

Metabolite and protein associations with general health in the population-based CHRIS study

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Supplementary Material

Supplementary Tables	2
Table S1. Characteristics of the CHRIS cohort with information on health status (any morbidity vs. healthy) ^a and CIRS domain specific morbidity ^b	2
Table S2. Medications used for adjustment of metabolite and protein abundances.	3
Table S3. Results of the regression analyses for association between health status, age and metabolite or protein abundances for significant predictors obtained from the random forest analysis.	4
Table S4. Results of the regression analyses for significant association between morbidity in CIRS organ domains and metabolite or protein abundances.	7
Table S5. Overview of the 174 metabolites included in the analysis.	12
Table S6. Overview of the 148 plasma proteins quantified using Scanning SWATH in the CHRIS cohort.	17
Supplementary Figures	22
Figure S1. Distribution of age and health status in the CHRIS cohort.	22
Figure S2. Biplot of ordinary correspondence analysis of comorbidities in the CHRIS cohort.	23
Figure S3. Performance evaluation of 100 random forest models including as predictors age, sex, 174 metabolites and 148 proteins to classify health status (any morbidity vs. healthy)	24
Supplementary Text	25
Text S1. Description of Random Forest Performance Evaluation Scores and model comparison.	25
Text S2. Discussion of additional metabolites and proteins.	30

Supplementary Tables

Table S1. Characteristics of the CHRIS cohort with information on health status (any morbidity vs. healthy)^a and CIRS domain specific morbidity^b.

	Overall	Healthy	Any morbidity
Sample size, n	13,373^c	5803	7570
Age, mean (SD)	45.3 (16.6)	37.9 (13.8)	51.0 (16.4)
Comorbidity Index, mean (SD)	1.02 (1.30)	0	1.80 (1.25)
Sex n (%)			
Females	7264 (54.3%)	3567 (61.5%)	3697 (48.8%)
Males	6109 (45.7%)	2236 (38.5%)	3873 (51.2%)
<i>Morbidity in CIRS domains, yes (%)</i>			
Hepatic	3987 (29.8%)		3987 (52.7%)
Vascular	2024 (15.1%)		2024 (26.7%)
Hypertension	1585 (11.9%)		1585 (20.9%)
Respiratory	1269 (9.5%)		1269 (16.8%)
Endocrine-Metabolic	1422 (10.6%)		1422 (18.8%)
Psychiatric and behavioral	598 (4.5%)		598 (7.9%)
Upper Gastrointestinal	577 (4.3%)		577 (7.6%)
MBJ ^d	548 (4.1%)		548 (7.2%)
Renal	482 (3.6%)		482 (6.4%)
Cardiac	405 (3.0%)		405 (5.4%)
Neurological	271 (2.0%)		271 (3.6%)
Genitourinary	231 (1.7%)		231 (3.1%)
Lower Gastrointestinal	142 (1.1%)		142 (1.9%)
EENT ^e	85 (0.6%)		85 (1.1%)

^aHealth status was assessed through the Cumulative Illness Rating Scale (CIRS) Comorbidity Index (CMI) by classifying individuals as having any morbidity (CMI \geq 1) or being healthy (CMI=0). ^bCIRS domain specific morbidity is defined as having a score \geq 2 in the given domain. ^cNumber of CHRIS baseline study participants available for analysis. ^dMBJ=Musculoskeletal, bones and joints. ^eEENT=Ears, eyes, nose and throat.

Table S2. Medications used for adjustment of metabolite and protein abundances.

ATC code level 4	ATC4 name	# participants taking the medication frequently
G03AA	Progestogens and estrogens, fixed combinations	214
A12AX	Calcium, combinations with vitamin D and/or other drugs	59
G04CA	Alpha-adrenoreceptor antagonists	40
MO4AA	Preparations inhibiting uric acid production	31
G03AB	Progestogens and estrogens, sequential preparations	27
G02BA	Intrauterine contraceptives	22
S01ED	Beta blocking agents	18
G03HB	Antiandrogens and estrogens	14
N04BC	Dopamine agonists	14
G03FA	Progestogens and estrogens, fixed combinations	13
G03CA	Natural and semisynthetic estrogens, plain	10
G03AC	Progestogens	8
J01FA	Macrolides	8
A11DB	Vitamin B1 in combination with vitamin B6 and/or vitamin B12	7
G04CB	Testosterone-5-alpha reductase inhibitors	7
R01AD	Corticosteroids	6
R06AE	Piperazine derivatives	6
R06AX	Other antihistamines for systemic use	6
S01EE	Prostaglandin analogues	6

Table S3. Results of the regression analyses for association between health status, age and metabolite or protein abundances for significant predictors obtained from the random forest analysis.

Feature name	Description	Class/Protein ID	coef-anymorb	%diff-anymorb	p-adj-anymorb	coef-age	p-adj-age	CV QC (%)
<i>Metabolites</i>								
Serotonin	Serotonin	biogenic amines	-0.287	22.031	1.03E-16	-0.006	4.52E-09	3.926
Glu	Glutamate	amino acids	0.160	11.754	8.27E-13	0.004	1.12E-09	3.756
Tyr	Tyrosine	amino acids	0.063	4.451	1.55E-06	0.001	4.62E-04	3.808
H1	Hexose	sugars	0.034	2.404	3.34E-04	0.003	1.65E-27	3.299
PC aa C32:1	Phosphatidylcholine diacyl C32:1	glycerophospholipids	0.118	8.530	3.80E-04	0.005	8.42E-10	7.670
lysoPC a C18:2	lysoPhosphatidylcholine acyl C18:2	glycerophospholipids	-0.079	5.645	4.23E-04	-0.004	5.11E-10	4.475
C18:1	Octadecenoylcarnitine	acylcarnitines	0.056	3.953	6.23E-04	0.004	2.98E-20	5.348
Kynurenine	Kynurenine	biogenic amines	0.049	3.427	5.66E-03	0.002	1.41E-08	6.675
C16:1	Hexadecenoylcarnitine	acylcarnitines	0.045	3.149	8.88E-03	0.004	3.11E-30	7.481

Taurine	Taurine	biogenic amines	-0.040	2.777	1.13E-02	0.000	1	3.036
C6 (C4:1-DC)	Hexanoylcarnitine (Fumaryl carnitine)	acylcarnitines	0.049	3.419	8.03E-02	0.006	4.57E-29	6.375
C16	Hexadecanoylcarnitine	acylcarnitines	0.038	2.698	1.71E-01	0.004	1.51E-18	18.773
PC aa C40:4	Phosphatidylcholine diacyl C40:4	glycerophospholipids	0.047	3.305	3.33E-01	0.004	1.24E-10	7.155
PC aa C38:4	Phosphatidylcholine diacyl C38:4	glycerophospholipids	0.044	3.094	4.38E-01	0.004	5.19E-14	5.153
C0	Carnitine	acylcarnitines	0.027	1.860	5.60E-01	0.002	3.81E-08	5.650
PC aa C40:5	Phosphatidylcholine diacyl C40:5	glycerophospholipids	0.041	2.848	8.47E-01	0.006	2.13E-26	6.630
alpha-AAA	alpha-Aminoadipic acid	biogenic amines	-0.038	2.669	1	0.006	2.05E-02	21.487
Cit	Citrulline	amino acids	-0.022	1.522	1	0.007	2.99E-67	4.038
Orn	Ornithine	amino acids	0.035	2.429	1	0.004	1.01E-10	6.629
SDMA	Symmetric dimethylarginine	biogenic amines	-0.005	0.322	1	0.004	7.55E-36	8.146
C18	Octadecanoylcarnitine	acylcarnitines	0.000	0.016	1	0.005	5.55E-30	16.274
<i>Proteins</i>								
g:AFM	Afamin	P43652	0.071	5.075	2.23E-08	-0.001	2.11E-02	9.574

g:A1BG*	Alpha-1B-glycoprotein	P04217	0.036	2.550	2.45E-04	0.002	4.36E-15	9.357
g:CFH	Complement factor H	P08603	0.035	2.447	4.98E-04	0.002	2.49E-08	7.930
g:RBP4	Retinol-binding protein 4	P02753	0.043	3.034	3.36E-03	-0.001	1.01E-01	9.483
g:A2M	Alpha-2-macroglobulin	P01023	-0.041	2.897	8.88E-02	-0.002	1.18E-05	7.058
g:APOH	Beta-2-glycoprotein 1	P02749	0.034	2.382	3.36E-01	0.002	5.00E-05	18.547
g:F2	Prothrombin	P00734	-0.016	1.116	3.57E-01	-0.002	5.37E-20	7.021
g:IGHM	Immunoglobulin heavy constant mu	P01871	-0.048	3.377	9.72E-01	-0.007	1.67E-14	10.951
g:IGFALS	Insulin-like growth factor-binding protein complex acid labile subunit	P35858;P35858-2	-0.002	0.148	1	-0.009	2.48E-81	20.125
g:C4BPA	C4b-binding protein alpha chain	P04003	0.014	0.972	1	0.004	2.59E-27	8.639

Metabolites and proteins are sorted by increasing p -value for the trait health status (any morbidity vs. healthy). *: Metabolites and proteins with a Bonferroni adjusted p -value < 0.05 and a difference in concentrations (expressed in %) larger than 2 times or one time the coefficient of variation (CV) in QC (study pool) samples (expressed in %) for metabolites and proteins, respectively, are considered statistically significant. coef-anyorb: coefficient for the trait any morbidity vs. healthy representing the average differential abundance in log₂ scale between the compared groups. Positive values indicate higher, negative values lower, average abundances in individuals with any morbidity compared to those without. coef-age: coefficient for the trait age representing the change in log₂ abundance in one year. Positive values indicate increasing, negative values decreasing abundances with age. %difference: represents the difference of (mean) concentrations on normal scale in %. p -adj-anyorb: p -value for the trait any morbidity vs healthy, adjusted for multiple hypothesis testing using the Bonferroni method. p -adj-age p -value for the trait age, adjusted for multiple hypothesis testing using the Bonferroni method.

Table S4. Results of the regression analyses for significant association between morbidity in CIRS organ domains and metabolite or protein abundances.

