importance	Raw	Holm	FDR	Impact
Citrate cycle (TCA cycle)	20	0.058	2	Isocitric acid (C00311): 0.058 cis-Aconitic acid (C00417): 0.055	0.001	0.11	0.11	0.113
Butanoate metabolism	40	0.116	2	(R)-Malate (C00497): 0.026 (R)-3-Hydroxybutyric acid (C01089): 0.005	0.005	0.42	0.21	0.031
Glyoxylate and dicarboxylate metabolism	50	0.145	2	Isocitric acid (C00311): 0.025 cis-Aconitic acid (C00417): 0.003	0.008	0.65	0.22	0.028
Synthesis and degradation of ketone bodies	6	0.017	1	(R)-3-Hydroxybutyric acid (C01089): 0	0.017	1	0.35	0
Taurine and hypotaurine metabolism	20	0.058	1	Taurocholic acid (C05122): 0	0.057	1	0.91	0
Glycerophospholipid metabolism	39	0.113	1	LPC 22:6 / PC 38:6 (C04230): 0.003	0.11	1	1	0.003
Primary bile acid biosynthesis	47	0.137	1	Taurocholic acid (C05122): 0.008	0.13	1	1	0.009

*Total number of analytes in the KEGG pathway.
Exp, number of analytes expected to be found by chance. Act, number of analytes actually found in association with the outcome. Raw, original P value calculated from enrichment analysis based on hypergeometric tests of relative betweeness centrality. Holm, P value is corrected for multiple testing using the Holm-Bonferroni method. FDR, P value is adjusted using the false discovery rate. Impact, pathway impact value calculated from pathway topology analysis, as the sum of the importance measures of all metabolites in each pathway.

Supplementary Table 8. Sample Size and Frequency of Longevity Achieved According to Varying Age Thresholds for Defining Longevity in the Framingham Cohort

Longevity defined as ability to reach…	Total Persons with Chance to Achieve Longevity	Achieved Longevity	Did Not Achieve Longevity
Age 85	329	215 (65%)	114 (35%)
Age 80	647	514 (79%)	133 (21%)
Age 75	996	881 (88%)	115 (12%)
Age 70	1248	1166 (93%)	82 (7%)

Supplementary Table 9. Metabolite clusters derived from principal components analyses: HILIC method

Cluster	Metabolite	R^2 Own Cluster	R^2 Next Closest
Cluster 1	isoleucine	0.76	0.30
	leucine	0.83	0.27
	methionine	0.54	0.35
	phenylalanine	0.55	0.20
	tryptophan	0.39	0.12
	tyrosine	0.54	0.26
	valine	0.72	0.25
Cluster 2	asparagine	0.47	0.08
	glutamate	0.68	0.17
	glutamine	0.74	0.11
	anthranilic	0.48	0.15
	alpha-glycerophosphocholine	0.52	0.21
	thiamine	0.38	0.09
Cluster 3	aminoisobutyric	0.26	0.08
	betaine	0.48	0.08
	choline	0.52	0.17
	dimethylglycine	0.54	0.13
	citrulline	0.41	0.17
	NG-monomethyl-arginine	0.41	0.14
Cluster 4	histidine	0.65	0.16
	lysine	0.65	0.32
	threonine	0.47	0.17
	ornithine	0.51	0.23
Cluster 5	creatinine	0.53	0.19
	xanthosine	0.48	0.13
	kynurenic	0.50	0.12
	trimethylamine	0.25	0.06
	5-hydroxyindoleacetic acid	0.19	0.03
Cluster 6	niacinamide	0.36	0.08
	taurine	0.51	0.09
	serotonin	0.57	0.02
Cluster 7	alanine	0.55	0.28
	proline	0.62	0.24
	carnitine	0.45	0.17
	hydroxyproline	0.37	0.10
Cluster 8	arginine	0.57	0.23
	glycine	0.45	0.05
	serine	0.78	0.18
Cluster 9	cotinine	1.00	0.01
Cluster 10	creatine	0.61	0.03
	thyroxine	0.61	0.04
Cluster 11	allantoin	0.69	0.15
	carbamoylalanine	0.69	0.18

Supplementary Table 10. Metabolite clusters derived from principal components analyses: CMH method

		R^2	
Cluster	**Metabolite**	**Own Cluster**	**Next Closest**
Cluster 1	aconitate	0.88	0.19
	citrate	0.70	0.12
	isocitrate	0.75	0.20
	malate	0.59	0.25
Cluster 2	aminoadipate	0.40	0.04
	kynurenine	0.67	0.08
	quinolinate	0.57	0.10
	urate	0.24	0.06
	indoxylsulfate	0.22	0.03
	xanthurenate	0.23	0.05
Cluster 3	alpha-glycerophosphate	0.54	0.11
	adenosine diphosphate	0.53	0.07
	lactose	0.59	0.12
Cluster 4	glycocholate	0.75	0.05
	glycodeoxycholate; glycochenodeoxycholate	0.85	0.08
	deoxycholates	0.33	0.02
Cluster 5	pantothenate	0.75	0.02
	pyridoxate	0.79	0.04
	oxalate	0.14	0.02
Cluster 6	hippurate	0.30	0.02
	gentisate	0.50	0.02
	salicylurate	0.41	0.02
	hydroxyphenylacetate	0.50	0.11
Cluster 7	fructose; glucose; galactose	0.50	0.07
	sorbitol	0.49	0.08
	sucrose	0.47	0.08
Cluster 8	alpha-hydroxybutyric acid	0.78	0.13
	beta-hydroxybutyric acid	0.78	0.15
Cluster 9	fumarate; maleate; alpha-ketoisovalerate	0.42	0.15
	glucuronate	0.28	0.04
	lactate	0.44	0.13
	hydroxyglutarate	0.53	0.06
Cluster 10	phosphoglycerate	0.51	0.01
	adenosine monophosphate	0.70	0.18
	fructose-1-phosphate; fructose-6-phosphate; glucose-1-phosphate; glucose-6-phosphate	0.55	0.17

