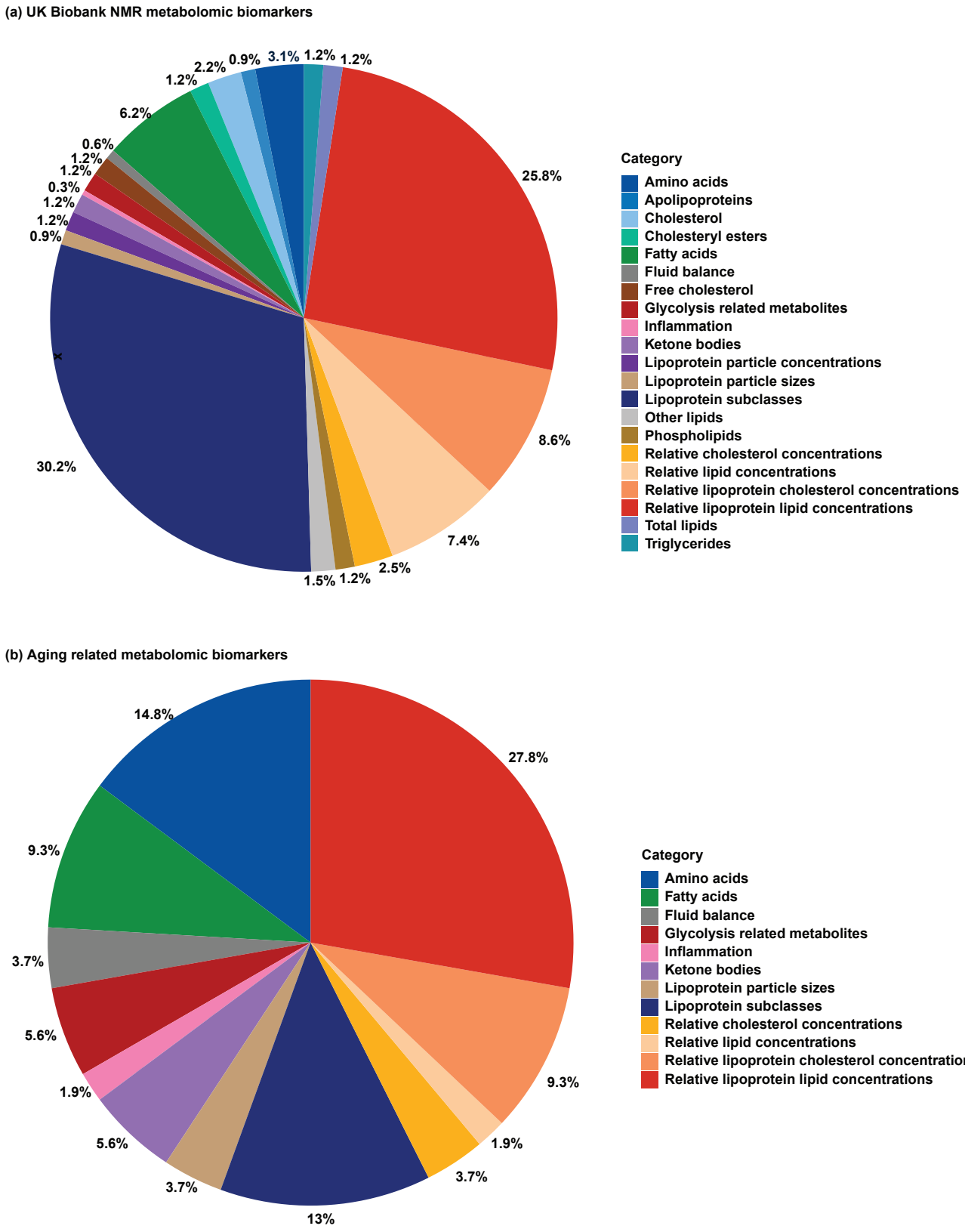
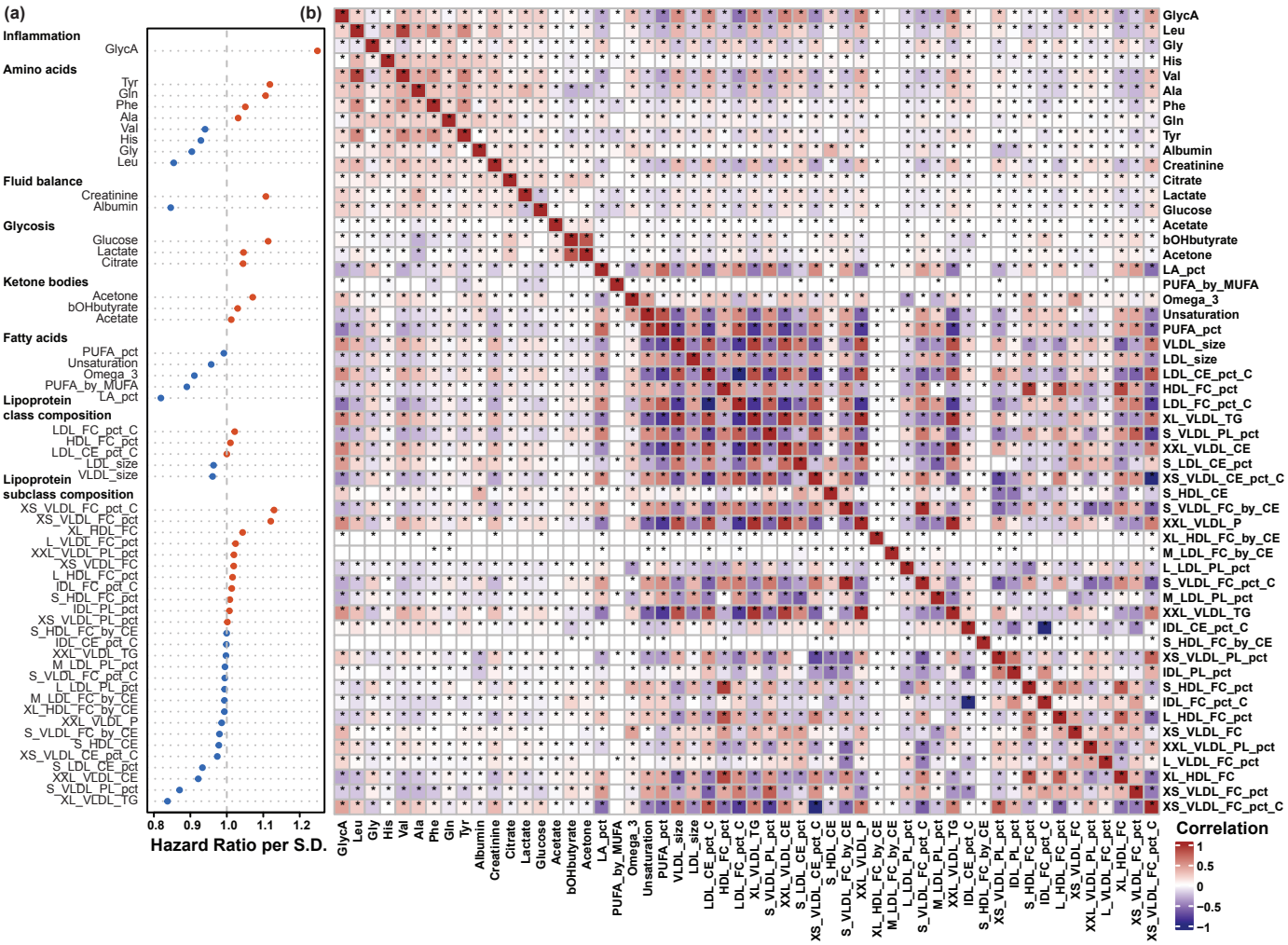
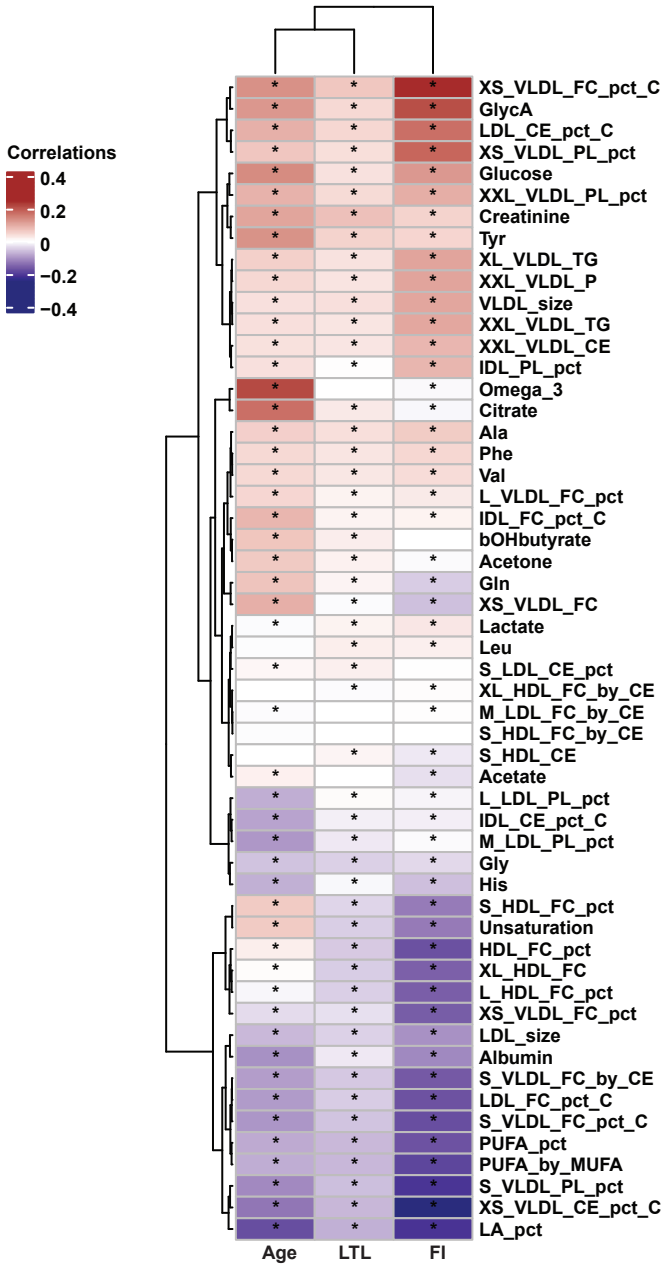