Feature	Description	Class/Protein ID	CIRS domain	Coef	p-adj	%diff	CV QC
<i>Metabolites</i>							
Serotonin	Serotonin	biogenic amines	Cardiac	-0.588	4.57E-09	50.276	3.926
Taurine	Taurine	biogenic amines	Cardiac	-0.126	2.55E-02	9.140	3.036
C6 (C4:1-DC)	Hexanoylcarnitine (Fumaryl carnitine)	acylcarnitines	Cardiac	0.188	1.82E-02	13.939	6.375
SM (OH) C22:1	Hydroxysphingomyeline C22:1	sphingolipids	Cardiac	-0.217	2.17E-03	16.195	7.374
SM C24:0	Sphingomyeline C24:0	sphingolipids	Cardiac	-0.216	8.75E-04	16.141	6.872
Ala	Alanine	amino acids	Endocrine-Metabolic	0.145	4.79E-12	10.582	4.790
Glu	Glutamate	amino acids	Endocrine-Metabolic	0.355	9.92E-24	27.933	3.756
Gly	Glycine	amino acids	Endocrine-Metabolic	-0.121	6.47E-05	8.756	3.743
Ile	Isoleucine	amino acids	Endocrine-Metabolic	0.162	4.26E-19	11.855	3.691
Leu	Leucine	amino acids	Endocrine-Metabolic	0.114	5.03E-10	8.199	4.051
Val	Valine	amino acids	Endocrine-Metabolic	0.115	3.05E-10	8.281	4.040
C6 (C4:1-DC)	Hexanoylcarnitine (Fumaryl carnitine)	acylcarnitines	Endocrine-Metabolic	0.190	7.95E-10	14.082	6.375
H1	Hexose	sugars	Endocrine-Metabolic	0.171	8.00E-41	12.553	3.299
lysoPC a C17:0	lysoPhosphatidylcholine acyl C17:0	glycerophospholipids	Endocrine-Metabolic	-0.222	1.64E-13	16.645	5.380

lysoPC a C18:1	lysoPhosphatidylcholine acyl C18:1	glycerophospholipids	Endocrine-Metabolic	-0.168	1.66E-07	12.331	3.155
lysoPC a C18:2	lysoPhosphatidylcholine acyl C18:2	glycerophospholipids	Endocrine-Metabolic	-0.248	2.43E-14	18.737	4.475
PC ae C32:1	Phosphatidylcholine acyl-alkyl C32:1	glycerophospholipids	Endocrine-Metabolic	-0.198	5.37E-10	14.676	7.084
PC ae C34:2	Phosphatidylcholine acyl-alkyl C34:2	glycerophospholipids	Endocrine-Metabolic	-0.264	9.17E-15	20.050	6.374
PC ae C34:3	Phosphatidylcholine acyl-alkyl C34:3	glycerophospholipids	Endocrine-Metabolic	-0.292	3.20E-16	22.430	6.138
PC ae C36:2	Phosphatidylcholine acyl-alkyl C36:2	glycerophospholipids	Endocrine-Metabolic	-0.228	7.26E-12	17.124	6.473
PC ae C36:3	Phosphatidylcholine acyl-alkyl C36:3	glycerophospholipids	Endocrine-Metabolic	-0.206	4.27E-09	15.332	6.131
SM (OH) C14:1	Hydroxysphingomyeline C14:1	sphingolipids	Endocrine-Metabolic	-0.188	1.18E-07	13.911	6.696
SM C16:0	Sphingomyeline C16:0	sphingolipids	Endocrine-Metabolic	-0.174	3.59E-09	12.842	5.838
DOPA	Dihydroxyphenylalanine	biogenic amines	Genitourinary	0.104	1.32E-02	7.504	2.927
Glu	Glutamate	amino acids	Hepatic	0.127	5.34E-05	9.211	3.756
C2	Acetylcarnitine	acylcarnitines	Hepatic	0.104	2.78E-04	7.451	2.333
Glu	Glutamate	amino acids	Hypertension	0.207	1.41E-07	15.408	3.756
Ile	Isoleucine	amino acids	Hypertension	0.124	1.27E-11	8.956	3.691
Serotonin	Serotonin	biogenic amines	Hypertension	-0.290	1.09E-05	22.303	3.926
C3	Propionylcarnitine	acylcarnitines	Hypertension	0.154	6.14E-07	11.256	4.274
lysoPC a C17:0	lysoPhosphatidylcholine acyl C17:0	glycerophospholipids	Hypertension	-0.158	1.21E-06	11.569	5.380
lysoPC a C18:1	lysoPhosphatidylcholine acyl C18:1	glycerophospholipids	Hypertension	-0.124	1.05E-03	8.969	3.155

lysoPC a C18:2	lysoPhosphatidylcholine acyl C18:2	glycerophospholipids	Hypertension	-0.166	4.71E-06	12.172	4.475
Spermine	Spermine	biogenic amines	Lower_GI	-0.420	6.53E-04	33.770	15.843
DOPA	Dihydroxyphenylalanine	biogenic amines	Neurological	0.093	3.14E-03	6.649	2.927
Serotonin	Serotonin	biogenic amines	Psychiatric	-2.203	1.87E-245	360.496	3.926
Creatinine	Creatinine	biogenic amines	Renal	0.227	2.31E-18	17.011	4.715
Ile	Isoleucine	amino acids	Renal	0.121	3.57E-03	8.767	3.691
Kynurenine	Kynurenine	biogenic amines	Renal	0.253	1.90E-12	19.138	6.675
Phe	Phenylalanine	amino acids	Renal	0.131	1.50E-05	9.478	3.829
Pro	Proline	amino acids	Renal	0.160	3.05E-02	11.702	5.280
t4-OH-Pro	trans-4-Hydroxyproline	biogenic amines	Renal	0.309	1.98E-06	23.916	7.068
C10	Decanoylcarnitine	acylcarnitines	Renal	0.228	9.91E-03	17.131	4.140
C10:1	Decenoylcarnitine	acylcarnitines	Renal	0.252	2.66E-07	19.106	5.294
C12	Dodecanoylcarnitine	acylcarnitines	Renal	0.223	1.46E-05	16.740	7.442
C12:1	Dodecenoylcarnitine	acylcarnitines	Renal	0.270	2.67E-09	20.586	5.369
C14:1	Tetradecenoylcarnitine	acylcarnitines	Renal	0.298	4.29E-05	22.975	5.826
C14:2	Tetradecadienylcarnitine	acylcarnitines	Renal	0.222	9.21E-03	16.675	7.463
C18:1	Octadecenoylcarnitine	acylcarnitines	Renal	0.147	8.23E-03	10.709	5.348
C2	Acetylcarnitine	acylcarnitines	Renal	0.218	1.04E-03	16.328	2.333
C3	Propionylcarnitine	acylcarnitines	Renal	0.176	1.22E-02	13.007	4.274
C3-DC (C4-OH)	Hydroxybutyrylcarnitine	acylcarnitines	Renal	0.229	5.18E-04	17.202	7.986
C5	Valerylcarnitine	acylcarnitines	Renal	0.182	3.67E-03	13.418	5.324
C6 (C4:1-DC)	Hexanoylcarnitine (Fumarylacarnitine)	acylcarnitines	Renal	0.252	4.30E-07	19.071	6.375
Glu	Glutamate	amino acids	Respiratory	0.233	1.72E-08	17.554	3.756
Serotonin	Serotonin	biogenic amines	Vascular	-0.228	6.66E-04	17.115	3.926
Taurine	Taurine	biogenic amines	Vascular	-0.120	5.21E-12	8.679	3.036
<i>Proteins</i>							
g:F2	Prothrombin	P00734	Cardiac	-0.246	2.51E-35	18.552	7.021

g:FCN3	Ficolin-3	O75636	Cardiac	-0.240	3.11E-02	18.063	17.674
g:C4BPA	C4b-binding protein alpha chain	P04003	Cardiac	-0.228	4.17E-14	17.141	8.639
g:APOB	Apolipoprotein B-100	P04114	Cardiac	-0.227	9.79E-06	17.014	9.899
g:A2M	Alpha-2-macroglobulin	P01023	Cardiac	0.189	3.59E-03	13.971	7.058
g:SERPINA1	Alpha-1-antitrypsin	P01009	Cardiac	0.120	2.22E-02	8.669	7.950
g:IGHM	Immunoglobulin heavy constant mu	P01871	Endocrine- Metabolic	-0.269	5.05E-06	20.458	10.951
g:CD5L	CD5 antigen-like	O43866	Endocrine- Metabolic	-0.249	4.64E-05	18.855	17.787
g:APOD	Apolipoprotein D	P05090	Endocrine- Metabolic	-0.223	2.78E-17	16.700	13.115
g:APOB	Apolipoprotein B-100	P04114	Endocrine- Metabolic	-0.182	7.24E-11	13.468	9.899
g:HP	Haptoglobin	P00738	Endocrine- Metabolic	0.180	3.69E-03	13.259	10.070
g:VTN	Vitronectin	P04004	Endocrine- Metabolic	0.135	2.44E-20	9.794	8.553
g:AFM	Afamin	P43652	Endocrine- Metabolic	0.134	1.25E-09	9.743	9.575
g:C3	Complement C3	P01024	Endocrine- Metabolic	0.131	2.24E-24	9.511	4.871
g:C3	Complement C3	P01024	Hypertension	0.102	1.90E-15	7.294	4.871
g:A2M	Alpha-2-macroglobulin	P01023	Renal	0.275	2.04E-10	21.037	7.058
g:APOM	Apolipoprotein M	O95445	Renal	-0.214	4.76E-08	15.988	14.761
g:APOB	Apolipoprotein B-100	P04114	Renal	-0.169	7.32E-03	12.427	9.899
g:PON1	Serum paraoxonase/arylesterase 1	P27169	Renal	-0.169	3.49E-02	12.418	11.318
g:F2	Prothrombin	P00734	Renal	-0.130	8.04E-10	9.440	7.021

g:HP	Haptoglobin	P00738	Respiratory	0.237	1.71E-06	17.842	10.070
g:IGHG2	Immunoglobulin heavy constant gamma 2	P01859	Respiratory	-0.212	2.15E-09	15.801	8.071
g:SERPIND1	Heparin cofactor 2	P05546	Respiratory	0.149	2.85E-09	10.917	7.994
g:IGKC	Immunoglobulin kappa constant	P01834	Respiratory	-0.120	4.76E-06	8.666	7.620
g:APOB	Apolipoprotein B-100	P04114	Vascular	-0.147	1.48E-09	10.738	9.899
g:A2M	Alpha-2-macroglobulin	P01023	Vascular	0.142	1.93E-08	10.373	7.058
<p>Metabolites and proteins related to specific CIRS domains with a Bonferroni adjusted p-value<0.05 and a difference in concentrations (expressed in %) larger than 2 times or one time the coefficient of variation (CV) in QC (study pool) samples (expressed in %) for metabolites and proteins, respectively, are considered statistically significant. coef: coefficient representing the average differential abundance in log2 scale between the compared groups (morbidity in CIRS domain vs. healthy). Positive values indicate higher, negative values lower, average abundances in individuals with CIRS domain specific morbidity compared to those without. %diff: represents the difference of (mean) concentrations on normal scale in %. p-adj: p-value adjusted for multiple hypothesis testing using the Bonferroni method.</p>							

Table S5. Overview of the 174 metabolites included in the analysis. 14 out of the in total 188 metabolites quantified with the Biocrates AbsoluteIDQ p180 kit were excluded because of poor quality or high number of missing values in the CHRIS cohort.

