Appendix

Supplementary methods

Dietary data sampling

The modified diet history method of the MDC is a validated (1) dietary assessment method more thoroughly described elsewhere (2). The method consist of a combination of a 7-day food record, an extensive diet history questionnaire combined with an interview. During seven consecutive days, participants recorded cooks meals, cold beverages, drugs, natural remedies and dietary supplements. The diet history questionnaire was design to examine the general meal pattern, frequency and portion size of food consumed regularly. In the interview, the 7- day food record and the questionnaire were checked for overlap. The dietary data was converted into energy and nutrient intake using the MDC-nutrient database, which contains information mostly from the PC-KOST2-93 from the National Food Agency in Sweden. Energy-adjusted intakes of food groups were calculated by regressing the intakes to the total non-alcohol energy intake. The alcohol intake was estimated using the 7-menu book.

Endpoint definition

Endpoints were retrieved by linking the ten digit Swedish personal identification number with three registers: the Swedish Hospital Discharge Register, the Swedish Cause of Death Register, and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (3) (4). These registers have been previously described and validated for classifications of outcomes (4). CAD was defined as coronary artery revascularization, fatal or non-fatal myocardial infarction, or death due to ischemic heart disease.

Myocardial infarction was defined on the basis of the International Classification of Diseases (ICD) 9 code 410 or ICD-10 code I21. Death attributable to ischemic heart disease was defined as ICD-9 codes 412 and 414, or ICD-10 codes I22, I23, or I25. Coronary artery bypass surgery was identified from the national Swedish classification systems of surgical procedures and defined as procedure codes 3065, 3066, 3068, 3080, 3092, 3105, 3127, or 3158 in the Op6 system; or as procedure code FN in the KKÅ97 system. Percutaneous coronary intervention was identified from SCAAR (3). Fatal and non-fatal stroke was defined using codes 430, 431, 434 and 436 (ICD9) and I60, I61, I63, and I64 (ICD10). Cardiovascular mortality was defined as primary cause of death classified as ICD-9 codes 390 – 459 and ICD-10 codes I00 – I99.

Incident diabetes cases were retrieved from six different national and regional diabetes registers as described elsewhere (5). Prevalent diabetes mellitus at baseline was defined as a fasting whole blood glucose ≥ 6.1 mmol/L (corresponding to a plasma glucose of ≥7.0 mmol/L) or a history of physician diagnosis of diabetes mellitus or being on antidiabetic medication or having been registered in any of the six different national and regional diabetes registers.

Metabolite measurement

Profiling of plasma metabolites was performed using LC-MS using a UPLC-QTOF-MS System (Agilent Technologies 1290 LC, 6550 MS, Santa Clara, CA, USA) and has been described elsewhere (6).

Briefly, over-night fasted citrate venous plasma samples stored at -80 °C were thawed and extracted by addition of 120 μl extraction solution (80:20 methanol/water) to 20 μl plasma. The samples were then incubated at 4 °C for 1 hour at 1250 rpm. After 15 min centrifugation at 14 000g, 100 μl supernatant was transferred into a glass vial for analysis. Extracted samples were separated on an Acquity UPLC BEH Amide column (1.7 μm, 2.1 $*$ 100mm; Waters Corporation, Milford, MA, USA).

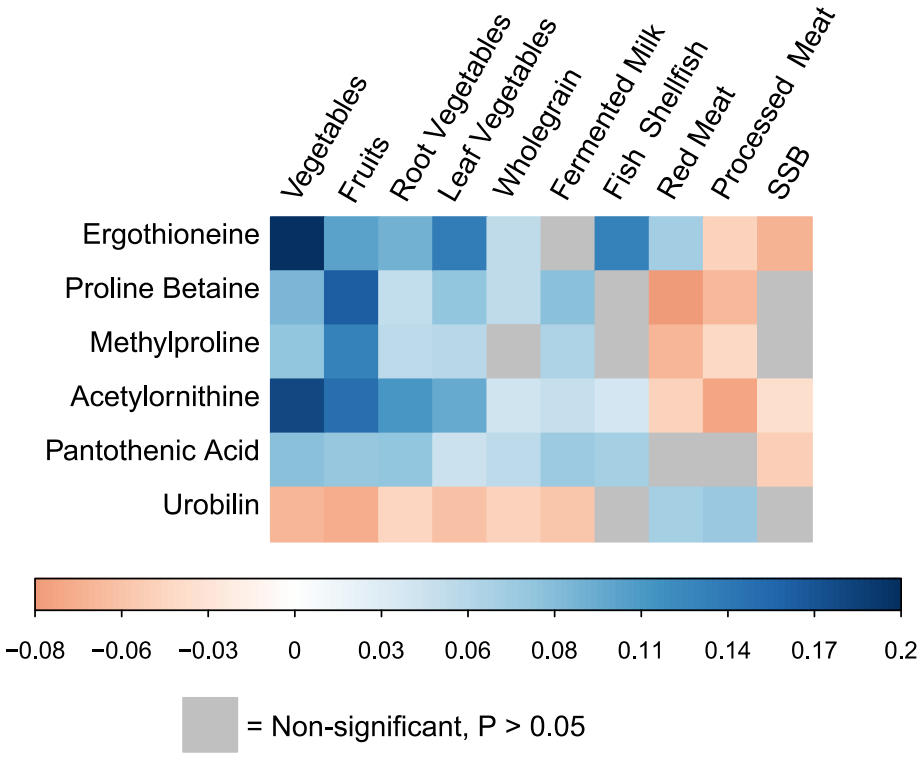
Metabolites were identified by matching the measured mass-over charge ratio (m/z) and chromatographic retention times with an in-house metabolite library (eTable 1). Metabolite peak areas were integrated using Agilent Profinder B.06.00 (Agilent Technologies, Santa Clara, CA, USA).

Samples were analyzed in batches if 180 samples, where quality control samples were injected in the beginning and after every eight analytical samples in order to ensure high analytical repeatability. All metabolites were normalized to standard curves calculated from the quality control samples. Briefly, a low-order nonlinear locally estimated smoothing function was fitted to the signals from each metabolite in the quality control samples as a function of the injection order. Using this function, correction curves for each metabolites' analytical samples were interpolated, to which the metabolite measurements in the analytical samples were normalized (7).

Coefficients of variation (CV) were calculated using all quality control samples, and features with a CV over 20 % were excluded (bilirubin, methionine-S-oxide, sarcosine and uracil). The technical Intraclass Correlation Coefficients (ICC) were calculated as described by Sampson et al. (8) $ICC = 1 - \frac{\text{technical variance}}{\text{total variance}}$.