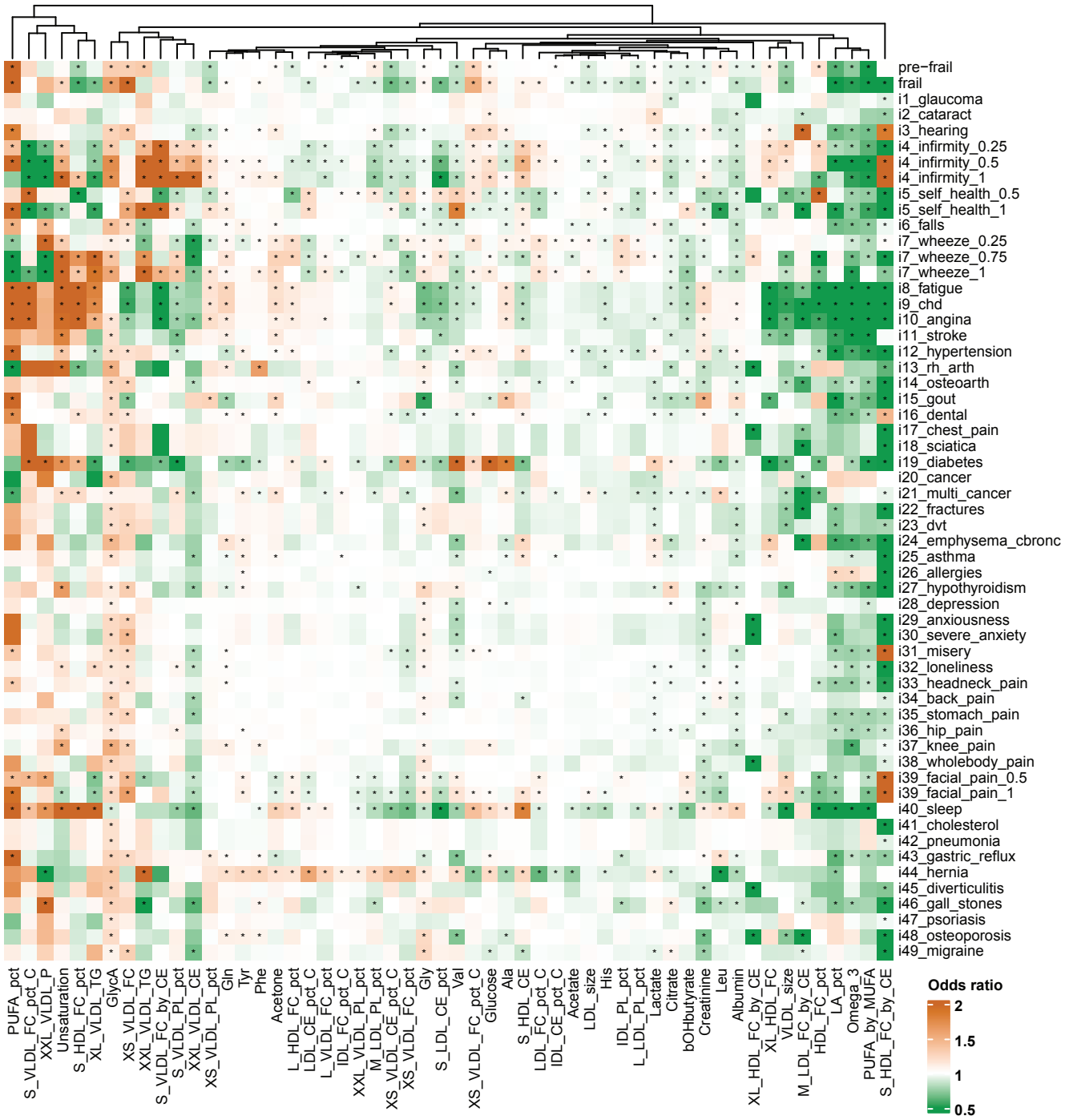
Supplementary Fig. 1| Pie charts depicting the distribution of metabolomic biomarker groups in the UK Biobank. a. Among 325 NMR biomarkers. b. Among 54 representative aging-related biomarkers. Source data are provided as a Source Data file.



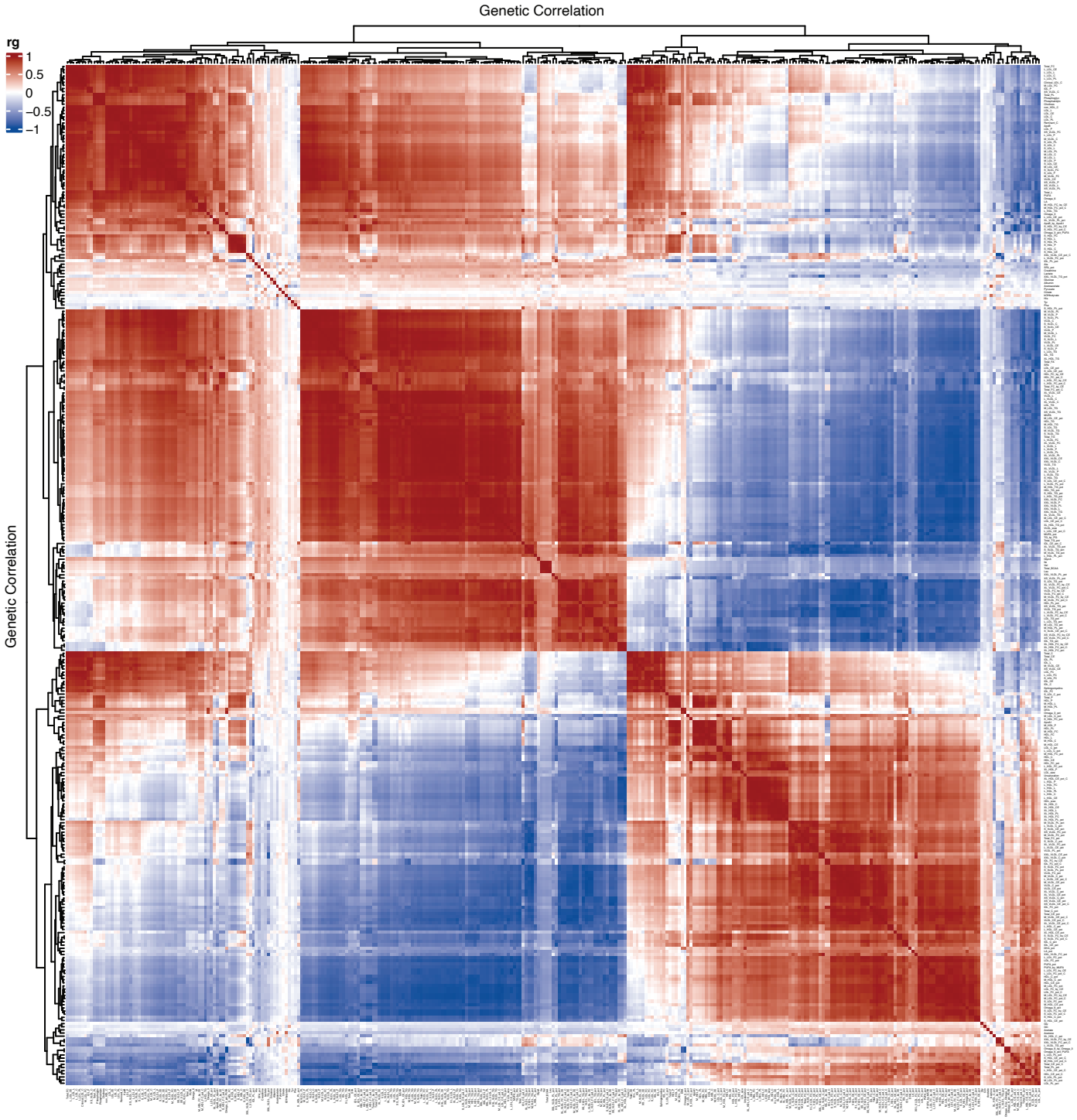
Supplementary Fig. 2| 54 representative aging-related NMR biomarkers. a. Hazard ratios (HR) of each representative aging-related biomarker for all-cause mortality (per SD). Blue dots, HR <1; red dots, HR >1. b. Phenotypic correlations among 54 representative aging-related biomarkers. Complete pairwise Pearson's correlation coefficients were estimated, and *p*-values were adjusted for multiple testing with the Benjamini-Hochberg (BH) procedure. *, BH-adjusted *p*-value < 0.01. The full name of each NMR biomarker is provided in Supplementary Table 1. Source data are provided as a Source Data file.