Analyte name	Biochemical name	Analyte class	Mean	Sd	CV QC (%)
ADMA	Asymmetric dimethylarginine	biogenic amines	0.49	3.20	6.63
Ala	Alanine	amino acids	344.80	72.83	4.79
alpha-AAA	alpha-Aminoadipic acid	biogenic amines	0.57	0.48	21.49
Arg	Arginine	amino acids	101.52	18.57	3.82
Asn	Asparagine	amino acids	45.74	7.28	3.14
Asp	Aspartate	amino acids	14.73	3.98	5.46
Cit	Citrulline	amino acids	30.05	7.90	4.04
Creatinine	Creatinine	biogenic amines	77.28	19.61	4.71
DOPA	Dihydroxyphenylalanine	biogenic amines	0.19	0.11	2.93
Gln	Glutamine	amino acids	646.42	97.92	4.85
Glu	Glutamate	amino acids	46.15	19.15	3.76
Gly	Glycine	amino acids	248.73	72.65	3.74
His	Histidine	amino acids	90.08	12.06	3.54
Histamine	Histamine	biogenic amines	0.14	0.02	0.99
Ile	Isoleucine	amino acids	66.02	15.21	3.69
Kynurenine	Kynurenine	biogenic amines	2.70	0.73	6.68
Leu	Leucine	amino acids	132.71	27.36	4.05
Lys	Lysine	amino acids	207.00	39.12	7.07
Met	Methionine	amino acids	22.78	4.26	4.85
Met-SO	Methioninesulfoxide	biogenic amines	0.23	0.37	51.51
Orn	Ornithine	amino acids	73.00	19.34	6.63
Phe	Phenylalanine	amino acids	63.71	9.63	3.83
Pro	Proline	amino acids	174.01	56.44	5.28
Putrescine	Putrescine	biogenic amines	0.14	0.05	8.71
SDMA	Symmetric dimethylarginine	biogenic amines	0.51	2.79	8.15
Ser	Serine	amino acids	124.46	21.76	4.49
Serotonin	Serotonin	biogenic amines	0.69	0.32	3.93
Spermidine	Spermidine	biogenic amines	0.20	0.04	5.21
Spermine	Spermine	biogenic amines	0.16	0.03	15.84
t4-OH-Pro	trans-4-Hydroxyproline	biogenic amines	8.60	6.07	7.07
Taurine	Taurine	biogenic amines	108.26	21.31	3.04
Thr	Threonine	amino acids	121.16	26.98	3.44
Trp	Tryptophan	amino acids	61.90	10.45	3.55
Tyr	Tyrosine	amino acids	64.71	14.19	3.81
Val	Valine	amino acids	220.60	43.32	4.04
C0	Carnitine	acylcarnitines	38.45	8.91	5.65
C10	Decanoylcarnitine	acylcarnitines	0.36	0.18	4.14
C10:1	Decenoylcarnitine	acylcarnitines	0.16	0.05	5.29
C10:2	Decadienylcarnitine	acylcarnitines	0.08	0.01	9.16
C12	Dodecanoylcarnitine	acylcarnitines	0.14	0.05	7.44
C12-DC	Dodecanedioylcarnitine	acylcarnitines	0.33	0.03	4.57
C12:1	Dodecenoylcarnitine	acylcarnitines	0.15	0.04	5.37
C14	Tetradecanoylcarnitine	acylcarnitines	0.06	0.02	16.24
C14:1	Tetradecenoylcarnitine	acylcarnitines	0.08	0.04	5.83
C14:1-OH	Hydroxytetradecenoylcarnitine	acylcarnitines	0.03	0.01	9.12
C14:2	Tetradecadienylcarnitine	acylcarnitines	0.04	0.02	7.46

C14:2-OH	Hydroxytetradecadienylcarnitine	acylcarnitines	0.03	0.01	8.47
C16	Hexadecanoylcarnitine	acylcarnitines	0.13	0.03	18.77
C16-OH	Hydroxyhexadecanoylcarnitine	acylcarnitines	0.03	0.01	8.81
C16:1	Hexadecenoylcarnitine	acylcarnitines	0.05	0.01	7.48
C16:1-OH	Hydroxyhexadecenoylcarnitine	acylcarnitines	0.02	0.00	12.17
C18	Octadecanoylcarnitine	acylcarnitines	0.07	0.02	16.27
C18:1	Octadecenoylcarnitine	acylcarnitines	0.13	0.03	5.35
C2	Acetylcarnitine	acylcarnitines	7.61	2.68	2.33
C3	Propionylcarnitine	acylcarnitines	0.38	0.13	4.27
C3-DC (C4-OH)	Hydroxybutyrylcarnitine	acylcarnitines	0.05	0.02	7.99
C3:1	Propenoylcarnitine	acylcarnitines	0.01	0.00	14.31
C4	Butyrylcarnitine	acylcarnitines	0.21	0.10	6.25
C4:1	Butenylcarnitine	acylcarnitines	0.02	0.00	11.91
C5	Valerylcarnitine	acylcarnitines	0.13	0.05	5.32
C5-DC (C6-OH)	Glutaryl carnitine (Hydroxyhexanoylcarnitine)	acylcarnitines	0.02	0.01	11.56
C5-M-DC	Methylglutaryl carnitine	acylcarnitines	0.03	0.01	11.13
C5-OH (C3-DC-M)	Hydroxyvalerylcarnitine (Methylmalonylcarnitine)	acylcarnitines	0.05	0.01	8.71
C5:1	Tiglylcarnitine	acylcarnitines	0.03	0.01	9.65
C5:1-DC	Glutaconylcarnitine	acylcarnitines	0.02	0.00	12.52
C6 (C4:1-DC)	Hexanoylcarnitine (Fumaryl carnitine)	acylcarnitines	0.07	0.03	6.38
C6:1	Hexenoylcarnitine	acylcarnitines	0.02	0.00	11.21
C8	Octanoylcarnitine	acylcarnitines	0.22	0.11	8.83
C9	Nonaylcarnitine	acylcarnitines	0.07	0.02	7.42
H1	Hexose	sugars	4491.72	750.67	3.30
lysoPC a C14:0	lysoPhosphatidylcholine acyl C14:0	glycerophospholipids	3.63	0.50	6.03
lysoPC a C16:0	lysoPhosphatidylcholine acyl C16:0	glycerophospholipids	58.18	12.81	4.56
lysoPC a C16:1	lysoPhosphatidylcholine acyl C16:1	glycerophospholipids	2.13	0.69	7.00
lysoPC a C17:0	lysoPhosphatidylcholine acyl C17:0	glycerophospholipids	1.27	0.39	5.38
lysoPC a C18:0	lysoPhosphatidylcholine acyl C18:0	glycerophospholipids	18.59	5.15	6.48
lysoPC a C18:1	lysoPhosphatidylcholine acyl C18:1	glycerophospholipids	14.79	4.70	3.15
lysoPC a C18:2	lysoPhosphatidylcholine acyl C18:2	glycerophospholipids	22.06	8.14	4.47
lysoPC a C20:3	lysoPhosphatidylcholine acyl C20:3	glycerophospholipids	2.09	0.67	4.88
lysoPC a C20:4	lysoPhosphatidylcholine acyl C20:4	glycerophospholipids	5.37	1.79	4.52
lysoPC a C24:0	lysoPhosphatidylcholine acyl C24:0	glycerophospholipids	0.10	0.02	15.55
lysoPC a C26:0	lysoPhosphatidylcholine acyl C26:0	glycerophospholipids	0.10	0.03	18.36
lysoPC a C26:1	lysoPhosphatidylcholine acyl C26:1	glycerophospholipids	0.06	0.02	18.74