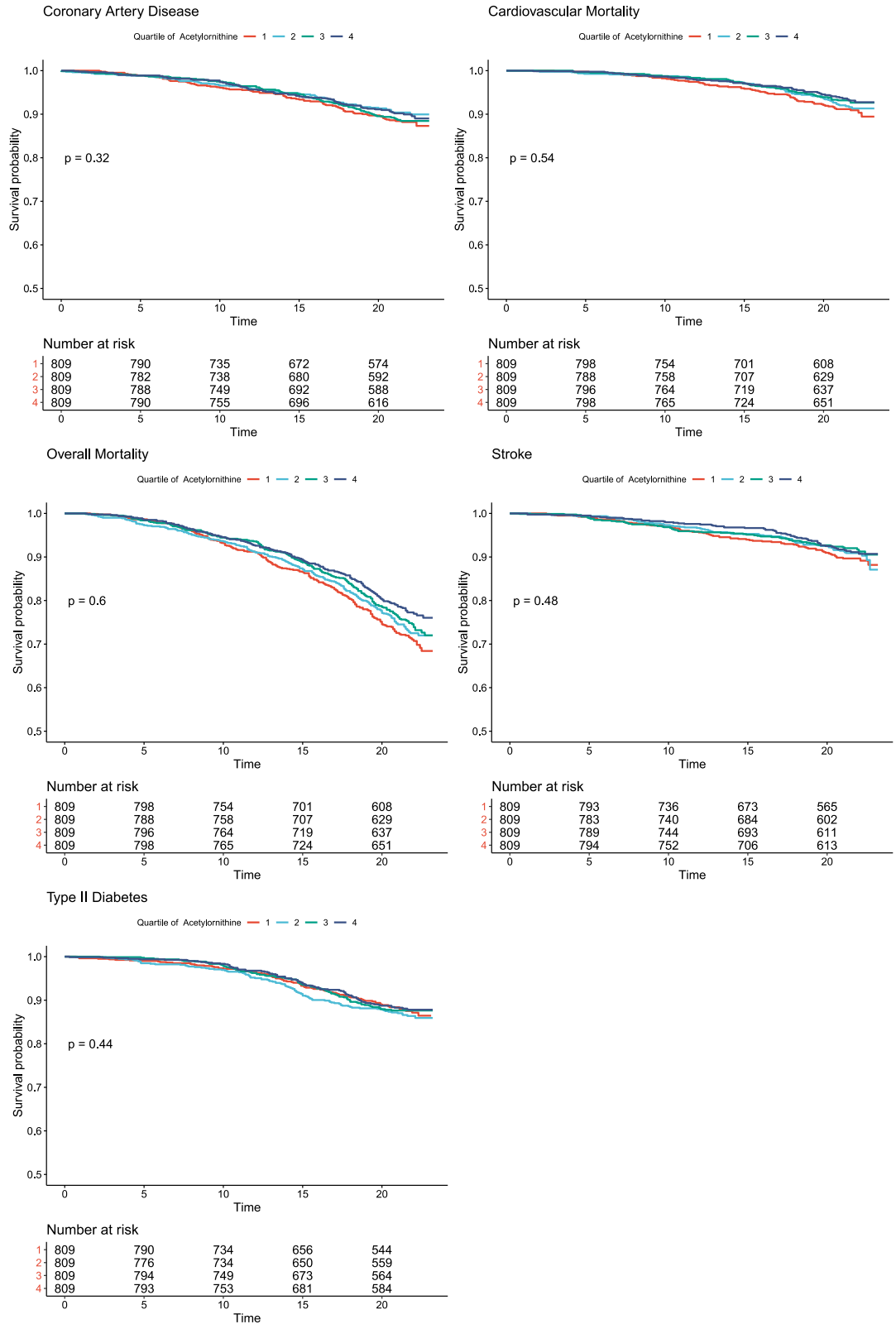
The average CV was 8.9 % and the average ICC 95.4%.

Supplementary figure 1: Metabolites correlations with food groups

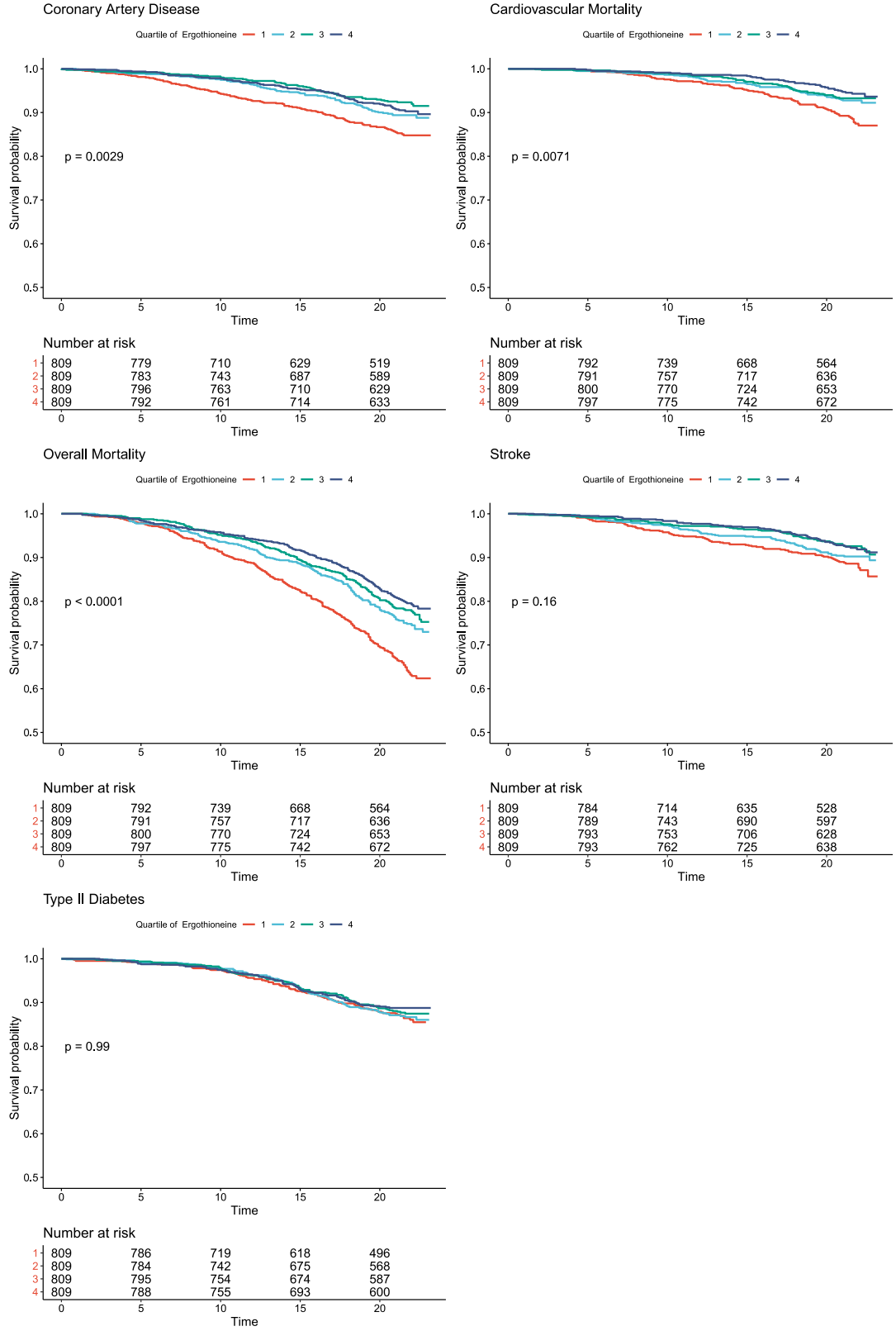


Pearson correlation coefficients between circulating levels of the health conscious dietary biomarkers and dietary intake groups. Non-significant correlation P > 0.05 are colored as grey. Food groups are adjusted for total energy intake. N= 3236. SSB: Sugar sweetened beverages.