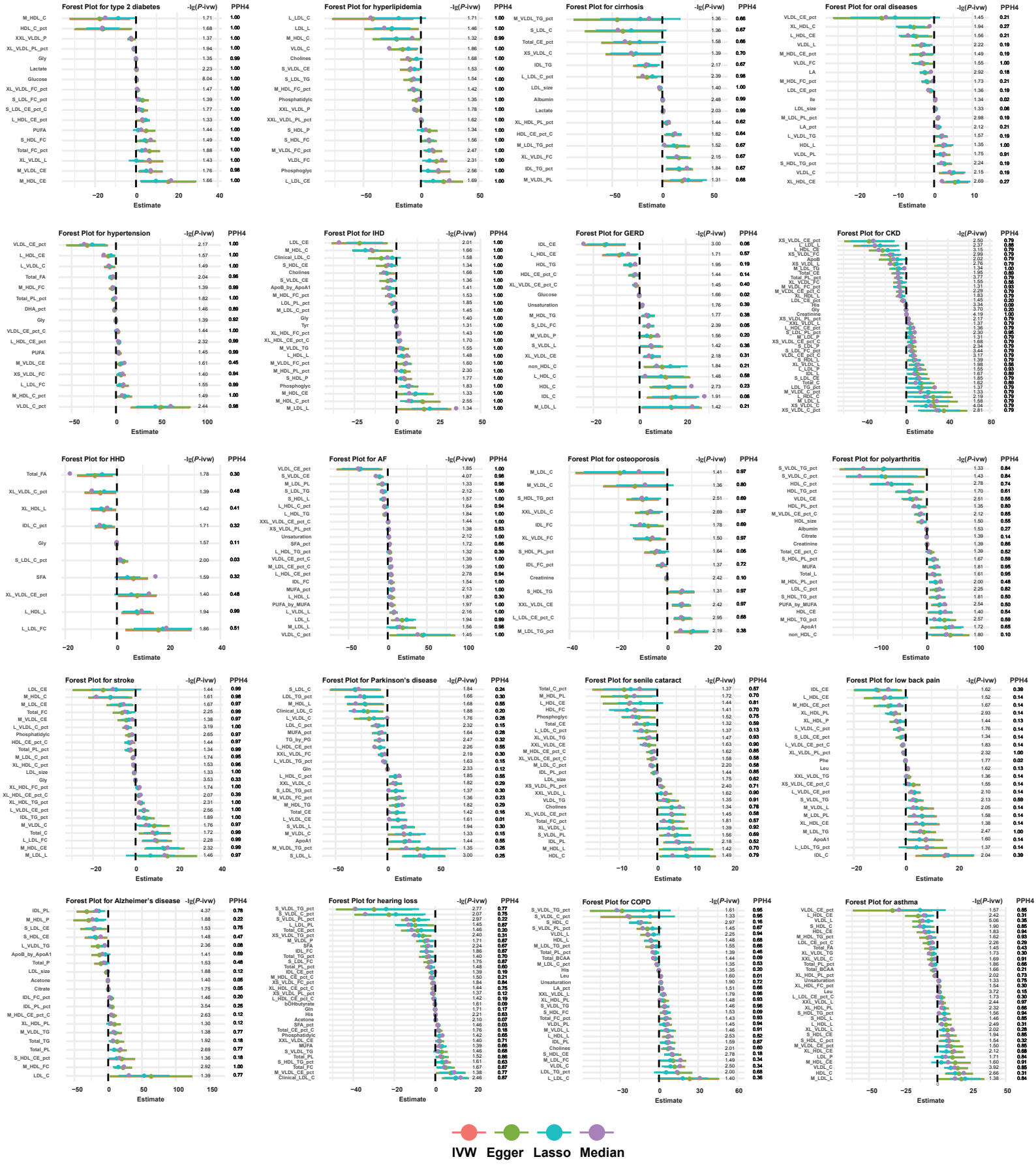
Supplementary Fig. 3| Heatmap of correlations between 54 representative aging-related biomarkers and three aging metrics. Pearson's correlation coefficients between each NMR biomarker and three aging metrics (chronological age, frailty index and leukocyte telomere length) were estimated. *, BH-adjusted *p*-value < 0.05. Rows and columns were hierarchically clustered with the *Ward.D2* method by Euclidean distances. FI, frailty index; LTL, leukocyte telomere length. The full name of each NMR biomarker is provided in Supplementary Table 1. Source data are provided as a Source Data file.



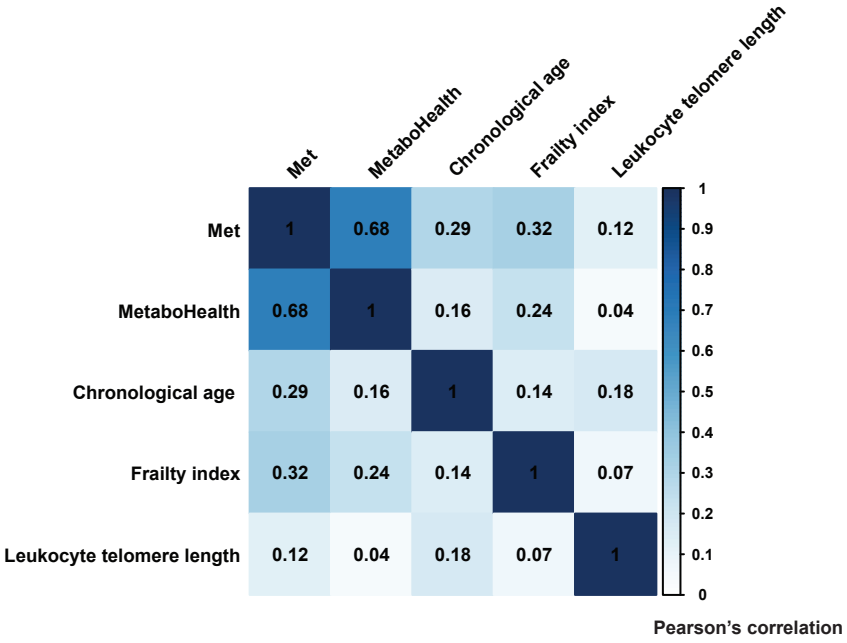
Supplementary Fig. 4| Heatmap of correlations between 54 representative aging-related biomarkers and 50 frailty-related phenotypes. Associations between 54 representative aging-related biomarkers and 50 frailty-related phenotypes were estimated by multivariable logistic regression with chronological age included as a covariate. Each biomarker was standardized and the 54 biomarkers were included together in the model as a group of independent variables, while each frailty-related phenotype (categorical variable) was included as the dependent variable. The odds ratio (OR) of each biomarker on the frailty-related phenotype was calculated by taking the exponent of the estimated coefficient. The *p*-value threshold adjusted for multiple testing was 2E-04 based on the Bonferroni-correction: 0.05 (the alpha level) / 5 (the number of PCs accounting for over 80% variation in the metabolomic data) / 50 (the number of frailty-related phenotypes included in the study). Biomarkers were hierarchically clustered with the *Ward.D2* method by their Euclidean distances. The full name of each NMR biomarker is provided in Supplementary Table 1. Exact *p*-values and estimated coefficients are provided in the Source data file. Source data are provided as a Source Data file.