Cluster 11	adipate	0.71	0.08
	3-methyladipic acid; pimelic acid	0.71	0.05
Cluster 12	uridine	0.57	0.05
	phosphocreatine	0.57	0.01

Supplementary Table 11. Metabolite clusters derived from principal components analyses: Lipid method

		R^2	
Cluster	**Metabolite**	**Own Cluster**	**Next Closest**
Cluster 1	DAG 34:1	0.69	0.60
	DAG 36:1	0.64	0.55
	TAG 44:1	0.82	0.49
	TAG 46:2	0.89	0.52
	TAG 48:3	0.88	0.56
	TAG 48:2	0.96	0.56
	TAG 48:1	0.90	0.53
	TAG 48:0	0.73	0.36
	TAG 50:3	0.83	0.59
	TAG 50:2	0.88	0.49
	TAG 52:1	0.85	0.48
Cluster 2	LPC 14:0	0.65	0.43
	PC 32:2	0.83	0.35
	PC 32:1	0.77	0.49
	PC 34:4	0.77	0.40
	PC 34:3	0.73	0.43
	PC 34:1	0.65	0.46
	PC 36:1	0.52	0.37
Cluster 3	TAG 48:4	0.63	0.55
	TAG 50:5	0.72	0.41
	TAG 50:4	0.83	0.66
	TAG 52:6	0.89	0.54
	TAG 52:5	0.94	0.64
	TAG 52:4	0.75	0.68
	TAG 54:8	0.82	0.57
	TAG 54:7	0.88	0.70
	TAG 54:6	0.90	0.59
	TAG 54:5	0.64	0.48
Cluster 4	LPC 16:1	0.68	0.36
	LPC 16:0	0.81	0.47
	LPC 18:1	0.73	0.50
	LPC 18:0	0.76	0.42
	LPC 20:3	0.59	0.45
	LPE 16:0	0.56	0.32
	LPE 18:1	0.56	0.30
	LPE 18:0	0.69	0.32
	LPE 20:4	0.49	0.35
	LPE 22:6	0.77	0.42
Cluster 5	CE 16:0	0.68	0.15
	CE 18:3	0.63	0.26
	CE 18:2	0.75	0.38

	CE 18:1	0.75	0.18
	CE 18:0	0.37	0.24
	CE 20:5	0.51	0.18
	CE 20:4	0.82	0.35
	CE 20:3	0.71	0.19
	CE 22:6	0.66	0.28
Cluster 6	SM 14:0	0.54	0.27
	SM 16:1	0.80	0.32
	SM 16:0	0.71	0.21
	SM 18:1	0.70	0.11
	SM 18:0	0.73	0.18
	SM 22:1	0.73	0.19
	SM 22:0	0.37	0.17
Cluster 7	DAG 34:2	0.68	0.55
	DAG 36:2	0.84	0.48
	TAG 52:3	0.72	0.44
	TAG 52:2	0.74	0.60
	TAG 54:4	0.44	0.27
	TAG 54:3	0.84	0.41
	TAG 54:2	0.81	0.56
	TAG 56:4	0.68	0.47
	TAG 56:3	0.81	0.47
Cluster 8	SM 24:0	0.44	0.24
	TAG 54:9	0.65	0.18
	TAG 56:10	0.83	0.28
	TAG 58:12	0.77	0.16
	TAG 58:11	0.68	0.15
	TAG 60:12	0.52	0.29
Cluster 9	LPE18:2	0.61	0.32
	PC 34:2	0.67	0.32
	PC A36:4	0.63	0.16
	PC 36:2	0.76	0.27
Cluster 10	PC 32:0	0.56	0.40
	PC B36:4	0.83	0.36
	PC 36:3	0.81	0.58
	PC 38:5	0.77	0.37
	PC 38:4	0.79	0.30
Cluster 11	PC 38:6	0.57	0.30
	PC 40:6	0.56	0.34
	TAG 56:9	0.60	0.52
	TAG 56:8	0.91	0.61
	TAG 56:7	0.94	0.56
	TAG 56:6	0.72	0.40
	TAG 56:5	0.59	0.47
	TAG 58:10	0.59	0.31

	TAG 58:9	0.90	0.41
	TAG 58:8	0.82	0.29
Cluster 12	LPC 18:2	0.60	0.42
	LPC 20:5	0.58	0.21
	LPC 20:4	0.85	0.57
	LPC 22:6	0.75	0.38
Cluster 13	PC 38:3	0.71	0.29
	PC 38:2	0.82	0.29
	SM 24:1	0.46	0.14
Cluster 14	CE 14:0	0.73	0.17
	CE 16:1	0.73	0.23

CE, cholesterol ester; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; SM, sphingomyelin; TAG, triacylglycerol.