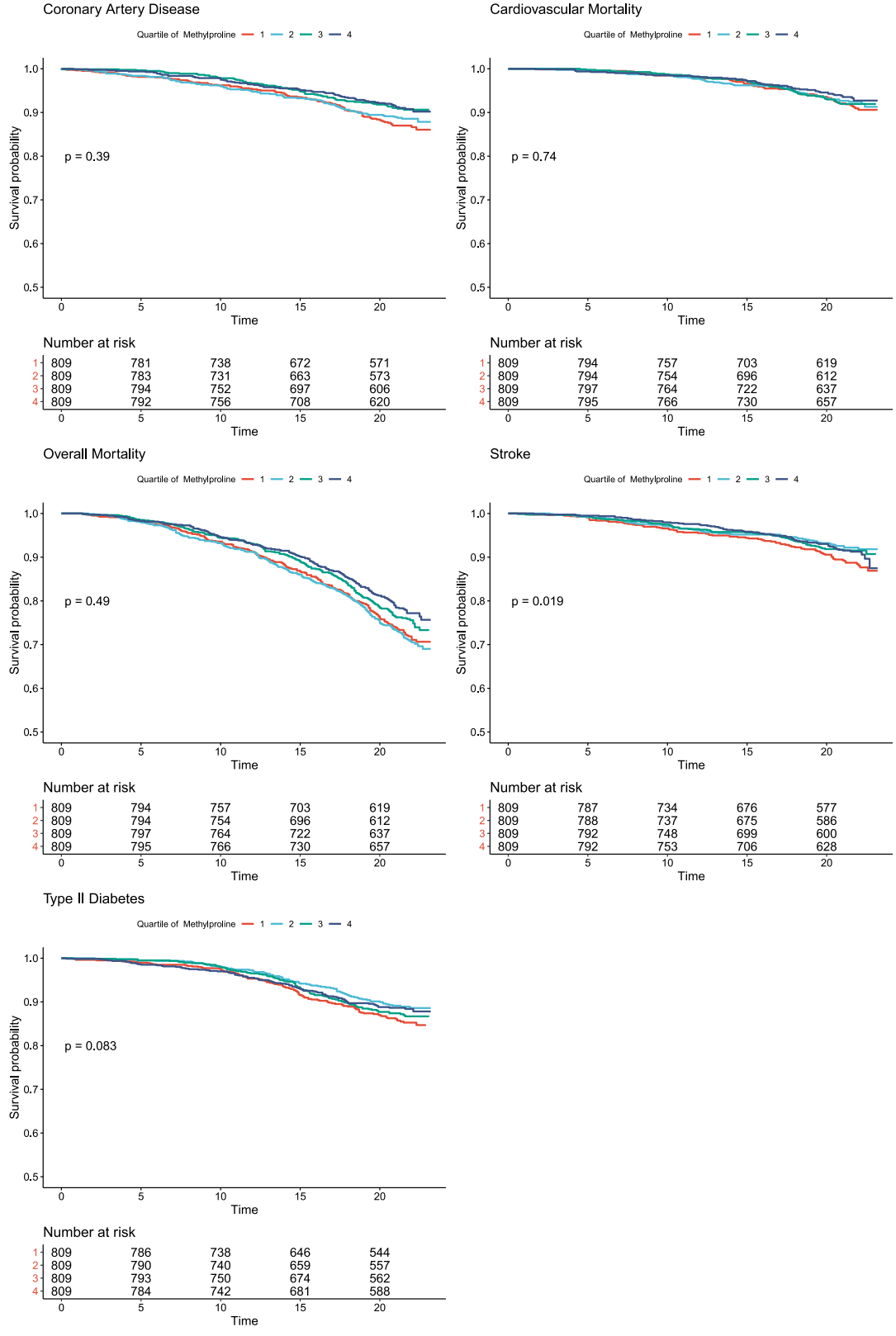
Supplementary figure 2: Kaplan Meier – Acetylornithine and endpoints



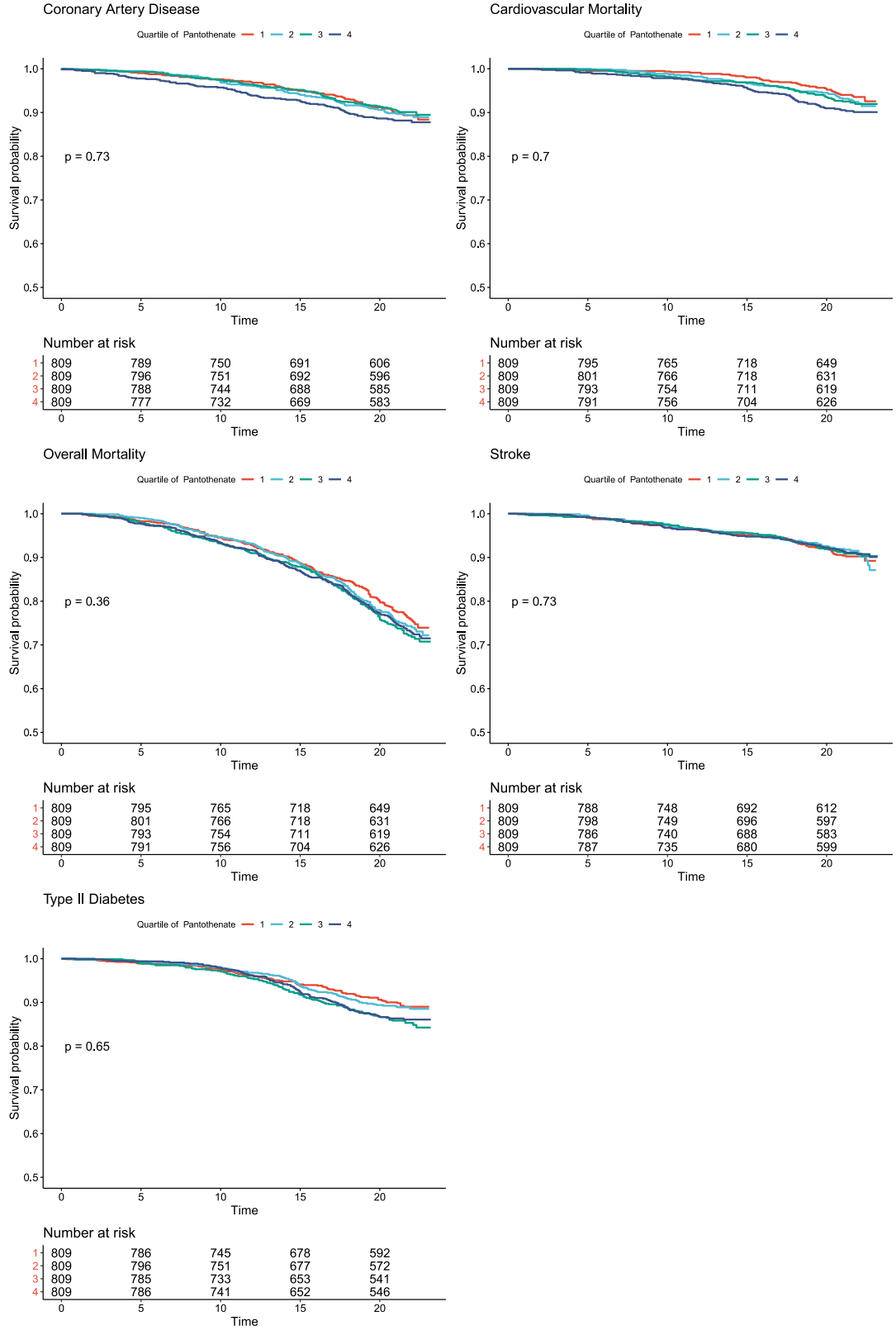
Supplementary figure 3: Kaplan Meier – Ergothioneine and endpoints