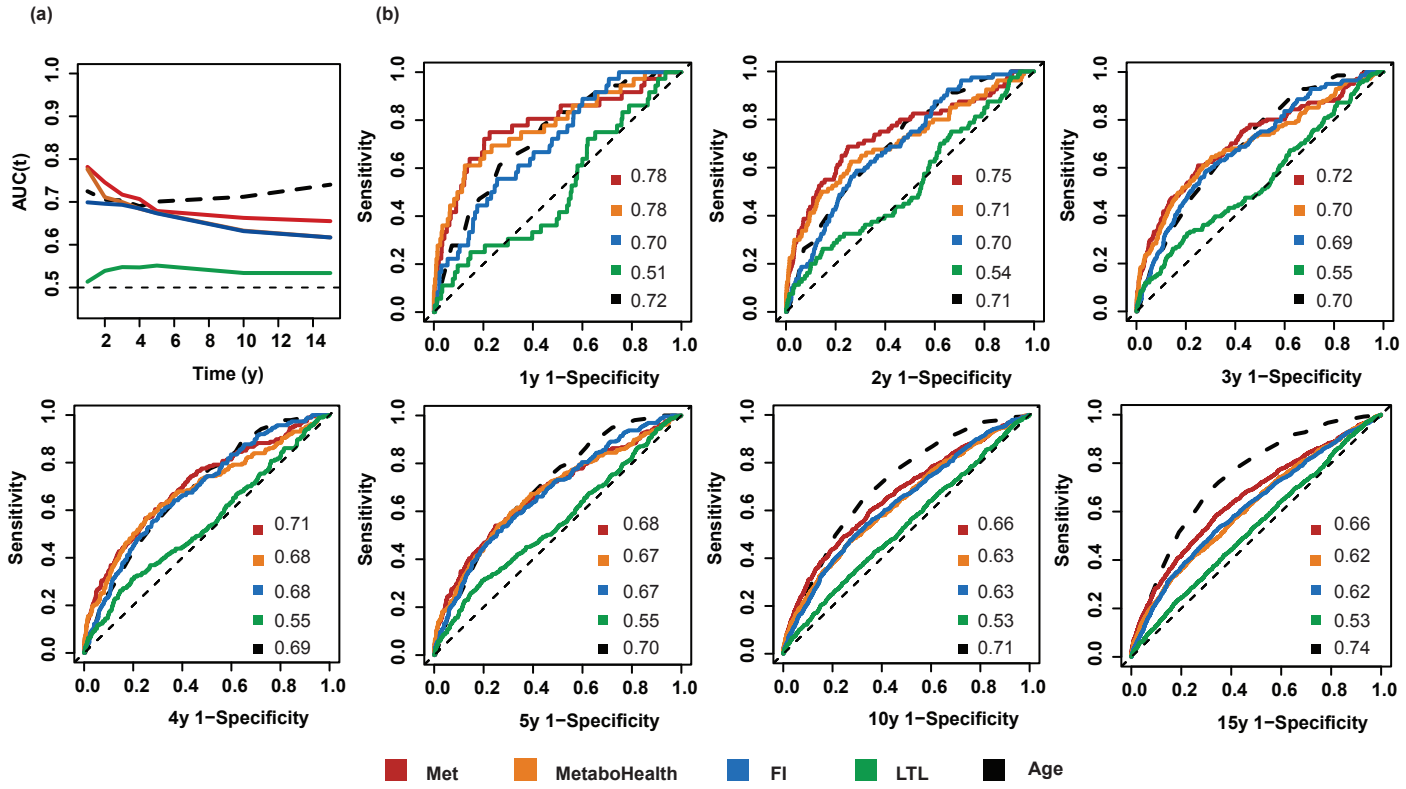
Supplementary Fig. 5| Genetic correlation heatmap of 325 NMR biomarkers calculated from linkage disequilibrium score regression (LDSC). Pairwise genetic correlations between 325 NMR biomarkers were calculated from LDSC based on their GWAS summary statistics (Methods). The *p*-value threshold was 0.01 after Bonferroni-correction: 0.05 (alpha) / 5 (PCs). Rows and columns were clustered with the *Ward.D2* method based on their Euclidean distances. The full name of each NMR biomarker is provided in Supplementary Table 1. Exact *p*-values and estimated genetic correlation coefficients are provided in the Source Data file. Source data are provided as a Source Data file.



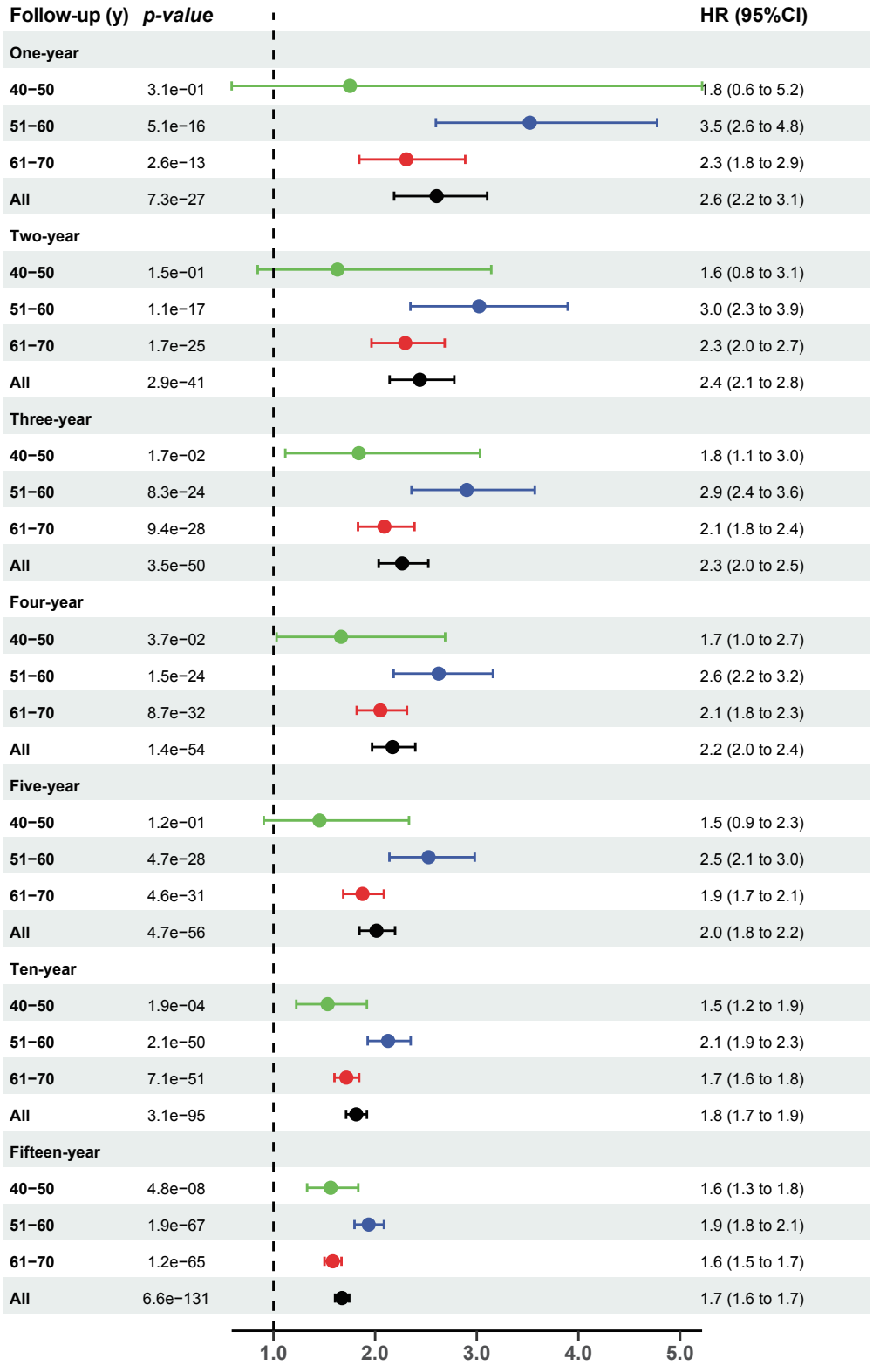
Supplementary Fig. 6| Forest plots of causal estimates from sensitivity analyses. a-d, Causal estimates with 95% confidence intervals from four MVMR methods (MVMR-IVW, MVMR-Egger, MVMR-Median, and MVMR-Lasso) were plotted for 439 candidate causal pairs. *P*-values from the MVMR-IVW method and PPH4 from the colocalization analyses were annotated on the right side of the figure. IHD, ischemic heart diseases; HHD, hypertensive heart diseases; AF, atrial fibrillation and flutter; COPD, chronic obstructive pulmonary disease; GERD, gastro-esophageal reflux disease; CKD, chronic kidney disease. The full name of each NMR biomarker is provided in Supplementary Table 1. Source data are provided as a Source Data file.