lysoPC a C28:0	lysoPhosphatidylcholine acyl C28:0	glycerophospholipids	0.17	0.04	13.62
lysoPC a C28:1	lysoPhosphatidylcholine acyl C28:1	glycerophospholipids	0.26	0.08	10.36
PC aa C24:0	Phosphatidylcholine diacyl C24:0	glycerophospholipids	0.06	0.09	257.42
PC aa C26:0	Phosphatidylcholine diacyl C26:0	glycerophospholipids	0.49	0.07	7.58
PC aa C28:1	Phosphatidylcholine diacyl C28:1	glycerophospholipids	2.93	0.86	6.20
PC aa C30:0	Phosphatidylcholine diacyl C30:0	glycerophospholipids	3.49	1.28	6.32
PC aa C30:2	Phosphatidylcholine diacyl C30:2	glycerophospholipids	0.21	0.11	58.25
PC aa C32:0	Phosphatidylcholine diacyl C32:0	glycerophospholipids	35.66	8.61	6.54
PC aa C32:1	Phosphatidylcholine diacyl C32:1	glycerophospholipids	51.14	27.80	7.67
PC aa C32:2	Phosphatidylcholine diacyl C32:2	glycerophospholipids	15.03	6.17	8.51
PC aa C32:3	Phosphatidylcholine diacyl C32:3	glycerophospholipids	1.43	0.43	8.42
PC aa C34:1	Phosphatidylcholine diacyl C34:1	glycerophospholipids	479.48	148.61	6.77
PC aa C34:2	Phosphatidylcholine diacyl C34:2	glycerophospholipids	1095.60	278.45	5.98
PC aa C34:3	Phosphatidylcholine diacyl C34:3	glycerophospholipids	37.45	12.94	5.82
PC aa C34:4	Phosphatidylcholine diacyl C34:4	glycerophospholipids	5.30	2.11	6.77
PC aa C36:0	Phosphatidylcholine diacyl C36:0	glycerophospholipids	3.97	1.27	11.85
PC aa C36:1	Phosphatidylcholine diacyl C36:1	glycerophospholipids	64.37	20.03	7.19
PC aa C36:2	Phosphatidylcholine diacyl C36:2	glycerophospholipids	424.21	107.47	5.72
PC aa C36:3	Phosphatidylcholine diacyl C36:3	glycerophospholipids	256.96	71.65	6.15
PC aa C36:4	Phosphatidylcholine diacyl C36:4	glycerophospholipids	389.24	114.39	5.39
PC aa C36:5	Phosphatidylcholine diacyl C36:5	glycerophospholipids	39.48	19.22	6.25
PC aa C36:6	Phosphatidylcholine diacyl C36:6	glycerophospholipids	1.75	0.73	8.51
PC aa C38:0	Phosphatidylcholine diacyl C38:0	glycerophospholipids	3.33	1.01	6.50
PC aa C38:1	Phosphatidylcholine diacyl C38:1	glycerophospholipids	1.18	0.66	44.81
PC aa C38:3	Phosphatidylcholine diacyl C38:3	glycerophospholipids	65.03	20.68	5.85
PC aa C38:4	Phosphatidylcholine diacyl C38:4	glycerophospholipids	153.27	45.87	5.15
PC aa C38:5	Phosphatidylcholine diacyl C38:5	glycerophospholipids	76.58	21.51	5.09
PC aa C38:6	Phosphatidylcholine diacyl C38:6	glycerophospholipids	104.84	35.65	5.92
PC aa C40:1	Phosphatidylcholine diacyl C40:1	glycerophospholipids	0.40	0.09	11.68
PC aa C40:2	Phosphatidylcholine diacyl C40:2	glycerophospholipids	0.30	0.09	15.82
PC aa C40:3	Phosphatidylcholine diacyl C40:3	glycerophospholipids	0.60	0.15	11.62
PC aa C40:4	Phosphatidylcholine diacyl C40:4	glycerophospholipids	3.75	1.19	7.15
PC aa C40:5	Phosphatidylcholine diacyl C40:5	glycerophospholipids	9.81	3.18	6.63
PC aa C40:6	Phosphatidylcholine diacyl C40:6	glycerophospholipids	25.30	8.91	5.98
PC aa C42:0	Phosphatidylcholine diacyl C42:0	glycerophospholipids	0.61	0.16	8.99
PC aa C42:1	Phosphatidylcholine diacyl C42:1	glycerophospholipids	0.32	0.08	11.89
PC aa C42:2	Phosphatidylcholine diacyl C42:2	glycerophospholipids	0.20	0.05	13.41
PC aa C42:4	Phosphatidylcholine diacyl C42:4	glycerophospholipids	0.18	0.05	14.39
PC aa C42:5	Phosphatidylcholine diacyl C42:5	glycerophospholipids	0.31	0.09	12.66
PC aa C42:6	Phosphatidylcholine diacyl C42:6	glycerophospholipids	0.40	0.11	12.18
PC ae C30:0	Phosphatidylcholine acyl-alkyl C30:0	glycerophospholipids	0.34	0.11	9.22
PC ae C30:1	Phosphatidylcholine acyl-alkyl C30:1	glycerophospholipids	0.19	0.09	39.59
PC ae C30:2	Phosphatidylcholine acyl-alkyl C30:2	glycerophospholipids	0.08	0.03	10.95
PC ae C32:1	Phosphatidylcholine acyl-alkyl C32:1	glycerophospholipids	8.52	2.15	7.08
PC ae C32:2	Phosphatidylcholine acyl-alkyl C32:2	glycerophospholipids	2.18	0.57	7.72

PC ae C34:0	Phosphatidylcholine acyl-alkyl C34:0	glycerophospholipids	3.48	1.08	9.04
PC ae C34:1	Phosphatidylcholine acyl-alkyl C34:1	glycerophospholipids	25.52	6.75	7.14
PC ae C34:2	Phosphatidylcholine acyl-alkyl C34:2	glycerophospholipids	33.53	9.75	6.37
PC ae C34:3	Phosphatidylcholine acyl-alkyl C34:3	glycerophospholipids	22.78	7.21	6.14
PC ae C36:0	Phosphatidylcholine acyl-alkyl C36:0	glycerophospholipids	1.46	0.43	12.87
PC ae C36:1	Phosphatidylcholine acyl-alkyl C36:1	glycerophospholipids	15.51	4.32	7.98
PC ae C36:2	Phosphatidylcholine acyl-alkyl C36:2	glycerophospholipids	29.32	8.47	6.47
PC ae C36:3	Phosphatidylcholine acyl-alkyl C36:3	glycerophospholipids	17.20	4.66	6.13
PC ae C36:4	Phosphatidylcholine acyl-alkyl C36:4	glycerophospholipids	38.84	11.28	6.06
PC ae C36:5	Phosphatidylcholine acyl-alkyl C36:5	glycerophospholipids	25.30	7.70	6.01
PC ae C38:0	Phosphatidylcholine acyl-alkyl C38:0	glycerophospholipids	2.92	0.93	7.10
PC ae C38:1	Phosphatidylcholine acyl-alkyl C38:1	glycerophospholipids	0.50	0.46	95.88
PC ae C38:2	Phosphatidylcholine acyl-alkyl C38:2	glycerophospholipids	2.78	0.88	15.76
PC ae C38:3	Phosphatidylcholine acyl-alkyl C38:3	glycerophospholipids	6.92	1.97	7.09
PC ae C38:4	Phosphatidylcholine acyl-alkyl C38:4	glycerophospholipids	22.59	5.63	6.00
PC ae C38:5	Phosphatidylcholine acyl-alkyl C38:5	glycerophospholipids	27.44	6.88	5.32
PC ae C38:6	Phosphatidylcholine acyl-alkyl C38:6	glycerophospholipids	11.04	3.11	5.72
PC ae C40:1	Phosphatidylcholine acyl-alkyl C40:1	glycerophospholipids	1.59	0.43	8.23
PC ae C40:2	Phosphatidylcholine acyl-alkyl C40:2	glycerophospholipids	1.99	0.53	7.29
PC ae C40:3	Phosphatidylcholine acyl-alkyl C40:3	glycerophospholipids	1.31	0.32	10.32
PC ae C40:4	Phosphatidylcholine acyl-alkyl C40:4	glycerophospholipids	2.91	0.70	6.29
PC ae C40:5	Phosphatidylcholine acyl-alkyl C40:5	glycerophospholipids	4.09	0.98	6.04
PC ae C40:6	Phosphatidylcholine acyl-alkyl C40:6	glycerophospholipids	5.42	1.50	6.15
PC ae C42:0	Phosphatidylcholine acyl-alkyl C42:0	glycerophospholipids	0.61	0.11	9.26
PC ae C42:1	Phosphatidylcholine acyl-alkyl C42:1	glycerophospholipids	0.43	0.10	10.62

PC ae C42:2	Phosphatidylcholine acyl-alkyl C42:2	glycerophospholipids	0.54	0.14	10.12
PC ae C42:3	Phosphatidylcholine acyl-alkyl C42:3	glycerophospholipids	0.78	0.20	8.37
PC ae C42:4	Phosphatidylcholine acyl-alkyl C42:4	glycerophospholipids	0.81	0.23	9.08
PC ae C42:5	Phosphatidylcholine acyl-alkyl C42:5	glycerophospholipids	2.02	0.50	6.50
PC ae C44:3	Phosphatidylcholine acyl-alkyl C44:3	glycerophospholipids	0.13	0.04	18.50
PC ae C44:4	Phosphatidylcholine acyl-alkyl C44:4	glycerophospholipids	0.30	0.09	15.16
PC ae C44:5	Phosphatidylcholine acyl-alkyl C44:5	glycerophospholipids	1.33	0.39	7.97
PC ae C44:6	Phosphatidylcholine acyl-alkyl C44:6	glycerophospholipids	1.01	0.29	7.95
SM (OH) C14:1	Hydroxysphingomyeline C14:1	sphingolipids	4.49	1.31	6.70
SM (OH) C16:1	Hydroxysphingomyeline C16:1	sphingolipids	1.89	0.54	6.82
SM (OH) C22:1	Hydroxysphingomyeline C22:1	sphingolipids	3.10	0.83	7.37
SM (OH) C22:2	Hydroxysphingomyeline C22:2	sphingolipids	2.85	0.79	7.42
SM (OH) C24:1	Hydroxysphingomyeline C24:1	sphingolipids	0.23	0.07	12.28
SM C16:0	Sphingomyeline C16:0	sphingolipids	63.10	13.77	5.84
SM C16:1	Sphingomyeline C16:1	sphingolipids	9.20	2.30	5.73
SM C18:0	Sphingomyeline C18:0	sphingolipids	10.07	2.59	6.33
SM C18:1	Sphingomyeline C18:1	sphingolipids	5.04	1.39	5.97
SM C20:2	Sphingomyeline C20:2	sphingolipids	0.15	0.06	20.48
SM C24:0	Sphingomyeline C24:0	sphingolipids	3.84	0.94	6.87
SM C24:1	Sphingomyeline C24:1	sphingolipids	8.73	2.14	7.71
SM C26:0	Sphingomyeline C26:0	sphingolipids	0.03	0.01	27.88
SM C26:1	Sphingomyeline C26:1	sphingolipids	0.05	0.02	26.15

Table S6. Overview of the 148 plasma proteins quantified using Scanning SWATH in the CHRIS cohort.

Protein	Gene	Description	Mean	SD	CV QC (%)
P02768	<i>ALB</i>	Serum albumin	16.64	0.20	9.47
P02766	<i>TTR</i>	Transthyretin	11.26	0.57	20.03
P19827	<i>ITIH1</i>	Inter-alpha-trypsin inhibitor heavy chain H1	13.36	0.21	6.75
P01023	<i>A2M</i>	Alpha-2-macroglobulin	13.72	0.42	7.06
P01042;P01042-2	<i>KNG1</i>	Kininogen-1	13.06	0.21	8.42
P02649	<i>APOE</i>	Apolipoprotein E	12.75	0.48	13.78
P01024	<i>C3</i>	Complement C3	13.88	0.20	4.87
P04196	<i>HRG</i>	Histidine-rich glycoprotein	12.63	0.39	9.18
P01011	<i>SERPINA3</i>	Alpha-1-antichymotrypsin	13.49	0.28	10.99
P02787	<i>TF</i>	Serotransferrin	14.26	0.25	7.59
P01834	<i>IGKC</i>	Immunoglobulin kappa constant	13.74	0.32	7.62
Q14624;Q14624-2	<i>ITIH4</i>	Inter-alpha-trypsin inhibitor heavy chain H4	12.98	0.22	7.54
P07360	<i>C8G</i>	Complement component C8 gamma chain	11.61	0.43	18.81
P00450	<i>CP</i>	Ceruloplasmin	12.85	0.35	8.33
P02647	<i>APOA1</i>	Apolipoprotein A-I	16.26	0.41	40.41
P02760	<i>AMBP</i>	Protein AMBP	14.50	0.22	8.80
P01008	<i>SERPINC1</i>	Antithrombin-III	13.24	0.20	7.37
O95445	<i>APOM</i>	Apolipoprotein M	14.07	0.35	14.76
P01031	<i>C5</i>	Complement C5	11.91	0.22	8.02
P01042-2	<i>KNG1</i>	Isoform LMW of Kininogen-1	13.30	0.41	17.43
P06396;P06396-2	<i>GSN</i>	Gelsolin	12.16	0.29	10.48
P25311	<i>AZGP1</i>	Zinc-alpha-2-glycoprotein	12.58	0.27	9.66
P22792	<i>CPN2</i>	Carboxypeptidase N subunit 2	11.28	0.49	21.87
Q96PD5	<i>PGLYRP2</i>	N-acetylmuramoyl-L-alanine amidase	12.30	0.38	11.70
P19823	<i>ITIH2</i>	Inter-alpha-trypsin inhibitor heavy chain H2	14.08	0.20	8.58
P02675	<i>FGB</i>	Fibrinogen beta chain	14.11	0.80	29.20
P02748	<i>C9</i>	Complement component C9	12.01	0.39	9.33
P05155;P05155-3	<i>SERPING1</i>	Plasma protease C1 inhibitor	12.68	0.93	16.47
P43652	<i>AFM</i>	Afamin	12.82	0.31	9.57
P02679;P02679-2	<i>FGG</i>	Fibrinogen gamma chain	14.88	0.75	27.52