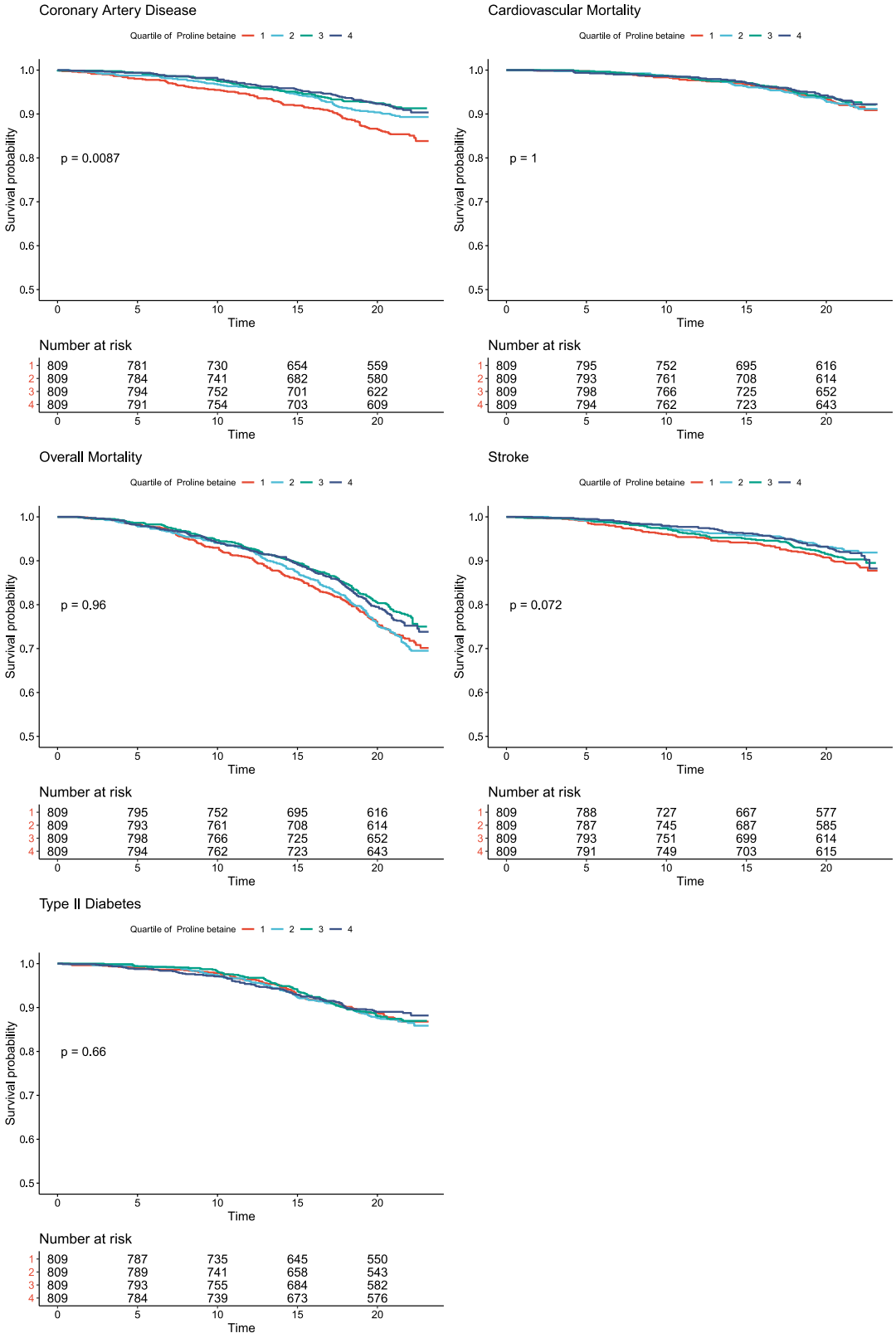
Supplementary figure 4: Kaplan Meier – Methylproline and endpoints



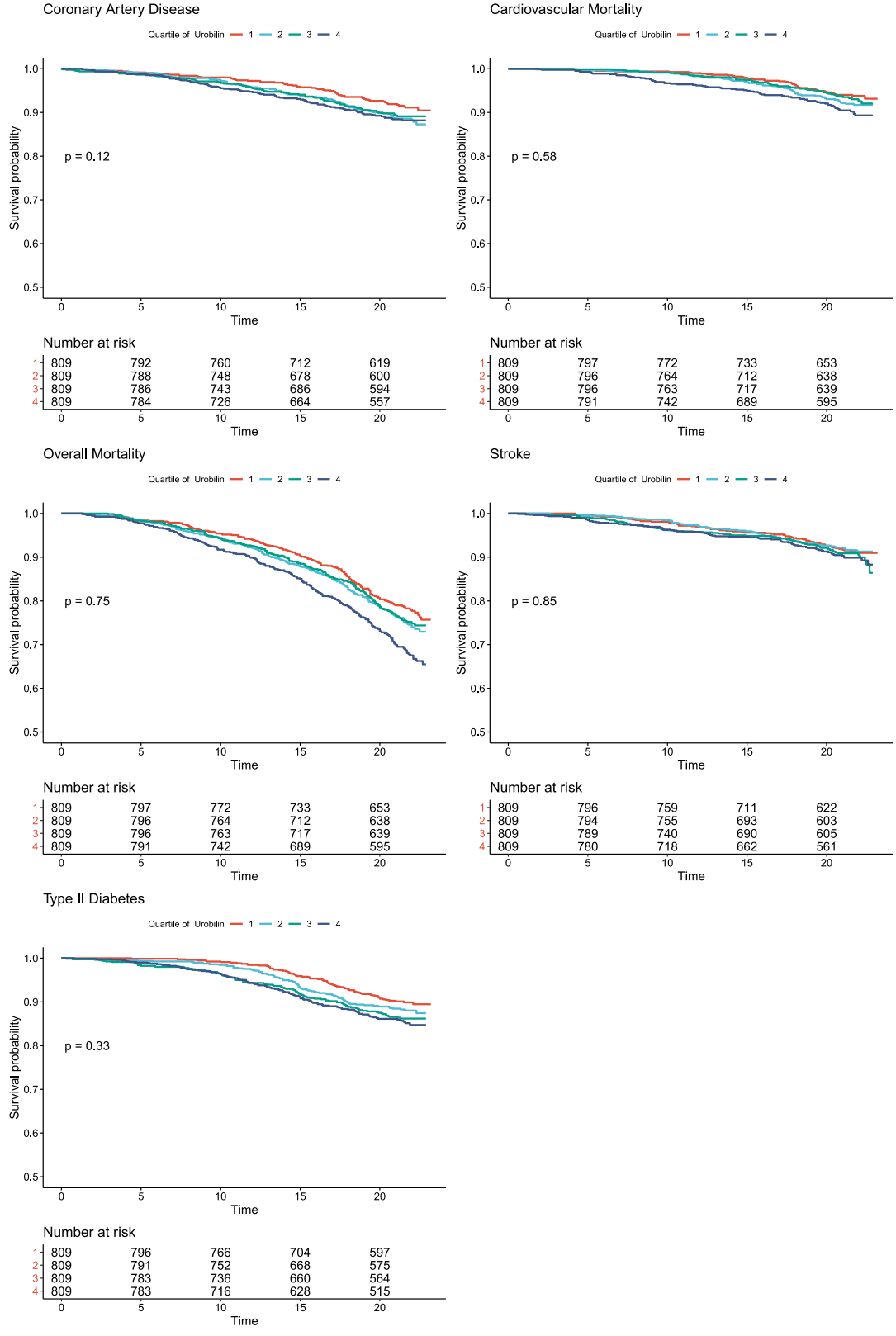
Supplementary figure 5: Kaplan Meier – Pantothenic acid and endpoints