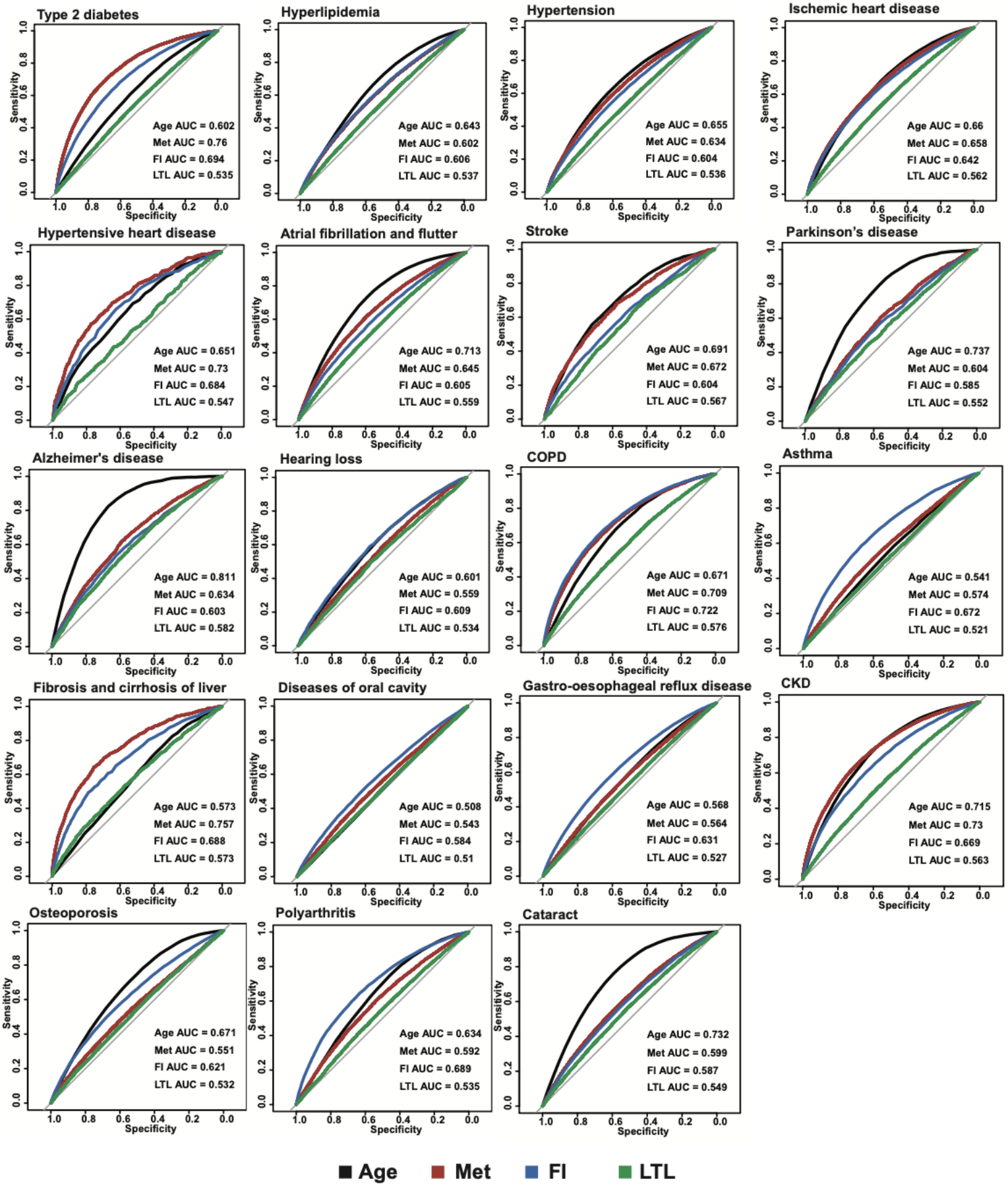
Supplementary Fig. 7| Pearson's correlations between five aging metrics. Pearson's correlations between the Metabolomic Aging Score (Met), MetaboHealth, chronological age, the frailty index and leukocyte telomere length (reverse coded) were estimated. Source data are provided as a Source Data file.



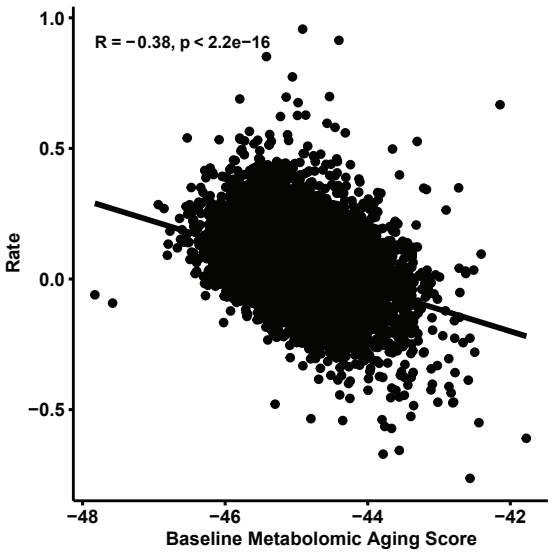
Supplementary Fig. 8| Predictive performance of different aging metrics (residuals of the four biological aging metrics taken from the regression against chronological age) for all-cause mortality across seven follow-up intervals (from one-year to 15-years). a. Time-dependent AUCs of the five aging metrics' predictive performance for all-cause mortality. The four biological aging metrics (the Metabolomic Aging Score, MetaboHealth, the frailty index and leukocyte telomere length) were regressed against chronological age, and the resulting residuals were taken into subsequent analysis. b. ROC curves for one-year, two-year, three-year, four-year, five-year, ten-year and fifteen-year mortality prediction for the five aging metrics (residuals). *P*-values from Delong's test comparing the residuals of the Metabolomic Aging Score and chronological age were 3.2E-01, 3.2E-01, 6.7E-01, 5.3E-01, 3.6E-01, 5.8E-04 and 4.2E-14 for 1y, 2y, 3y, 4y, 5y, 10y and 15y-prediction, respectively. Met, Metabolomic Aging score; FI, frailty index; LTL, leukocyte telomere length. Source data are provided as a Source Data file.



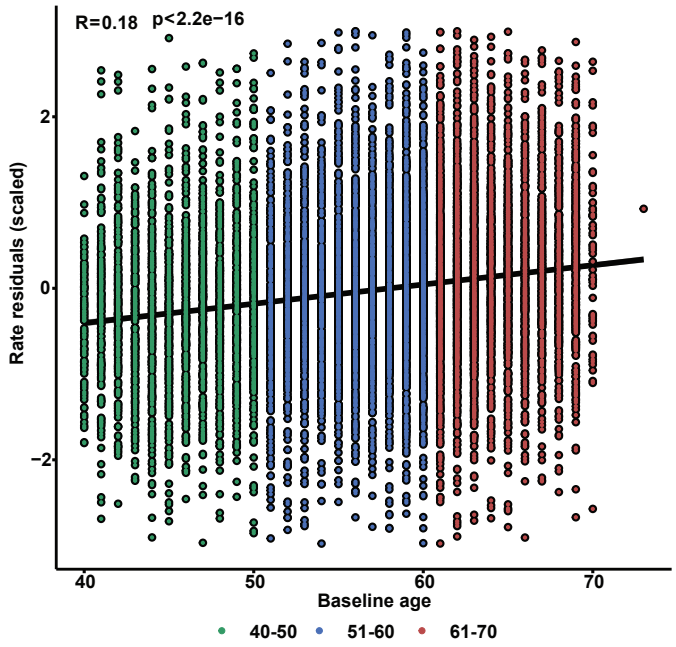
Supplementary Fig. 9| Forest plot of the hazard ratios of the residuals of the Metabolomic Aging Score for all-cause mortality stratified by different chronological age groups. The hazard ratios of the residuals of the Metabolomic Aging Score regressed against chronological age for all-cause mortality were estimated using Cox proportional hazards regression. Age-stratified analyses were conducted among the 40-50, 51-60 and 61-70 chronological age groups across seven follow-up intervals: one-year, two-year, three-year, four-year, five-year, ten-year and fifteen-year follow-up.



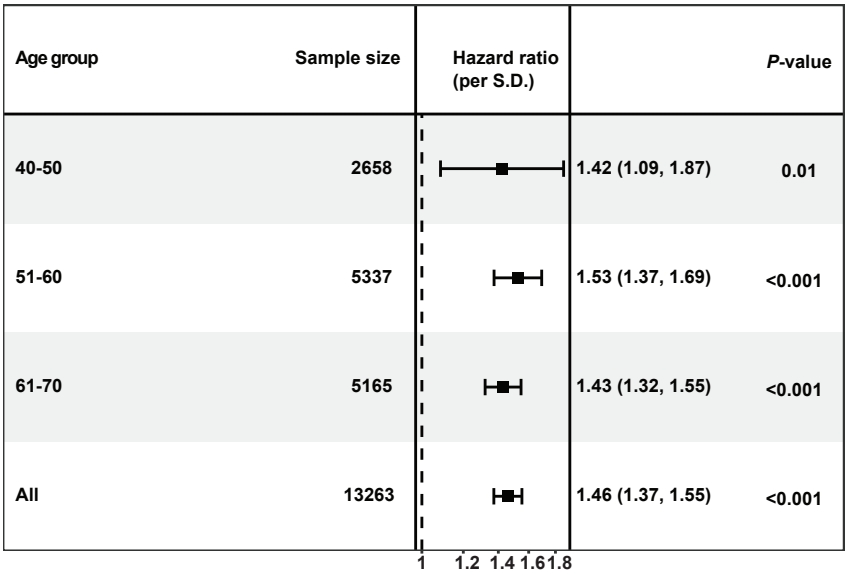
Supplementary Fig. 10| ROC curves showing the predictive performance of four aging metrics as independent predictors of 19 aging-related diseases. Black lines represent chronological age, red lines represent the Metabolomic Aging Score (Met), blue lines represented the frailty index (FI) and green lines represent leukocyte telomere length (LTL). COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease. Source data are provided as a Source Data file.