P01861	<i>IGHG4</i>	Immunoglobulin heavy constant gamma 4	12.57	1.16	12.48
P06727	<i>APOA4</i>	Apolipoprotein A-IV	12.90	0.43	7.04
O14791;O14791-2;O14791-3	<i>APOLI</i>	Apolipoprotein L1	11.68	0.46	14.86
P00751	<i>CFB</i>	Complement factor B	12.41	0.24	7.50
P02750	<i>LRG1</i>	Leucine-rich alpha-2-glycoprotein	12.71	0.43	10.84
P20851;P20851-2	<i>C4BPB</i>	C4b-binding protein beta chain	13.27	0.48	22.64
P13671	<i>C6</i>	Complement component C6	12.71	0.32	14.02
P01019	<i>AGT</i>	Angiotensinogen	13.45	0.66	10.60
P35858;P35858-2	<i>IGFALS</i>	Insulin-like growth factor-binding protein complex acid labile subunit	11.87	0.45	20.12
P02671	<i>FGA</i>	Fibrinogen alpha chain	14.43	0.83	31.07
P04114	<i>APOB</i>	Apolipoprotein B-100	12.52	0.41	9.90
P36955	<i>SERPINF1</i>	Pigment epithelium-derived factor	11.52	0.30	13.08
P07357	<i>C8A</i>	Complement component C8 alpha chain	12.52	0.28	12.18
P02751	<i>FNI</i>	Fibronectin	11.60	0.94	61.10
P02765	<i>AHSG</i>	Alpha-2-HS-glycoprotein	12.77	0.28	9.31
P00488	<i>F13A1</i>	Coagulation factor XIII A chain	10.90	0.67	30.23
A0A0C4DH29	<i>IGHV1-3</i>	Immunoglobulin heavy variable 1-3	10.67	0.67	42.75
P01602	<i>IGKV1-5</i>	Immunoglobulin kappa variable 1-5	12.53	0.54	14.57
P01619	<i>IGKV3-20</i>	Immunoglobulin kappa variable 3-20	12.80	0.53	16.85
P10909;P10909-2;P10909-4;P10909-5	<i>CLU</i>	Clusterin	12.86	0.16	6.27
P00746	<i>CFD</i>	Complement factor D	10.40	0.56	26.58
P15814	<i>IGLL1</i>	Immunoglobulin lambda-like polypeptide 1	13.73	0.46	23.85
P00747	<i>PLG</i>	Plasminogen	13.36	0.22	6.52
P08571	<i>CD14</i>	Monocyte differentiation antigen CD14	9.58	0.60	36.80
P02749	<i>APOH</i>	Beta-2-glycoprotein 1	12.95	0.42	18.55
P04217;P04217-2	<i>A1BG</i>	Alpha-1B-glycoprotein	13.22	0.26	10.61
P00738	<i>HP</i>	Haptoglobin	14.76	0.63	10.07
P06681	<i>C2</i>	Complement C2	11.59	0.40	21.37
P05543	<i>SERPINA7</i>	Thyroxine-binding globulin	10.48	0.52	18.28
P01009	<i>SERPINA1</i>	Alpha-1-antitrypsin	14.28	0.31	7.95
P04004	<i>VTN</i>	Vitronectin	13.34	0.26	8.55
P05154	<i>SERPINA5</i>	Plasma serine protease inhibitor	10.18	0.80	39.75

P01859	<i>IGHG2</i>	Immunoglobulin heavy constant gamma 2	16.03	0.47	8.07
P08603	<i>CFH</i>	Complement factor H	11.99	0.23	7.93
P04003	<i>C4BPA</i>	C4b-binding protein alpha chain	12.59	0.30	8.64
P01860	<i>IGHG3</i>	Immunoglobulin heavy constant gamma 3	13.75	0.66	17.12
P02790	<i>HPX</i>	Hemopexin	13.85	0.20	7.89
P01591	<i>JCHAIN</i>	Immunoglobulin J chain	11.23	0.62	16.03
P02656	<i>3</i>	Apolipoprotein C-III	14.56	0.43	9.07
P01877	<i>IGHA2</i>	Immunoglobulin heavy constant alpha 2	14.42	0.65	11.79
P01876	<i>IGHA1</i>	Immunoglobulin heavy constant alpha 1	15.90	0.67	13.14
P01857	<i>IGHG1</i>	Immunoglobulin heavy constant gamma 1	15.83	0.37	12.26
P01871	<i>IGHM</i>	Immunoglobulin heavy constant mu	14.59	0.76	10.95
P00734	<i>F2</i>	Prothrombin	12.28	0.20	7.02
A0A0J9YX35	<i>IGHV3-64D</i>	Immunoglobulin heavy variable 3-64D	12.44	0.53	19.31
P02753	<i>RBP4</i>	Retinol-binding protein 4	13.20	0.34	9.48
P02746	<i>CIQB</i>	Complement C1q subcomponent subunit B	12.54	0.33	13.13
P08697	<i>SERPINF2</i>	Alpha-2-antiplasmin	12.40	0.27	12.31
P06310	<i>IGKV2-30</i>	Immunoglobulin kappa variable 2-30	12.42	0.58	16.24
P0C0L4	<i>C4A</i>	Complement C4-A	12.60	0.70	18.79
P03952	<i>KLKB1</i>	Plasma kallikrein	11.17	0.32	13.15
P07358	<i>C8B</i>	Complement component C8 beta chain	12.02	0.36	17.69
P02654	<i>APOC1</i>	Apolipoprotein C-I	13.65	0.79	31.39
P02774;P02774-3	<i>GC</i>	Vitamin D-binding protein	13.95	0.22	6.13
P68871	<i>HBB</i>	Hemoglobin subunit beta	14.19	0.48	17.13
P23142	<i>FBLN1</i>	Fibulin-1	10.83	0.69	34.48
Q9HCU4	<i>CELSR2</i>	Cadherin EGF LAG seven-pass G-type receptor 2	14.07	1.12	45.74
Q16610;Q16610-4	<i>ECM1</i>	Extracellular matrix protein 1	11.61	0.50	23.91
P02652	<i>APOA2</i>	Apolipoprotein A-II	16.55	0.22	8.17
P00748	<i>F12</i>	Coagulation factor XII	13.45	0.47	11.65
P27169	<i>PON1</i>	Serum paraoxonase/arylesterase 1	12.14	0.44	11.32
P80108	<i>GPLDI</i>	Phosphatidylinositol-glycan-specific phospholipase D	10.42	0.43	18.47
P51884	<i>LUM</i>	Lumican	11.31	0.39	14.57
P02747	<i>CIQC</i>	Complement C1q subcomponent subunit C	13.75	0.32	10.57

A0A075B6I0	<i>IGLV8-61</i>	Immunoglobulin lambda variable 8-61	12.74	0.79	15.60
A0A075B6H9	<i>IGLV4-69</i>	Immunoglobulin lambda variable 4-69	10.90	0.79	34.15
P05546	<i>SERPIND1</i>	Heparin cofactor 2	12.87	0.35	7.99
P22352	<i>GPX3</i>	Glutathione peroxidase 3	11.08	0.49	23.44
P06396	<i>GSN</i>	Gelsolin	13.10	0.53	28.30
P09871	<i>C1S</i>	Complement C1s subcomponent	11.83	0.27	11.64
P05156	<i>CFI</i>	Complement factor I	12.40	0.29	11.31
A0A0B4J1U7	<i>IGHV6-1</i>	Immunoglobulin heavy variable 6-1	15.42	1.28	15.19
A0A0J9YXX1	<i>IGHV5-10-1</i>	Immunoglobulin heavy variable 5-10-1	13.54	1.44	19.24
P01780	<i>IGHV3-7</i>	Immunoglobulin heavy variable 3-7	13.03	0.64	23.46
A0A0A0MS15	<i>IGHV3-49</i>	Immunoglobulin heavy variable 3-49	13.68	0.56	23.31
P00736	<i>C1R</i>	Complement C1r subcomponent	12.16	0.30	15.11
Q06033;Q06033-2	<i>ITIH3</i>	Inter-alpha-trypsin inhibitor heavy chain H3	11.89	0.57	24.09
P08519	<i>LPA</i>	Apolipoprotein(a)	11.75	1.87	56.51
P08185	<i>SERPINA6</i>	Corticosteroid-binding globulin	13.53	0.57	17.06
P04217	<i>A1BG</i>	Alpha-1B-glycoprotein	13.33	0.23	9.36
P04278	<i>SHBG</i>	Sex hormone-binding globulin	11.10	1.25	34.72
P15169	<i>CPN1</i>	Carboxypeptidase N catalytic chain	10.91	0.43	20.21
P05090	<i>APOD</i>	Apolipoprotein D	12.00	0.40	13.12
P10643	<i>C7</i>	Complement component C7	11.73	0.41	17.89
Q14624	<i>ITIH4</i>	Inter-alpha-trypsin inhibitor heavy chain H4	11.92	0.32	15.29
P02763	<i>ORM1</i>	Alpha-1-acid glycoprotein 1	14.97	0.43	11.61
P20742	<i>PZP</i>	Pregnancy zone protein	13.21	0.84	31.92
P18428	<i>LBP</i>	Lipopolysaccharide-binding protein	10.81	0.76	37.90
O43866	<i>CD5L</i>	CD5 antigen-like	12.22	0.75	17.79
P02745	<i>CIQA</i>	Complement C1q subcomponent subunit A	12.75	0.46	24.05
P07225	<i>PROS1</i>	Vitamin K-dependent protein S	11.23	0.31	14.38
P29622	<i>SERPINA4</i>	Kallistatin	11.69	0.49	16.81
O75636	<i>FCN3</i>	Ficolin-3	12.17	0.60	17.67
P01701	<i>IGLV1-51</i>	Immunoglobulin lambda variable 1-51	12.48	0.78	30.98
P01703	<i>IGLV1-40</i>	Immunoglobulin lambda variable 1-40	11.47	0.88	35.82
P06312	<i>IGKV4-1</i>	Immunoglobulin kappa variable 4-1	11.34	0.58	22.12