Supplementary figure 6: Kaplan Meier – Proline betaine and endpoints



Supplementary figure 7: Kaplan Meier – Urobilin and endpoints



Supplementary figure 2-6: The Kaplan-Meier plots show cumulative percentage of individuals free from events during follow up according to the quartiles of metabolite at baseline examination, 1 being the lowest quartile and 4 the highest. P values displayed were calculated using log rank test for trend. N = 3236.

Supplementary table 1: In-house metabolite library

Compound Name	Formula	M/Z	RT (min)	CV (%)	ICC
1-Methylhistidine	C7H11N3O2	169.08513	9.954	6.7	0.962
1-Methylnicotinamide	C7H9N2O	137.07149	4.958	8.5	0.997
25-Hydroxycholecalciferol	C27H44O2	400.33413	0.809	18.9	0.720
2-Aminoisobutyric acid	C4H9NO2	103.06333	6.998	11.1	0.915
3-Hydroxy-trimethyllysine	C9H21N2O3	205.15522	10.8	6.9	0.950
3-Methyl-histidine	C7H11N3O2	169.08513	10.818	5.5	0.993
4-Oxoproline	C5H7NO3	129.04259	1.916	17.2	0.938
4-Trimethylammoniobutanoic acid	C7H16NO2	146.1181	4.55	8.7	0.902
5-methylthioadenosine	C11H15N5O3S	297.08956	10.568	8.0	0.972
7-Methylguanine	C6H7N5O	165.06506	4.708	10.5	0.883
5-Acetylamino-6-amino-3-methyluracil	C7H10N4O3	198.07529	4.701	7.4	0.995
Acetamidophenol	C8H9NO2	151.06333	1.12	-	-
C2:0-carnitine	C9H18NO4	204.12358	4.448	6.5	0.962
Acetylornithine	C7H14N2O3	174.10044	7.995	4.9	0.985
Acisoga	C9H16N2O2	184.12118	1.576	7.1	0.944
Asymmetric dimethylarginine	C8H18N4O2	202.14298	9.518	15.6	0.697
Alanine	C3H7NO2	89.04768	7.497	10.0	0.935
Alpha-N-Phenylacetyl-glutamine	C13H16N2O4	264.11101	1.915	13.4	0.958
Arginine	C6H14N4O2	174.11168	10.919	12.5	0.887
Asparagine	C4H8N2O3	132.05349	8.704	7.2	0.913
Betaine	C5H12NO2	118.0868	6.14	7.5	0.951
Butyrylcarnitine	C11H22NO4	232.15488	3.625	6.3	0.988
C10:3-Carnitine	C17H28NO4	310.20183	2.458	7.0	0.989
Caffeine	C8H10N4O2	194.08038	0.965	10.8	0.986
Carnitine	C7H16NO3	162.11302	6.185	7.9	0.983
Choline	C5H14NO	104.10754	4.014	6.9	0.973
Citrulline	C6H13N3O3	175.09569	9.044	5.2	0.973
Cotinine	C10H12N2O	176.09496	1.279	-	-
Creatine	C4H9N3O2	131.06948	7.264	5.4	0.963
Creatinine	C4H7N3O	113.05891	4.625	4.7	0.950
C10:2-carnitine	C17H30NO4	312.21748	2.342	7.7	0.980
C10:0-carnitine	C17H34NO4	316.24878	2.177	7.6	0.988
C10:1-carnitine	C17H32NO4	314.23313	2.243	8.7	0.983
Dimethylglycine	C4H9NO2	103.06333	6.588	20.0	0.979
C9:0-carnitine	C16H32NO4	302.23313	2.232	7.2	0.989
Dimethyllysine	C8H18N2O2	174.13683	10.155	6.9	0.985
Dimethylguanidino valerate	C8H16N3O3	202.11917	6.017	10.3	0.994
C12:3-carnitine	C19H34NO4	340.24878	2.126	10.6	0.946
C12:0-carnitine	C19H38NO4	344.28008	2.01	7.6	0.980
C12:1-carnitine	C19H36NO4	342.26443	2.057	8.9	0.972
Ergothioneine	C9H15N3O2S	229.0885	7.227	8.5	0.975
Glutamate-Glutamine	C10H17N3O6	275.11174	10.569	6.1	0.986
Glucose	C6H1206	180.0634	6.807	7.5	0.934
Glutamate	C5H9NO4	147.0532	8.136	6.2	0.999