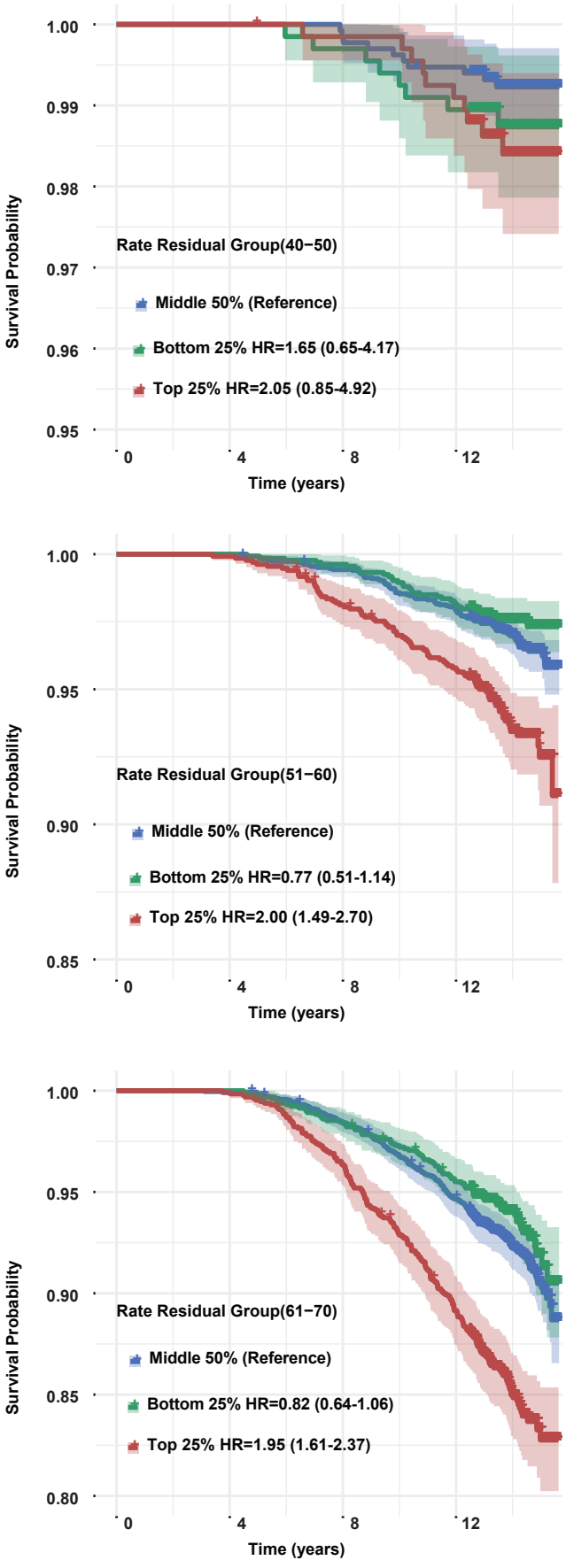
Supplementary Fig. 11| Scatter plot showing the correlation between the baseline Metabolomic Aging Score and the Metabolomic Aging Rate. The association between the baseline Metabolomic Aging Score and the Metabolomic Aging Rate was estimated using Pearson's correlation (*N*=13,263 samples).



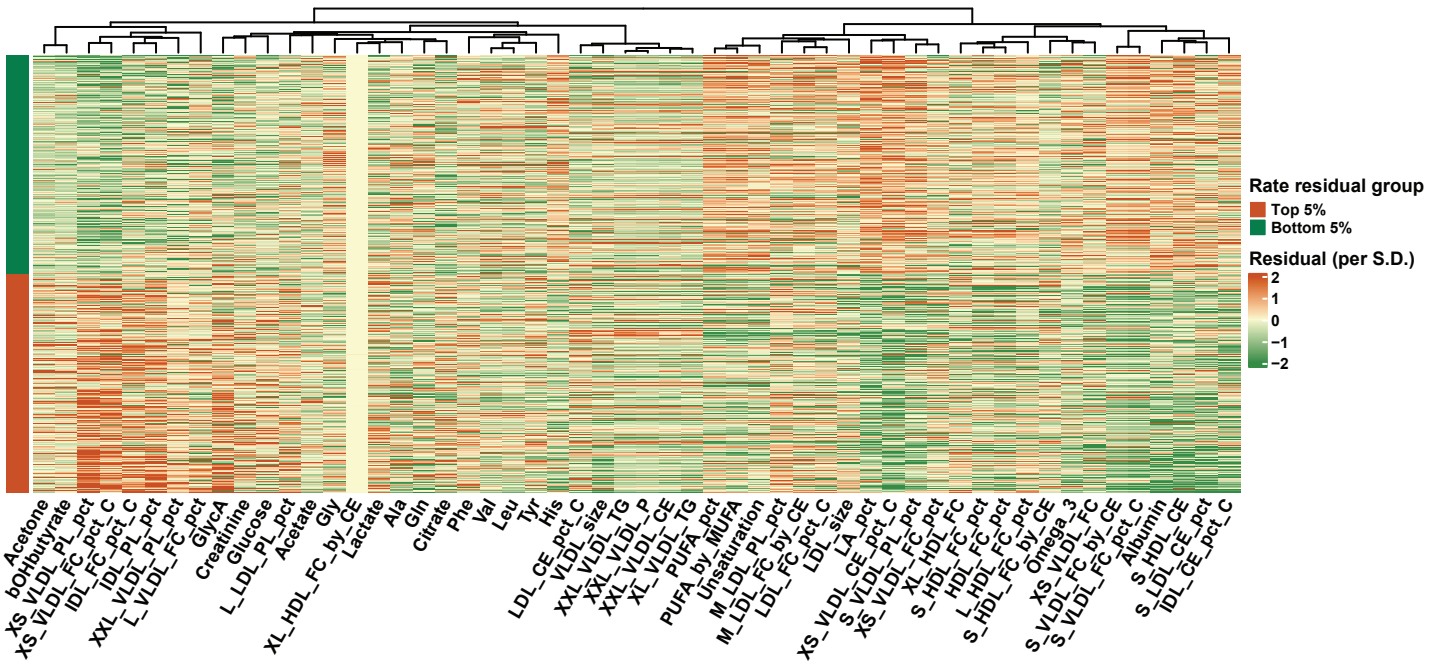
Supplementary Fig. 12| Scatter plot showing the correlation between the residuals of the Metabolomic Aging Rate and chronological age. The Metabolomic Aging Rate was regressed against the baseline Metabolomic Aging Score and the resulting residuals were standardized and used in subsequent analysis. Pearson's correlation between the rate residual and chronological age was estimated. Green dots, chronological age ranging from 40-50; blue dots, chronological age ranging from 51-60; red dots, chronological age ranging from 61-70 (*N*=13,263 samples).



Supplementary Fig. 13| Forest plot showing the hazard ratio of the residuals of the Metabolomic Aging Rate for all-cause mortality across different chronological age groups. Residuals of the Metabolomic Aging Rate regressed against the baseline Metabolomic Aging Score were calculated and standardized to assess their association with all-cause mortality using Cox proportional hazards models. Chronological age was included in the model as a covariate. Age-stratified analyses were conducted across three chronological age groups: 40-50, 51-60 and 61-70 years.



Supplementary Fig. 14| Survival curves of different Metabolomic Aging Rate groups stratified by three chronological age groups: 40-50, 51-60 and 61-70 years. Three aging rate groups were defined based on the distribution of the residuals of the Metabolomic Aging Rate regressed against the baseline Metabolomic Aging Score: top 25% (colored in red), middle 50% (colored in blue) and bottom 25% (colored in green). Age-stratified analyses were conducted among three chronological age groups: 40-50, 51-60 and 61-70 years. Hazard ratios for all-cause mortality and 95% CIs were estimated using Cox proportional hazards models with the middle rate group as the reference. Source data are provided as a Source Data file.



Supplementary Fig. 15| Personalized changing trajectories in the aging-related metabolomic profile. Each representative aging-related biomarker's change against the baseline level was calculated and then regressed against the baseline level. The resulting residuals were standardized for subsequent analyses. Two rate groups were defined based on the distribution of the residuals of the Metabolomic Aging Rate regressed against the baseline Metabolomic Aging Score: the top 5% (colored in red) and the bottom 5% (colored in green). The metabolomic changing profiles of these two groups were plotted and clustered with the *Ward.D2* method by their Euclidean distances (*N*=1,326 samples).