P01705	<i>IGLV2-23</i>	Immunoglobulin lambda variable 2-23	11.73	0.84	29.62
P49908	<i>SELENOP</i>	Selenoprotein P	11.07	0.59	29.36
O75882-2	<i>ATRN</i>	Isoform 2 of Attractin	11.87	0.34	17.01
Q9UGM5	<i>FETUB</i>	Fetuin-B	11.81	0.87	30.66
P05452	<i>CLEC3B</i>	Tetranectin	12.78	0.32	13.91
A0A0B4J1V2	<i>IGHV2-26</i>	Immunoglobulin heavy variable 2-26	13.31	0.68	15.91
P00742	<i>F10</i>	Coagulation factor X	12.81	0.32	16.85
P00739	<i>HPR</i>	Haptoglobin-related protein	11.94	0.61	11.90
P01599	<i>IGKV1-17</i>	Immunoglobulin kappa variable 1-17	12.56	0.78	22.94
P00740	<i>F9</i>	Coagulation factor IX	11.19	0.81	30.10
P19652	<i>ORM2</i>	Alpha-1-acid glycoprotein 2	14.04	0.44	10.02
P05160	<i>F13B</i>	Coagulation factor XIII B chain	10.87	0.66	30.77
A0A075B6K4	<i>IGLV3-10</i>	Immunoglobulin lambda variable 3-10	11.19	0.94	38.84
A0A0C4DH31	<i>IGHV1-18</i>	Immunoglobulin heavy variable 1-18	11.63	0.81	36.85
P80748	<i>IGLV3-21</i>	Immunoglobulin lambda variable 3-21	12.51	0.79	34.45
A0A0B4J1Y9	<i>IGHV3-72</i>	Immunoglobulin heavy variable 3-72	11.02	0.85	50.65
P23142;P23142-4	<i>FBLN1</i>	Fibulin-1	12.16	0.59	22.00
P69905	<i>HBA1</i>	Hemoglobin subunit alpha	14.20	0.52	20.06
A0A075B6J9	<i>IGLV2-18</i>	Immunoglobulin lambda variable 2-18	10.54	0.99	34.59
A0A0C4DH34	<i>IGHV4-28</i>	Immunoglobulin heavy variable 4-28	11.63	0.66	22.39
B9A064	<i>IGLL5</i>	Immunoglobulin lambda-like polypeptide 5	16.33	0.43	13.59
P06276	<i>BCHE</i>	Cholinesterase	10.84	0.62	34.76

Supplementary Figures

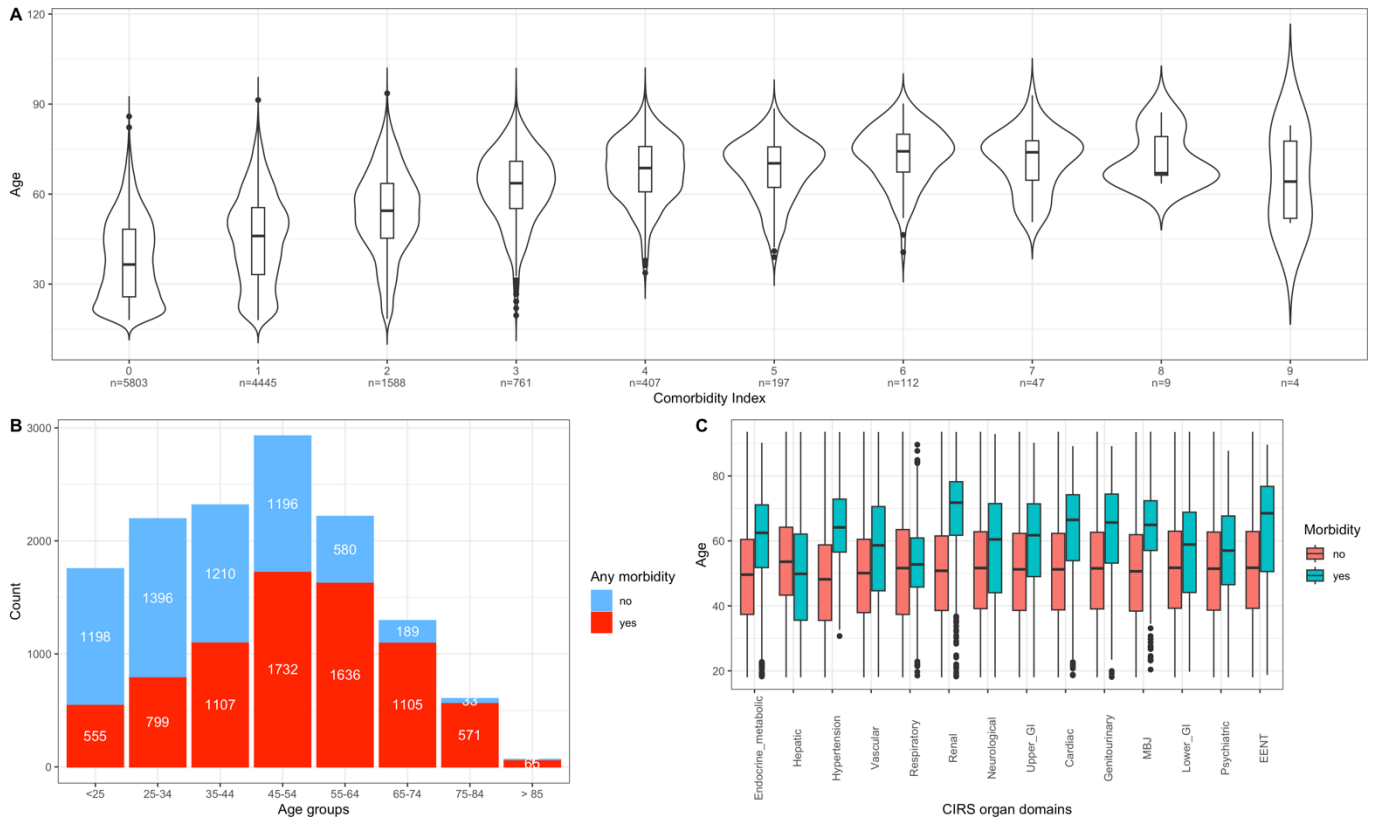


Figure S1. Distribution of age and health status in the CHRIS cohort. **A**) Age distribution (y-axis) by Comorbidity Index values, which range from 0-9 (x-axis). The x-axis additionally provides information on the total number of participants with each corresponding index value. The Comorbidity Index value expresses the total number of CIRS organ domains scoring ≥ 2 . **B**) Absolute distribution of "Any morbidity" (yes+no) by age-group. The relative proportion of red-bars within each stacked column-bar represents the age-group specific prevalence of any morbidity. **C**) Age distribution by morbidity conditions in the specific CIRS domains.

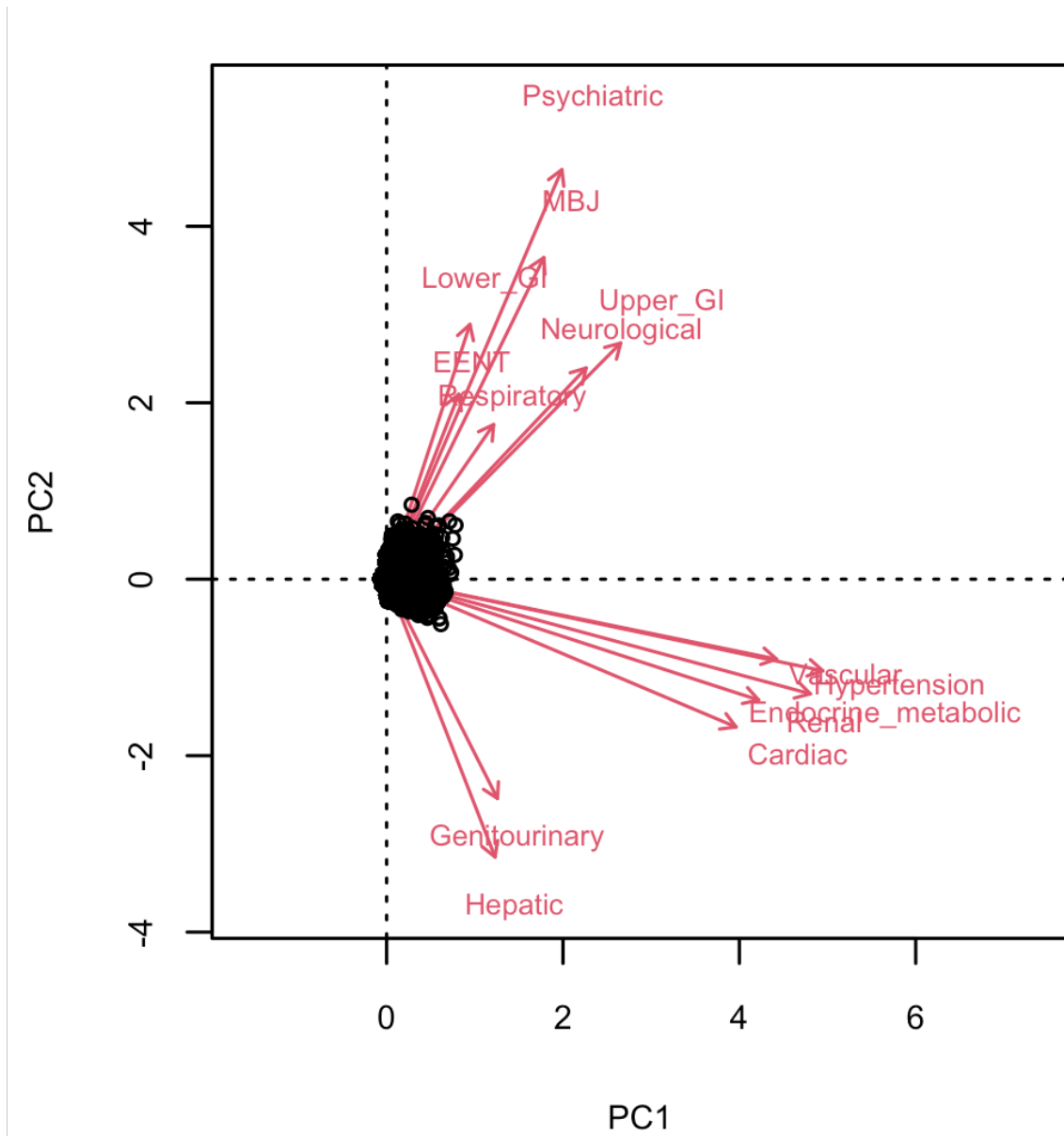


Figure S2. Biplot of ordinary correspondence analysis of comorbidities in the CHRIS cohort. CIRS domains with a stronger relation have longer (size consistency) and closer (direction consistency) loadings.