Supplementary table 1: In-house metabolite library

Glutamine	C5H10N2O3	146.06914	8.477	5.6	0.968
Guanidineacetate	C3H7N3O2	117.05383	7.423	5.5	0.971
C6:1-carnitine	C23H44NO4	398.32703	1.838	7.7	0.970
Hippurate	C9H9NO3	179.05824	1.19	6.1	0.995
Histidine	C6H9N3O2	155.06948	10.847	9.4	0.834
Homoarginine	C7H16N4O2	188.12733	10.557	5.4	0.983
Homocitrulline	C7H15N3O3	189.11134	8.672	14.7	0.976
Homostachydrine	C8H15NO2	157.11028	6.022	7.2	0.996
Hydroxycotinine	C10H12N2O2	192.08988	1.766	-	-
C8:OH-carnitine	C15H30NO5	304.2124	4.055	12.5	0.980
Hypoxanthine	C5H4N4O	136.03851	3.88	7.3	0.996
Isoleucine	C6H13NO2	131.09463	6.091	6.7	0.950
Isovalerylcarnitine	C12H23NO4	245.16271	3.234	7.7	0.999
Kynurenine	C10H12N2O3	208.08479	5.942	6.0	0.966
Cystine	C6H12N2O4S2	240.02385	12.967	9.4	0.898
Leucine	C6H13NO2	131.09463	5.917	6.8	0.949
C6-carnitine	C13H26NO4	260.18618	2.798	8.5	0.980
Lysine	C6H14N2O2	146.10553	11.395	6.3	0.942
Methionine	C5H11NO2S	149.05105	6.318	9.7	0.867
Methyllysine	C7H16N2O2	160.12118	10.53	4.5	0.995
Myristoylcarnitine	C21H42NO4	372.31138	1.943	7.8	0.973
N2,N2-Dimethylguanosine	C12H17N5O5	311.12297	4.678	14.2	0.945
N-Acetylcarnosine	C11H16N4O4	268.11716	8.159	6.7	0.975
Nicotinamide	C6H6N2O	122.04801	1.358	19.2	0.994
N-Methyl-2-pyridone-5-carboxamide	C7H8N2O2	152.05858	1.708	8.5	0.989
N-Methyl-4-pyridone-3-carboxamide	C7H8N2O2	152.05858	1.88	14.1	0.972
N-Methylproline	C6H11NO2	129.07898	6.187	10.6	0.983
N-monomethylarginine	C7H16N4O2	188.12733	10.071	12.9	0.815
N-Acetylarginine	C8H16N4O3	216.12224	7.128	7.7	0.969
C18:1-carnitine	C25H48NO4	426.35833	1.752	8.0	0.953
C18:2-carnitine	C25H46NO4	424.34268	1.769	7.4	0.968
C18:0-carnitine	C25H50NO4	428.37398	1.728	9.7	0.949
C8:0-carnitine	C15H30NO4	288.21748	2.489	3.9	0.997
C8:1-carnitine	C15H28NO4	286.20183	2.627	7.1	0.986
Ornithine	C5H12N2O2	132.08988	11.581	6.7	0.973
C16:0-carnitine	C23H46NO4	400.34268	1.851	5.0	0.988
Pantothenate	C9H17NO5	219.11067	1.577	11.7	0.940
Paraxanthine	C7H8N4O2	180.06473	1.289	6.0	0.987
Phenylalanine	C9H11NO2	165.07898	5.883	5.8	0.985
Pipecolate	C6H11NO2	129.07898	6.773	14.2	0.993
Piperine	C17H19NO3	285.13649	0.846	6.2	0.992
Proline	C5H9NO2	115.06333	6.639	6.9	0.982
Proline betaine	C7H13NO2	143.09463	6.151	4.3	0.995
Propionylcarnitine	C10H20NO4	218.13923	4.061	6.8	0.970

Supplementary table 1: In-house metabolite library

Pyroglutamate	C5H7NO3	129.04259	2.492	19.8	0.843
symmetric dimethylarginine	C8H18N4O2	202.14298	9.505	17.6	0.764
Serine	C3H7NO3	105.04259	8.561	6.1	0.943
Taurine	C2H7NO3S	125.01466	6.609	7.2	0.923
C14:3-Carnitine	C21H38NO4	368.28008	1.967	8.3	0.973
C14:2-carnitine	C21H40NO4	370.29573	1.922	7.9	0.975
Threonine	C4H9NO3	119.05824	7.848	10.9	0.903
C13:0-carnitine	C20H40NO4	358.29573	1.919	7.9	0.998
C13:1-carnitine	C20H38NO4	356.28008	1.958	10.2	0.977
Trigonelline	C7H8NO2	138.0555	6.338	7.3	0.996
Trimethylamine N-oxide	C3H9NO	75.06841	4.276	6.4	0.996
Trimethyllysine	C9H21N2O2	189.1603	10.26	5.5	0.990
Tryptophan	C11H12N2O2	204.08988	5.927	9.0	0.916
Tyrosine	C9H11NO3	181.07389	6.636	13.0	0.937
C11:0-carnitine	C18H36NO4	330.26443	2.2026	9.4	0.975
C11:1-carnitine	C18H34NO4	328.24878	2.174	7.0	0.977
Urea	CH4N2O	60.03236	2.046	7.1	0.881
Urobilin	C33H46N4O6	594.34174	1.19	13.2	0.969
Urocanate	C6H6N2O2	138.04293	2.444	18.2	0.976
Valine	C5H12NO2	118.0868	6.574	14.0	0.795

The in-house metabolite library used when measuring metabolites with the liquid chromatography and mass spectrometry (LC-MS). M/Z: mass to charge ratio. CV: Coefficient of variation. ICC: Intraclass Correlation Coefficient RT: Retention time in minutes.

Supplementary table 2: Linear regressions between the health conscious dietary pattern and metabolites

metabolites	**p**	**Beta**
Ergothioneine	3.42E-21	0.29 (0.23 – 0.35)
Proline betaine	1.59E-17	0.25 (0.19 – 0.30)
N-Methylproline	1.41E-11	0.61 (0.43 – 0.79)
Acetylornithine	5.73E-10	0.18 (0.12 – 0.23)
Urobilin	2.97E-06	-0.13 (-0.19 – -0.08)
Pantothenic-Acid	5.13E-06	0.13 (0.08 – 0.19)
Hippurate	4.44E-04	0.14 (0.06 – 0.22)
Citrulline	7.37E-04	-0.10 (-0.16 – -0.04)
N-Methyl-2-pyridone-5-carboxamide	1.02E-03	0.10 (0.04 – 0.16)
Pipecolate	1.06E-03	0.09 (0.04 – 0.15)
Tryptophan	1.12E-03	0.09 (0.04 – 0.15)
c13:2-carnitine	1.24E-03	0.13 (0.05 – 0.21)
Trimethylamine-N-oxide	1.80E-03	0.12 (0.04 – 0.19)
c10:3-Carnitine	1.85E-03	-0.11 (-0.18 – 0.04)
c6:0-carnitine	2.98E-03	-0.09 (-0.14 – -0.03)
Tyrosine	3.56E-03	0.59 (0.19 – 0.98)
Lysine	4.38E-03	0.08 (0.03 – 0.14)
N-Methyl-4-pyridone-3-carboxamide	4.52E-03	0.09 (0.03 – 0.14)
c8:1-carnitine	6.75E-03	-0.08 (-0.13 – -0.02)
c13:0-carnitine	8.30E-03	0.09 (0.02 – 0.15)
4-Trimethylammoniobutanoate	8.42E-03	-0.10 (-0.17 – -0.03)
Asparagine	8.50E-03	0.07 (0.02 – 0.13)
c14:3-carnitine	1.15E-02	-0.07 (-0.13 – -0.02)
Homostachydrine	1.76E-02	0.22 (0.04 – 0.39)
Sarcosine	2.13E-02	-0.69 (-1.28 – -0.10)
c8:0-carnitine	2.14E-02	-0.07 (-0.12 – 0.01)
c10:0-carnitine	2.31E-02	-0.07 (-0.12 – 0.01)
c11:1-carnitine	2.37E-02	0.07 (0.01 – 0.12)
Proline	2.44E-02	-0.07 (-0.13 – -0.01)
c14:1-carnitine	2.81E-02	-0.06 (-0.12 – -0.01)
Methyllysine	3.05E-02	-0.06 (-0.12 – -0.01)
Betaine	3.43E-02	0.06 (0.00 – 0.12)
Homoarginine	3.54E-02	0.06 (0.00 – 0.12)
c10:1-carnitine	4.59E-02	-0.11 (-0.21 – 0.00)
c18:0-carnitine	6.54E-02	-0.06 (-0.11 – 0.00)
Dimethyllysine	7.78E-02	-0.05 (-0.12 – 0.01)
Dimethylglycine	7.84E-02	-0.13 (-0.27 – 0.01)
c18:1-carnitine	7.85E-02	-0.05 (-0.11 – 0.01)
c12:0-carnitine	7.99E-02	-0.05 (-0.11 – 0.01)
c11:0-carnitine	8.15E-02	0.08 (-0.01 – 0.17)
N-Acetylarginine	8.48E-02	-0.05 (-0.10 – 0.01)
Paraxanthine	8.79E-02	0.06 (0.01 – 0.12)
Kynurenine	9.73E-02	-0.05 (-0-11 – 0.01)
5-Acetylamino-6-amino-3-methyluracil	9.88E-02	-0.28 (-0.60 – -0.05)
7-Methylguanine	9.90E-02	-0.09 (-0.20 – 0.02
Propionylcarnitine	1.00E-01	0.05 (-0.01 – 0.10)
Histidine	1.07E-01	0.05 (-0.01 – 0.10)