	Scotland , *N* = 15,788 [1]	England & Wales , *N* = 234,553 [1]	*p*-value [2]
Follow-up Time(year)			<0.001
Median (IQR)	14.85 (14.68 - 15.06)	13.74 (13.00 - 14.41)	
Mean (SD)	14.29 (2.22)	13.39 (1.96)	
Survival Status			<0.001
Survival	14053 / 15,788 (89.011%)	214907 / 234,553 (91.624%)	
Mortality	1735 / 15,788 (10.989%)	19646 / 234,553 (8.3759%)	
Leukocyte Telomere Length (T/S)			<0.001
Median (IQR)	0.83 (0.75 - 0.91)	0.82 (0.74 - 0.91)	
Mean (SD)	0.84 (0.13)	0.83 (0.13)	
Missing	504	8,361	
Frailty Index			<0.001
Median (IQR)	0.11 (0.06 - 0.16)	0.11 (0.07 - 0.17)	
Mean (SD)	0.12 (0.08)	0.12 (0.07)	
Missing	40	799	
Age			<0.001
Median (IQR)	57 (50 - 63)	58 (50 - 63)	
Mean (SD)	56 (8)	57 (8)	
Ethnic			<0.001
Asian or Asian British	417 / 15,745 (2.6485%)	7,629 / 233,465 (3.2677%)	
Black or Black British	37 / 15,745 (0.2350%)	1,259 / 233,465 (0.5393%)	
Chinese	39 / 15,745 (0.2477%)	688 / 233,465 (0.2947%)	
Mixed	727 / 15,745 (4.6173%)	8,282 / 233,465 (3.5474%)	
Other ethnic group	75 / 15,745 (0.4763%)	2,026 / 233,465 (0.8678%)	
White	14,450 / 15,745 (91.775%)	213,581 / 233,465 (91.483%)	
Missing	43	1,088	
Sex			<0.001
Female	8,744 / 15,788 (55.384%)	126,209 / 234,553 (53.808%)	
Male	7,044 / 15,788 (44.616%)	108,344 / 234,553 (46.192%)	
Alcohol Intake Frequency			<0.001
Daily or almost daily	2,817 / 15,766 (17.868%)	46,952 / 234,085 (20.058%)	
Never	1,240 / 15,766 (7.8650%)	18,672 / 234,085 (7.9766%)	
Once or twice a week	4,413 / 15,766 (27.991%)	61,052 / 234,085 (26.081%)	
One to three times a month	1,818 / 15,766 (11.531%)	26,180 / 234,085 (11.184%)	
Special occasions only	1,729 / 15,766 (10.967%)	26,841 / 234,085 (11.466%)	
Three or four times a week	3,749 / 15,766 (23.779%)	54,388 / 234,085 (23.234%)	
Missing	22	468	
Systolic Blood Pressure(mmHg)			0.5
Median (IQR)	138 (126 - 153)	138 (126 - 152)	
Mean (SD)	140 (20)	140 (20)	
Missing	8,292	6,817	
Smoking Status			<0.001
Current	1,970 / 15,728 (12.525%)	24,095 / 233,380 (10.324%)	
Never	8,730 / 15,728 (55.506%)	127,668 / 233,380 (54.704%)	
Previous	5,028 / 15,728 (31.968%)	81,617 / 233,380 (34.972%)	
Missing	60	1,173	
Body Mass Index(kg/m^2)			0.046
Median (IQR)	26.7 (24.1 - 29.9)	26.8 (24.2 - 29.9)	
Mean (SD)	27.4 (4.8)	27.4 (4.8)	
Missing	31	900	
Townsend Deprivation Index			<0.001
Median (IQR)	-1.91 (-3.71 - 1.24)	-2.23 (-3.68 - 0.37)	
Mean (SD)	-1.00 (3.56)	-1.39 (3.03)	
Missing	32	273	
Cholesterol(mmol/l)			<0.001
Median (IQR)	5.68 (4.93 - 6.46)	5.64 (4.89 - 6.41)	
Mean (SD)	5.72 (1.15)	5.68 (1.14)	
Missing	351	10,545	
Creatinine(umol/l)			<0.001
Median (IQR)	69 (60 - 80)	71 (62 - 81)	
Mean (SD)	71 (17)	73 (17)	
Missing	347	10,674	
Glucose(mmol/l)			<0.001
Median (IQR)	4.85 (4.52 - 5.23)	4.94 (4.61 - 5.32)	
Mean (SD)	5.04 (1.23)	5.13 (1.23)	
Missing	1,733	29,335	
Triglycerides(mmol/l)			0.5
Median (IQR)	1.47 (1.03 - 2.14)	1.48 (1.05 - 2.13)	
Mean (SD)	1.74 (1.04)	1.74 (1.01)	
Missing	352	10,733	

[1] n / N (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test

Supplementary Table 1| Summary statistics of the studied cohort. Participants recruited from England and Wales (*N*=234,553) and Scotland (*N*=15,788) were grouped respectively and compared for their baseline characteristics. Continuous variables are presented as the mean with standard deviation (SD) and the median with interquartile range (IQR); categorical variables are presented as the number of participants and the corresponding proportions. T/S, telomere length (*T*) to single-copy gene length (*S*) ratio. Two-sided P-values were calculated with Wilcoxon rank sum tests and Pearson's Chi-squared tests.

Supplementary table 2 Alzheimer's Disease				
	Disease-free, N[1] = 248,124	Early-onset, N[1] = 221	Other-onset, N[1] = 1,985	p-value[2]
Met Score	-45.02 (-45.36, -44.63)	-44.82 (-45.25, -44.46)	-44.74 (-45.10, -44.34)	<0.001
Age	58 (50, 63)	57 (54, 61)	66 (64, 68)	<0.001
Sex				0.11
0	133,796 (54%)	106 (48%)	1,046 (53%)	
1	114,328 (46%)	115 (52%)	939 (47%)	
BMI	26.8 (24.2, 29.9)	27.2 (24.4, 30.6)	27.0 (24.4, 30.0)	0.15
SBP	138 (126, 152)	138 (127, 150)	146 (132, 159)	<0.001
Deprivation	-2.21 (-3.68, 0.42)	-1.76 (-3.37, 2.31)	-2.18 (-3.71, 0.51)	0.006
Alcohol				<0.001
1	49,358 (20%)	33 (15%)	377 (19%)	
2	57,709 (23%)	46 (21%)	382 (19%)	
3	64,905 (26%)	66 (30%)	491 (25%)	
4	27,781 (11%)	20 (9.0%)	197 (10.0%)	
5	28,257 (11%)	26 (12%)	284 (14%)	
6	19,631 (7.9%)	30 (14%)	248 (13%)	
Smoking				<0.001
0	135,326 (55%)	109 (50%)	959 (49%)	
1	85,701 (35%)	85 (39%)	855 (44%)	
2	25,887 (10%)	26 (12%)	151 (7.7%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary Table 2-20 | Summary statistics of 19 aging-related disease cohorts. Individuals from each disease cohort were divided into early-onset, other-onset and disease-free groups based on the age at diagnosis as top 10% youngest or not. Prevalent cases were excluded from the analysis for each disease. The distributions of several basic socioeconomic and health characteristics were compared among the three groups. Continuous variables are presented as the median with interquartile range (IQR); categorical variables are presented as the number of participants and the corresponding proportions. Two-sided p-values were calculated with Wilcoxon rank sum tests and Pearson's Chi-squared tests. Met score, Metabolomic Aging Score; Sex, 0-female, 1-male; BMI, body mass index; SBP, systolic blood pressure; Deprivation, Townsend deprivation index; Alcohol, alcohol intake frequency, 1-daily or almost daily, 2-three or four times a week, 3-once or twice a week, 4-one to three times a month, 5-special occasions only, 6-never; smoking, smoking status, 0-never, 1-previous, 2-current.