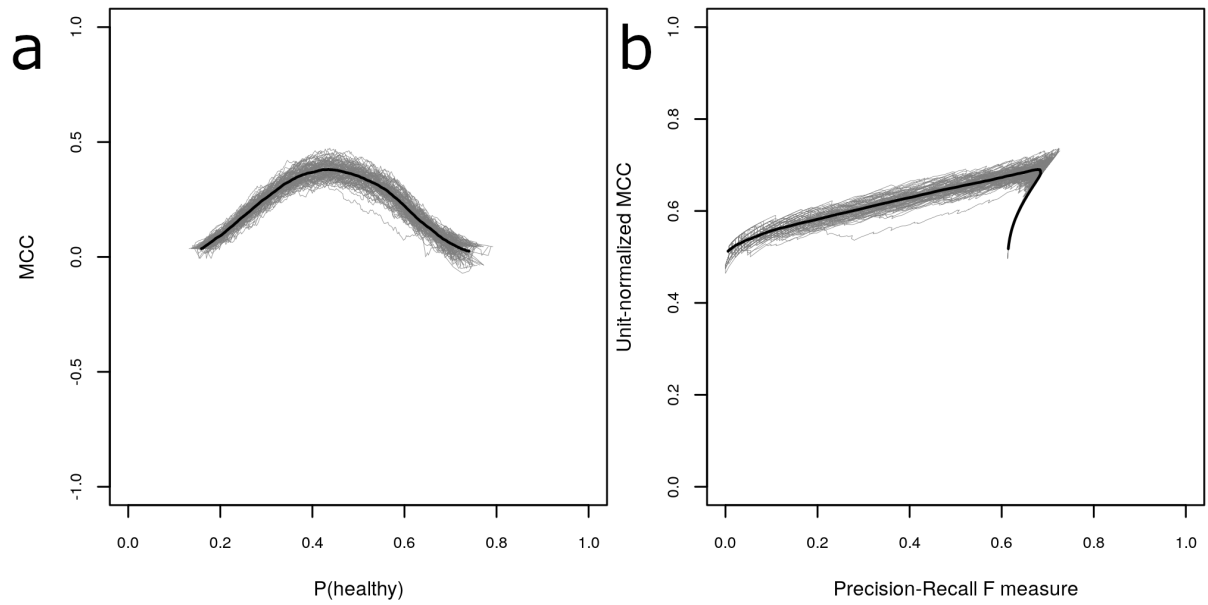


Figure S3. Performance evaluation of 100 random forest models including as predictors age, sex, 174 metabolites and 148 proteins to classify health status (any morbidity vs. healthy). The performance is expressed by A) MCC and B) MCC-F1. In the plots each validation run is represented as a gray line and the averaged curves are shown as a thicker black line.

Supplementary Text

Text S1. Description of Random Forest Performance Evaluation Scores and model comparison.

Random Forest Performance Evaluation Scores

We make use of the following measures:

- AUC area under the receiver operating characteristic (ROC) curve.
- Precision, positive predictive value;
- F1, F1 score, which is the harmonic mean between precision and sensitivity. i.e. $F1 = (\text{precision} \times \text{TPR}) / (\text{precision} + \text{TPR})$ with TPR, true positive rate;
- MCC, the Matthews correlation coefficient. It uses absolute numbers instead of ratios. $MCC = 0$ corresponds to a pure chance guess. TP, true positive; TN, true negative; FP, false positive; FN, false negative.

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP) \times (TP + FN) \times (TN + FP) \times (TN + FN)}}$$

- MCC-F1, the unit-normalized Matthews correlation coefficient $(MCC+1)/2$. $MCC-F1 = 0.5$ corresponds to the chance event.

Random forest model comparison.

For the RF analysis we built different models that included varying sets of the predictors, which were a) age and sex, b) age, sex and metabolites, c) age, sex and proteins, and d) age, sex, metabolites, proteins, and compared the performance across all models.

In general, model performance increased by adding metabolites and proteins to age and sex, whereas addition of proteins alone did not improve model performance. An overview of the performance of all models is provided in **Table S7** below.

Table S7. Overview of performance summary measures for the random forest models. The calculated mean from the 100 model performance evaluations on the respective test set and the 95% confidence intervals (95% CI).

Model	TPR	FPR	AUC	MCC
a) age + sex	0.706 (0.697, 0.715)	0.320 (0.312, 0.329)	0.723 (0.719, 0.727)	0.385 (0.378, 0.391)
b) age + sex + mbx	0.750 (0.737, 0.763)	0.351 (0.338, 0.364)	0.748 (0.744, 0.752)	0.400 (0.394, 0.406)
c) age + sex + ptx	0.749 (0.739, 0.759)	0.338 (0.329, 0.348)	0.740 (0.736, 0.744)	0.410 (0.404, 0.416)
d) age + sex + mbx + ptx	0.740 (0.729, 0.750)	0.342 (0.332, 0.352)	0.747 (0.743, 0.751)	0.397 (0.391, 0.404)

TPR = true positive rate (or sensitivity). FPR = false positive rate (or specificity). AUC = area under the receiver operating characteristic (ROC) curve. MCC = Matthew's correlation coefficient. MCC = 0 corresponds to a pure chance guess

To evaluate whether there was a statistically significant (p -value<0.05) difference in the performance, we compared the standardized differences of mean AUC and MCC values for the different predictor sets (models a-d) to estimate effect sizes and apply Student's t-test (see Figures S4 and S5 below). Overall, a statistically significant (p -value<0.05 for AUCs and MCCs) improvement was observed for models b), c) and d) with respect to model a). When comparing mean AUCs (Figure S4), model b) and d) showed significantly higher performance over model c), but no differences in mean AUCs were observed between model d) and b). When comparing mean MCCs, model c) showed significantly higher performance over models b) and d), whereas no difference in performance for models b) and d) was observed (Figure S5). Upon further investigation of potential correlations between the metabolites and proteins (Spearman's correlations), we identified several omics markers being moderately correlated with each other (Figure S6). Given these observations and the similarity of the performance for models d) and b), we decided to focus the proceeding analyses on the full model d).

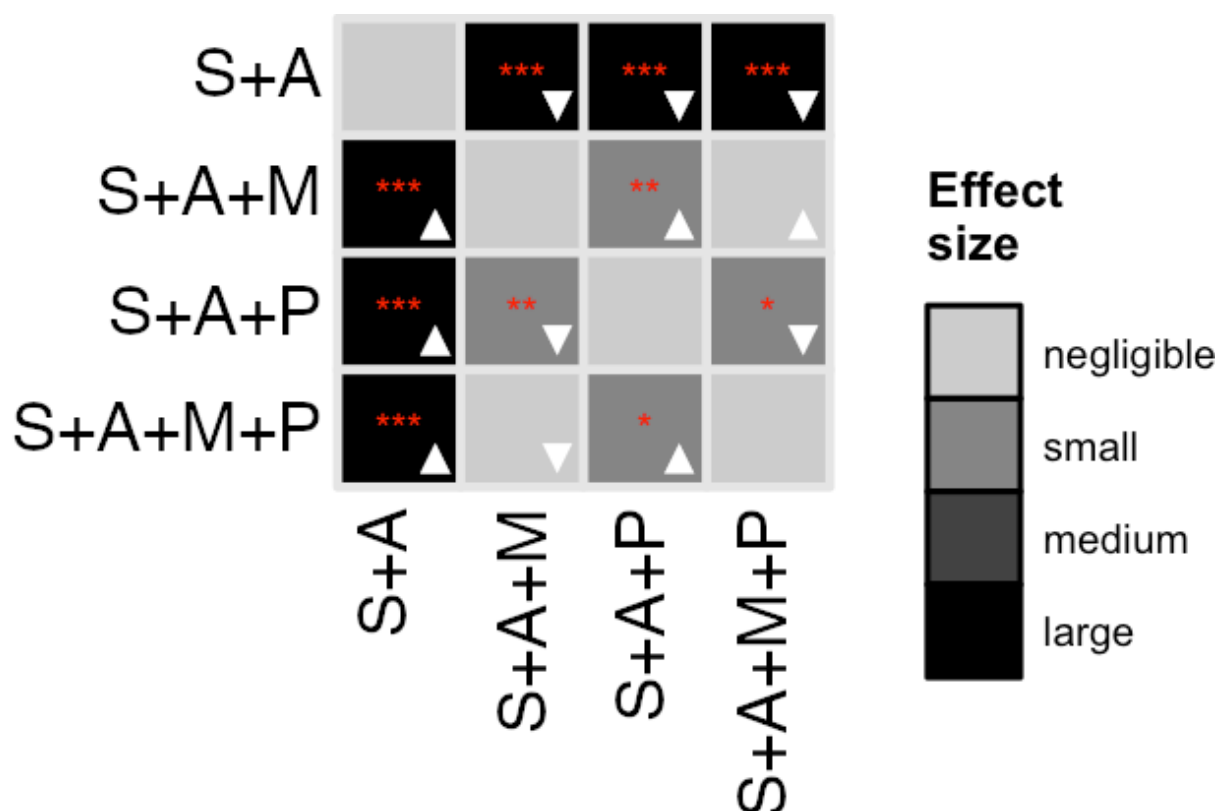


Figure S4. Assessment of RF model performance comparing the standardized AUCs across the different predictor sets. In the following plots we have categorized the effect sizes by magnitude: $0 \leq s < 0.2$: negligible; $0.2 \leq s < 0.5$: small; $0.5 \leq s < 0.8$: medium; and $s \geq 0.8$: large. Comparisons of the effect sizes (standardized differences between the meanAUCs) for different predictor sets. The predictor sets are as follows: S+A, sex and age; S+A+M, sex, age, and metabolites; S+A+P, sex, age, and proteins; and S+A+M+P, sex, age, metabolites, and proteins. A two-sided Student's t-test was performed for each comparison. The predictor set combination in the column serves as the reference against which the predictor set combination in the row is compared. The asterisks on top of the effect size cells indicate the level of significance: no asterisk, $P \geq 0.05$; *, $0.01 \leq P < 0.05$; **, $0.001 \leq P < 0.01$; ***, $P < 0.001$. Triangles represent the directionality of the difference in means: a downward-pointing triangle indicates a higher mean in the reference column, while an upward-pointing triangle indicates a lower mean in the reference column.