Supplementary table 2: Linear regressions between the health conscious dietary pattern and metabolites

Cystine	1.09E-01	-0.05 (-0.11 – 0.01)
Carnitine	1.18E-01	-0.04 (-0.10 – 0.01)
c18:3-carnitine	1.34E-01	-0.04 (0.10 – 0.01)
Methionine	1.49E-01	0.04 (-0.01 – 0.10)
c12:1-carnitine	1.61E-01	-0.05 (-0.11 – 0.02)
Isovalerylcarnitine	1.67E-01	0.04 (-0.02 – 0.10)
Phenylalanine	1.71E-01	0.04 (-0.02 – 0.10)
Urocanate	1.72E-01	0.16 (-0.07 – 0.40)
Dimethylguanidino valerate	1.93E-01	-0.07 (-0.17 – 0.03)
Leucine	1.98E-01	0.04 (-0.02 – 0.11)
Creatine	2.10E-01	-0.04 (-0.11 – 0.02)
Paracetamol	2.21E-01	0.04 (-0.03 – 0-11)
Glucose	2.24E-01	0.04 (-0.02 – 0.10)
Trigonelline	2.43E-01	0.04 (-0.03 – 0.11)
Caffeine	2.66E-01	0.15 (-0.11 – 0.41)
N2-N2-Dimethylguanosine	2.69E-01	-0.06 (-0.17 – 0.05)
c16:1-carnitine	2.82E-01	-0.03 (-0.09 – 0.03)
N-Acetylcarnosine	2.84E-01	0.04 (-0.03 – 0.12)
2-Aminoisobutyric-acid	3.10E-01	0.03 (-0.03 – 0.09)
4-Oxoproline	3.10E-01	-0.10 (-0.30 – 0.10)
Alpha-N-Phenylacetyl-glutamine	3.24E-01	-0.03 (0.09 – 0.03)
1-Methylnicotinamide	3.26E-01	0.03 (-0.03 – 0.09)
symmetric dimethylarginine	3.29E-01	-0.21 (-0.67 – 0.22)
3-Hydroxy-trimethyllysine	3.29E-01	-0.06 (-0.19 -0.06)
Butyrylcarnitine	3.41E-01	0.03 (-0.03 – 0.08)
Arginine	3.57E-01	-0.03 (-0.08 – 0.03)
c8:OH-carnitine	3.93E-01	-0.03 (-0.08 – 0.03)
Isoleucine	4.34E-01	0.04 (-0.06 – 0.13)
c9:0-carnitine	4.36E-01	0.03 (-0.04 – 0.09)
Piperine	4.56E-01	-0.02 (-0.09 – 0.04)
25-Hydroxycholecalciferol-25-hydroxyvitamin-D3	4.73E-01	-0.02 (-0.08 – 0.04)
Taurine	4.73E-01	0.02 (-0.04 – 0.08)
Hydroxycotinine	5.05E-01	0.05 (0.10-0.21)
Adenosine	5.13E-01	0.80 (-1.59 – 3.20)
Cotinine	5.13E-01	-0.21 (-0.86 – 0.43)
Guanidineacetate	5.21E-01	0.02 (-0.04 – 0.08)
c12:3-carnitine	5.21E-01	-0.05 (-0.20 – 0.10)
3-Methyl-L-histidine	5.35E-01	0.02 (-0.04 – 0.08)
Valine	6.00E-01	0.02 (-0.04 – 0.07)
Alanine	6.06E-01	0.02 (-0.05 – 0.08)
Serine	6.09E-01	-0.01 (-0.07 – 0.04)
Choline	6.61E-01	-0.01 (-0.07 – 0.04)
Hypoxanthine	6.76E-01	0.01 (-0.04 – 0.04)
Urea	6.83E-01	0.01 (-0.05 – 0.07)
Glutamate	6.88E-01	0.01 (-0.05 – 0.07)
C2-carnitine	7.29E-01	-0.01 (-0.07 – 0.05)
Ornithine	7.38E-01	-0.01 (-0.06 – 0.05)
c14:0-carnitine	7.77E-01	0.01 (-0.05 – 0.07)
c16:0-carnitine	7.87E-01	0.01 (-0.05 – 0.07)
1-Methylhistidine	8.03E-01	-0.01 (-0.07 – 0.05)
Glutamine-Glutamate	8.10E-01	0.01 (-0.05 -0.07)
Threonine	8.33E-01	0.01 (-0.05 – 0.06)
c10:3-carnitine	8.35E-01	-0.01 (-0.08 – 0.07)
Nicotinamide	8.58E-01	0.01 (-0.12 – 0.14)

Supplementary table 2: Linear regressions between the health conscious dietary pattern and metabolites

Asymmetric dimethylarginine	9.16E-01	0.00 (-0.05 – 0.06)
Glutamine	9.21E-01	0.00 (-0.06 – 0.05)
Homocitrulline	9.35E-01	0.01 (-0.19 – 0.21)
n-monomethylarginine	9.47E-01	0.00 (-0.09 – 0.09)
Pyroglutamate	9.47E-01	0.01 (-0.16 – 0.17)
Trimethyllysine	9.64E-01	0.00 (-0.06 – 0.06)
Creatinine	9.71E-01	0.00 (-0.06 – 0.07)
Acisoga	9.82E-01	0.00 (-0.06 – 0.06)
5-methylthioadenosine	9.91E-01	0.00 (0.23 – 0.23)

Linear regression models between the HCFP and fasting metabolite levels, adjusted for age, sex, BMI, fasting glucose, fasting LDL cholesterol, fasting HDL cholesterol, fasting triglycerides, systolic blood pressure, anti-hypertensive treatment, season for dietary sampling, alcohol intake and smoking status. Beta represents a quintile increase or decrease in the five quintile scaled HCFP per SD increment of a metabolite with the 95 % confidence interval in paranthesis. The cut-off for significance (P = 0.00044) was calculated using Bonferroni correction. N=2515.

Supplementary table 3: Sensitivity analysis physical activity in adjusted linear regressions

	Beta model 1	**P model 1**	**Beta model 2**	**P model 2**
Ergothioneine	0.29 (0.22 – 0.35)	2.7E-20	0.28 (0.22 – 0.34)	1.3E-19
Proline betaine	0.24 (0.18 – 0.30)	1.7E-15	0.24 (0.18 – 0.29)	3.5E-15
Methylproline	0.58 (0.39 – 0.76)	5.5E-10	0.57 (0.39 – 0.75)	5.7E-10
Acetylornithine	0.17 (0.11 – 0.23)	7.3E-09	0.17 (0.11 – 0.22)	1.4E-08
Pantothenate	0.13 (0.07 – 0.19)	1.8E-05	0.13 (0.07 – 0.19)	1.9E-05
Urobilin	-0.12 (-0.18 – -0.06)	3.7E-05	-0.12 (-0.17 – 0.06)	5.8E-05

Linear regression models between the health conscious food pattern (HCFP) and circulating metabolite levels. Beta represents a quintile increase or decrease in the five quintile scaled HCFP per SD increment of a metabolite with the 95 % confidence interval in parenthesis.

Model 1: adjusted for age, sex, BMI, fasting glucose, fasting LDL cholesterol, fasting HDL cholesterol, fasting triglycerides, systolic blood pressure, anti-hypertensive treatment, season for dietary sampling, alcohol intake and smoking status.

Model 2: adjusted for all of the covariates in model 1 as well as physical activity

N= 2323 after exclusion of participants with incomplete data on physical activity.

Supplementary table 4: Fully adjusted cox regressions

Metabolite	Disease	Hazard ratio	p-value	PH assumption p-value
Ergothioneine	CAD	0.85 (0.75-0.96)	0.01	0.5
Ergothioneine	CVD-mortality	0.79 (0.69-0.92)	0.002	0.9
Ergothioneine	Overall mortality	0.86 (0.79-0.92)	0.00004	0.5
Acetylornithine	CAD	0.93 (0.83-1.04)	0.2	0.8
Acetylornithine	CVD-mortality	0.86 (0.75-0.98)	0.03	1
Acetylornithine	Overall mortality	0.89 (0.83-0.96)	0.002	0.7
Acetylornithine	Stroke	0.87 (0.77-0.99)	0.03	0.1
Proline betaine	CAD	0.87 (0.77-0.98)	0.02	0.8
Proline betaine	Overall mortality	0.93 (0.86-1.00)	0.04	0.1
Urobilin	CVD-mortality	1.10 (0.98-1.24)	0.1	0.1
Urobilin	Overall mortality	1.12 (1.05-1.19)	0.0006	0.0005
Urobilin	T2DM	1.16 (1.05-1.28)	0.003	0.1
Methylproline	CAD	0.69 (0.47-1.00)	0.05	0.3
Methylproline	Overall mortality	0.77 (0.62-0.97)	0.02	0.7

Cox proportional hazard models comparing the health conscious dietary biomarker levels with risk for overall and cardiovascular mortality as well as for incident stroke, diabetes mellitus and coronary artery disease during the median follow time of 21.4 years. The models were adjusted for age, sex, BMI, fasting glucose, fasting LDL cholesterol, fasting HDL cholesterol, fasting triglycerides, systolic blood pressure, anti-hypertensive treatment, alcohol intake and smoking status. The hazard ratio is calculated as the increase or decrease in risk per one standard deviation increment of metabolite levels with 95% confidence interval. The proportional hazard was tested using the schoenfeld residual test. N = 3236.

CAD: Coronary heart disease, CVD-mortality: Cardiovascular mortality, T2DM – Type II diabetes mellitus, PH: proportional hazard

Supplementary table 5: Sensitivity analysis physical activity in adjusted cox regressions

	HR Model 1	**P Model 1**	**HR Model 2**	**P Model 2**
Ergothioneine and coronary artery disease	0.87 (0.77 –0.99)	0.04	0.87 (0.76 – 0.99)	0.03
Ergothioneine and overall mortality	0.86 (0.80 – 0.93)	0.0002	0.86 (0.80 – 0.93)	0.0002
Ergothioneine and cardiovascular mortality	0.82 (0-71 – 0.96)	0.01	0.82 (0.71– 0.96)	0.01
Proline betaine and coronary artery disease	0.88 (0.78 – 1.00)	0.05	0.88 (0.78 – 1.00)	0.05

Cox regression models created using metabolite levels as the independent variable and the endpoint as the independent. The continuous hazard ratio (HR) is expressed per one standard deviation increment of metabolite with the 95 % Confidence interval in parenthesis

Model 1: adjusted for age, sex, BMI, fasting glucose, fasting LDL cholesterol, fasting HDL cholesterol, fasting triglycerides, systolic blood pressure, anti-hypertensive treatment, season for dietary sampling, alcohol intake and smoking status.

Model 2: adjusted for all of the covariates in model 1 as well as physical activity.

N= 2993 after exclusion of participants with incomplete data on physical activity.

Supplementary table 6: Associations between risk factors and quartiles of ergothioneine

	Q1 n=809	Q2 n=809	Q3 n=809	Q4 n=809	Total n = 3236	Beta or χ^2 (df)	p-value
Age (years)	58.8 ± 5.9	57.6± 6.0	57.0 ± 6.0	56.5 ± 5.9	57.4 ± 6.0	-0.8	<0.001
Sex (% female)	63 %	65 %	63 %	54 %	61 %	23 (3)	<0.001
Smokers	35 %	31 %	24 %	20 %	27 %	53 (3)	<0.001
BMI ($kg\ m^{-2}$)	25.1 ± 3.9	25.4 ± 3.7	25.3 ± 3.5	25.4 ± 3.6	25.3 ± 3.7	0.08	0.2
SBP (mm hg)	142 ± 19	141 ± 19	141 ± 18	139 ± 18	141 ± 19	-1.1	<0.001
DBP (mm hg)	87.1 ± 9.4	86.5 ± 9.4	86.4 ± 9.4	85.9 ± 9.2	86.5 ± 9.3	-0.035	0.02
Fasting Glucose ($mmol\ L^{-1}$)	4.88 ± 0.42	4.90 ± 0.43	4.88 ± 0.43	4.93 ± 0.46	4.90 ± 0.43	0.01	0.06
Fasting TG ($mmol\ L^{-1}$)	1.28 ± 0.6	1.27 ± 0.6	1.20 ± 0.6	1.24 ± 0.6	1.25 ± 0.59	-0.02	0.06
Fasting HDL ($mmol\ L^{-1}$)	1.35 ± 0.34	1.41 ± 0.37	1.47 ± 0.38	1.44 ± 0.37	1.42 ± 0.37	0.03	<0.001
Fasting LDL ($mmol\ L^{-1}$)	4.16 ± 1.0	4.21 ± 1.0	4.14 ± 1.0	4.13 ± 1.0	4.16 ± 0.99	-0.02	0.4
AHT	12 %	13 %	13 %	14 %	13 %	1.8 (3)	0.6
Alcohol intake ($g\ day^{-1}$)	6.04 ± 8.9	9.14 ± 12	11.6 ± 12	13.8 ± 13	10.1 ± 12	2.6	<0.001

Values are displayed as mean ± SD

Beta coefficients is calculated using the quartile of ergothioneine as the independent variable and the respective clinical parameter as the dependent variable. Pearson chi square test was used to calculate the χ^2 for the categorical variables. Q1 is the quartile with lowest ergothioneine level at baseline, and Q4 the highest.

AHT: antihypertensive treatment. DBP: diastolic blood pressure. HDL: HDL cholesterol. LDL: LDL cholesterol. SBP: systolic blood pressure. df: degrees of freedom

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