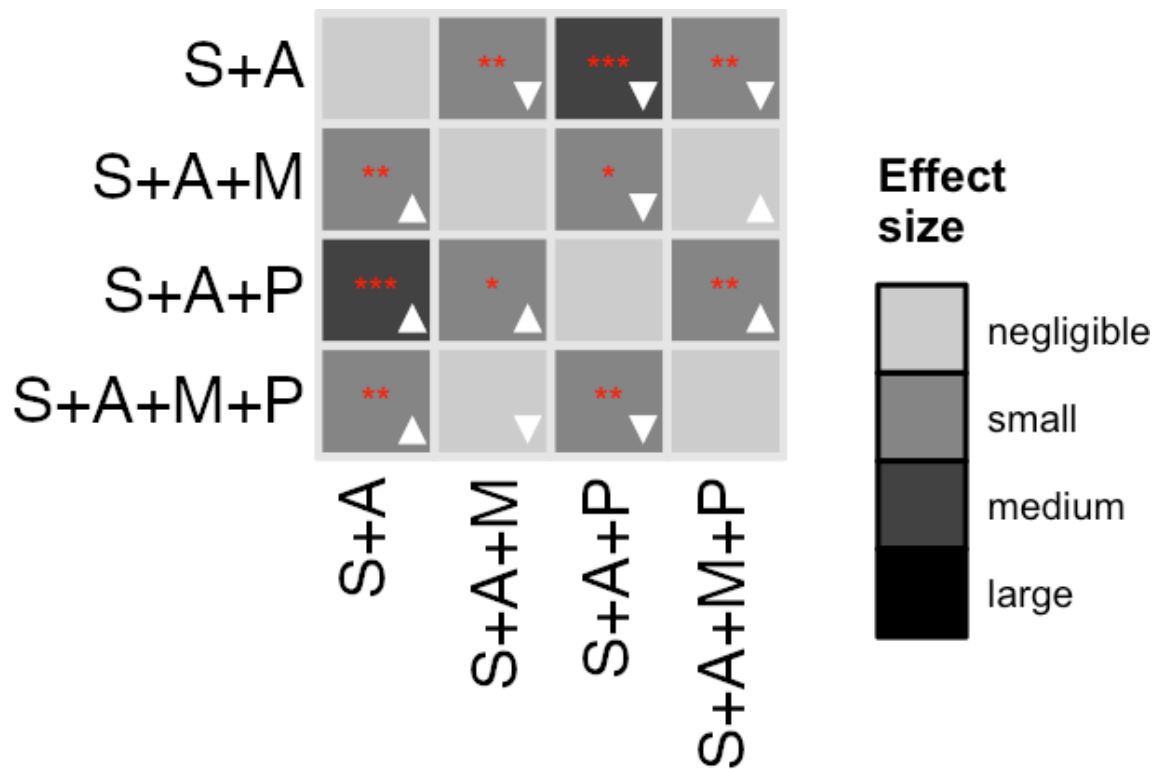


Figure S5. Assessment of RF model performance comparing the standardized MCCs across the different predictor sets. Figure legend as in Figure S4, taking performance measure MCC instead of AUC.

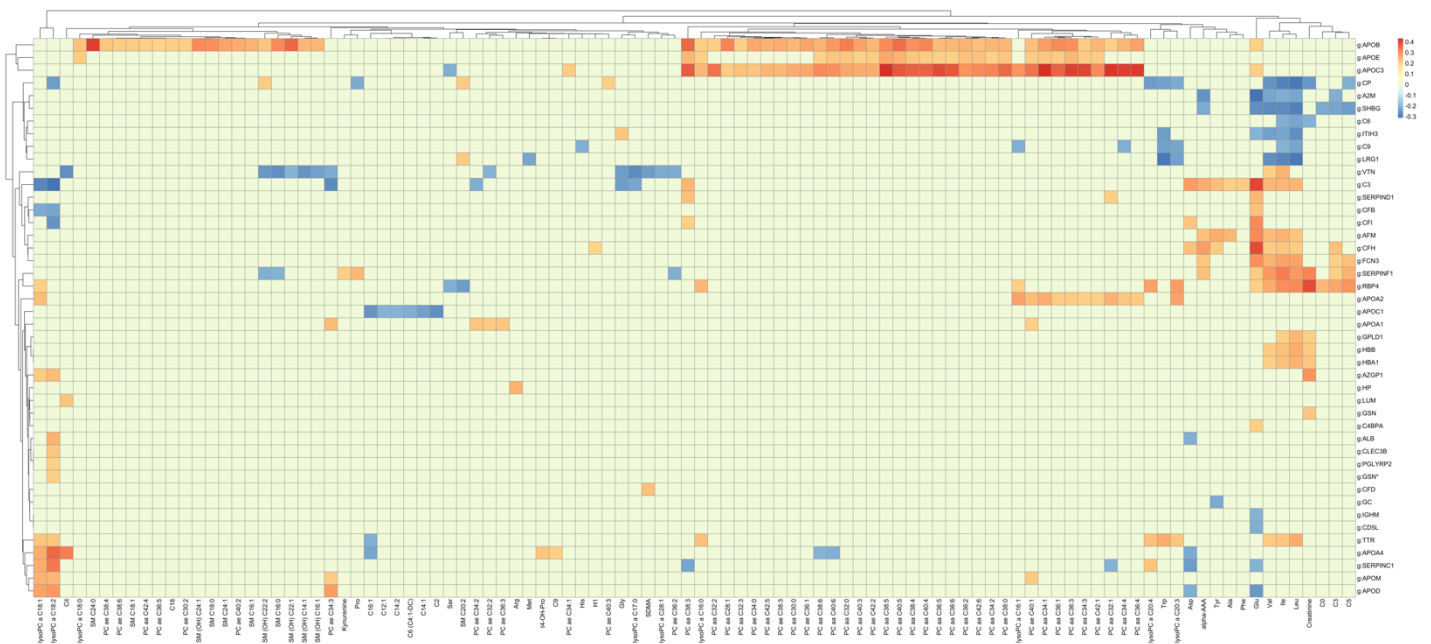


Figure S6. Heatmap presenting Spearman's correlations between metabolites and proteins. Only correlations with an $|\rho| > 0.20$ are displayed. Red indicates positive correlations, while blue indicates negative correlations.

An overview of all significant results for the RF analyses for the different predictor sets is presented in **Figure S7** below.

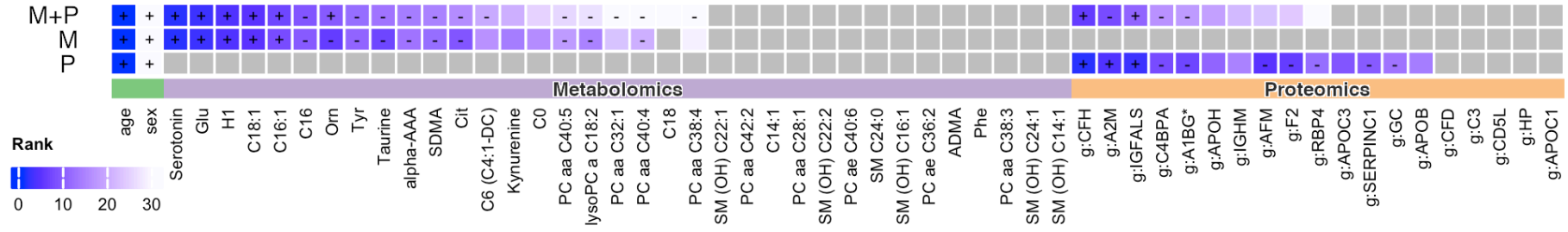


Figure S7. Overview of drop in Gini index for most important predictor sets. The models included only metabolites (M), only proteins (P) and the combined predictors (M+P), healthy:amorb: any morbidity vs healthy. Predictors are marked by the number of times a p -value was significant in the permutation runs for such a variable ($p < 0.05$): +: all 100 runs resulted a significant p -value; -: between 80 and 99 runs were associated with significant p -values; no sign: between 50 and 79 runs were associated with significant p -values. Results are restricted to variables that are significant in at least 50% of all permutation runs.

Text S2. Discussion of additional metabolites and proteins

In this section we are discussing relevant metabolites and proteins that were determined with the RF model, where the age-independent associations were confirmed by linear regression, but for which the difference in abundances was lower than the coefficient of variation cut-off.

Overall, twelve such markers were identified (hexose, C18:1, C16:1, lyso PC a C18:2, PC aa C32:1, tyrosine, taurine, kynurenine, AFM, CFH, RBP4, A1BG). Hexoses have been previously associated with metabolic health^{1,2}. Several long-chain glycerophospholipids and long-chain acylcarnitines were also related to health status. Acylcarnitine levels are known to increase with age, as they accumulate because of incompletely oxidized fatty acids in the mitochondria beta oxidation pathway^{3,4}. More specifically, circulating long-chain acylcarnitine concentrations are indicators of mitochondrial functionality, with increased levels indicating reduced oxidative phosphorylation capacity⁵ and previous studies reported an increase of carnitines in cardiometabolic disease and cancer⁵⁻⁷. Tyrosine, kynurenine and taurine have been associated with increased risk of type 2 diabetes⁸, mortality⁹, metabolic syndrome, neurodegeneration and frailty¹⁰⁻¹³. Taurine is involved in mitochondrial function, apoptosis and serves as an anti-oxidant showing anti-inflammatory properties¹⁴. Afamin (AFM) has been reported to play a role in vitamin E transport and higher afamin levels are associated with poor metabolic health¹⁵⁻¹⁸. Tanaka et al further reported associations between AFM and mortality¹⁹. Retinol-binding protein 4 (RBP4) is a specific carrier for retinol in the blood and has been implicated in metabolic health and inflammation²⁰⁻²². The complement factor H (CFH) plays a key role in the regulation of alternative pathway of complement system²³. Alpha-1B-glycoprotein (A1BG) has been reported as potential urinary biomarker for chronic kidney disease²⁴.

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