Supplementary table 3 Atrial fibrillation and flutter				
	Disease-free, N[1] = 228,799	Early-onset, N[1] = 1,734	Other-onset, N[1] = 15,601	p-value[2]
Met Score	-45.04 (-45.38, -44.67)	-44.99 (-45.34, -44.52)	-44.73 (-45.10, -44.31)	<0.001
Age	57 (49, 63)	50 (46, 53)	64 (61, 67)	<0.001
Sex				<0.001
0	126,967 (55%)	596 (34%)	6,129 (39%)	
1	101,832 (45%)	1,138 (66%)	9,472 (61%)	
BMI	26.6 (24.1, 29.7)	28.4 (25.0, 32.4)	28.2 (25.3, 31.6)	<0.001
SBP	138 (125, 151)	137 (125, 150)	146 (133, 160)	<0.001
Deprivation	-2.22 (-3.68, 0.40)	-1.62 (-3.41, 1.31)	-2.17 (-3.62, 0.57)	<0.001
Alcohol				<0.001
1	44,693 (20%)	334 (19%)	3,758 (24%)	
2	53,404 (23%)	389 (23%)	3,438 (22%)	
3	60,298 (26%)	472 (27%)	3,691 (24%)	
4	25,921 (11%)	172 (10.0%)	1,491 (9.6%)	
5	26,084 (11%)	203 (12%)	1,850 (12%)	
6	17,959 (7.9%)	156 (9.0%)	1,338 (8.6%)	
Smoking				<0.001
0	126,657 (56%)	909 (53%)	6,903 (45%)	
1	77,170 (34%)	533 (31%)	6,965 (45%)	
2	23,883 (10%)	286 (17%)	1,625 (10%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 4 Asthma				
	Disease-free, N[1] = 213,092	Early-onset, N[1] = 759	Other-onset, N[1] = 6,831	p-value[2]
Met Score	-45.03 (-45.37, -44.65)	-45.11 (-45.44, -44.71)	-44.85 (-45.23, -44.44)	<0.001
Age	58 (50, 63)	44 (42, 46)	60 (54, 65)	<0.001
Sex				<0.001
0	113,613 (53%)	448 (59%)	3,949 (58%)	
1	99,479 (47%)	311 (41%)	2,882 (42%)	
BMI	26.6 (24.1, 29.7)	27.7 (24.5, 31.3)	28.0 (25.1, 31.5)	<0.001
SBP	138 (126, 152)	129 (118, 141)	140 (127, 154)	<0.001
Deprivation	-2.25 (-3.70, 0.33)	-0.91 (-3.05, 2.38)	-1.90 (-3.55, 1.08)	<0.001
Alcohol				<0.001
1	42,755 (20%)	99 (13%)	1,294 (19%)	
2	50,181 (24%)	147 (19%)	1,371 (20%)	
3	56,101 (26%)	200 (26%)	1,706 (25%)	
4	23,622 (11%)	94 (12%)	791 (12%)	
5	23,686 (11%)	117 (15%)	938 (14%)	
6	16,330 (7.7%)	100 (13%)	714 (10%)	
Smoking				<0.001
0	116,804 (55%)	423 (56%)	3,272 (48%)	
1	73,080 (34%)	185 (25%)	2,683 (40%)	
2	22,192 (10%)	147 (19%)	820 (12%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 5 Cataract				
	Disease-free, N[1] = 231,365	Early-onset, N[1] = 1,753	Other-onset, N[1] = 15,773	p-value[2]
Met Score	-45.03 (-45.37, -44.65)	-45.01 (-45.35, -44.57)	-44.82 (-45.17, -44.41)	<0.001
Age	57 (50, 63)	52 (48, 56)	64 (61, 67)	<0.001
Sex				<0.001
0	123,749 (53%)	992 (57%)	9,460 (60%)	
1	107,616 (47%)	761 (43%)	6,313 (40%)	
BMI	26.7 (24.1, 29.8)	27.3 (24.5, 30.9)	27.3 (24.7, 30.5)	<0.001
SBP	138 (125, 152)	134 (124, 147)	144 (131, 157)	<0.001
Deprivation	-2.22 (-3.68, 0.41)	-1.37 (-3.20, 1.93)	-2.26 (-3.67, 0.38)	<0.001
Alcohol				<0.001
1	45,934 (20%)	284 (16%)	3,256 (21%)	
2	54,168 (23%)	389 (22%)	3,306 (21%)	
3	60,901 (26%)	413 (24%)	3,843 (24%)	
4	25,997 (11%)	201 (12%)	1,643 (10%)	
5	25,966 (11%)	261 (15%)	2,126 (14%)	
6	17,958 (7.8%)	198 (11%)	1,566 (9.9%)	
Smoking				<0.001
0	126,908 (55%)	1,027 (59%)	7,766 (50%)	
1	78,969 (34%)	498 (29%)	6,566 (42%)	
2	24,375 (11%)	219 (13%)	1,342 (8.6%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 6 CKD				
	Disease-free, N[1] = 234,434	Early-onset, N[1] = 1,283	Other-onset, N[1] = 11,547	p-value[2]
Met Score	-45.04 (-45.38, -44.67)	-44.76 (-45.16, -44.24)	-44.53 (-44.92, -44.09)	<0.001
Age	57 (50, 63)	49 (46, 53)	64 (61, 67)	<0.001
Sex				<0.001
0	127,093 (54%)	719 (56%)	5,559 (48%)	
1	107,341 (46%)	564 (44%)	5,988 (52%)	
BMI	26.6 (24.1, 29.7)	28.8 (25.8, 33.2)	28.7 (25.9, 32.3)	<0.001
SBP	138 (125, 152)	135 (124, 148)	145 (132, 159)	<0.001
Deprivation	-2.23 (-3.69, 0.37)	-0.71 (-2.94, 2.65)	-2.02 (-3.50, 0.99)	<0.001
Alcohol				<0.001
1	47,194 (20%)	131 (10%)	1,975 (17%)	
2	55,368 (24%)	204 (16%)	2,051 (18%)	
3	61,503 (26%)	335 (26%)	2,848 (25%)	
4	26,114 (11%)	190 (15%)	1,348 (12%)	
5	25,952 (11%)	223 (17%)	1,875 (16%)	
6	17,857 (7.6%)	192 (15%)	1,418 (12%)	
Smoking				<0.001
0	128,942 (55%)	736 (58%)	5,185 (45%)	
1	80,011 (34%)	340 (27%)	5,040 (44%)	
2	24,355 (10%)	195 (15%)	1,243 (11%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 7 COPD				
	Disease-free, N[1] = 235,335	Early-onset, N[1] = 1,016	Other-onset, N[1] = 9,138	p-value[2]
Met Score	-45.04 (-45.38, -44.67)	-44.76 (-45.15, -44.28)	-44.58 (-44.96, -44.16)	<0.001
Age	57 (50, 63)	48 (45, 51)	63 (60, 66)	<0.001
Sex				<0.001
0	128,047 (54%)	498 (49%)	4,066 (44%)	
1	107,288 (46%)	518 (51%)	5,072 (56%)	
BMI	26.7 (24.1, 29.8)	27.8 (24.5, 32.5)	27.7 (24.7, 31.3)	<0.001
SBP	138 (126, 152)	131 (120, 144)	142 (130, 156)	<0.001
Deprivation	-2.28 (-3.71, 0.26)	1.14 (-1.84, 4.04)	-1.01 (-3.09, 2.28)	<0.001
Alcohol				<0.001
1	46,567 (20%)	158 (16%)	2,100 (23%)	
2	55,552 (24%)	147 (15%)	1,632 (18%)	
3	62,015 (26%)	251 (25%)	2,104 (23%)	
4	26,486 (11%)	131 (13%)	855 (9.4%)	
5	26,213 (11%)	182 (18%)	1,377 (15%)	
6	18,062 (7.7%)	139 (14%)	1,040 (11%)	
Smoking				<0.001
0	133,297 (57%)	211 (21%)	1,735 (19%)	
1	79,703 (34%)	240 (24%)	4,278 (47%)	
2	21,235 (9.1%)	559 (55%)	3,042 (34%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 8 Type 2 diabetes				
	Disease-free, N[1] = 226,761	Early-onset, N[1] = 1,675	Other-onset, N[1] = 15,063	p-value[2]
Met Score	-45.06 (-45.39, -44.71)	-44.61 (-44.97, -44.20)	-44.50 (-44.88, -44.11)	<0.001
Age	57 (50, 63)	45 (43, 48)	62 (57, 65)	<0.001
Sex				<0.001
0	125,483 (55%)	692 (41%)	6,279 (42%)	
1	101,278 (45%)	983 (59%)	8,784 (58%)	
BMI	26.4 (24.0, 29.4)	32.4 (28.6, 37.0)	30.4 (27.4, 34.2)	<0.001
SBP	138 (125, 151)	137 (127, 148)	145 (133, 158)	<0.001
Deprivation	-2.28 (-3.71, 0.25)	0.49 (-2.45, 3.54)	-1.56 (-3.32, 1.70)	<0.001
Alcohol				<0.001
1	46,382 (20%)	156 (9.3%)	2,319 (15%)	
2	54,299 (24%)	202 (12%)	2,681 (18%)	
3	59,817 (26%)	409 (25%)	3,708 (25%)	
4	25,091 (11%)	242 (14%)	1,791 (12%)	
5	24,410 (11%)	329 (20%)	2,500 (17%)	
6	16,359 (7.2%)	331 (20%)	2,027 (13%)	
Smoking				<0.001
0	125,997 (56%)	895 (54%)	6,576 (44%)	
1	76,759 (34%)	428 (26%)	6,404 (43%)	
2	22,982 (10%)	341 (20%)	1,977 (13%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 9 Hearing loss				
	Disease-free, N[1] = 245,821	Early-onset[1], N = 248	Other-onset, N[1] = 2,224	p-value[2]
Met Score	-45.02 (-45.36, -44.63)	-45.14 (-45.44, -44.80)	-44.88 (-45.22, -44.48)	<0.001
Age	58 (50, 63)	45 (43, 48)	62 (57, 66)	<0.001
Sex				<0.001
0	132,801 (54%)	134 (54%)	1,061 (48%)	
1	113,020 (46%)	114 (46%)	1,163 (52%)	
BMI	26.8 (24.2, 29.9)	26.6 (23.7, 30.4)	27.0 (24.6, 30.2)	0.002
SBP	138 (126, 152)	129 (119, 142)	142 (129, 155)	<0.001
Deprivation	-2.22 (-3.68, 0.42)	-0.85 (-3.12, 2.58)	-2.05 (-3.60, 0.87)	<0.001
Alcohol				<0.001
1	48,842 (20%)	31 (13%)	488 (22%)	
2	57,172 (23%)	44 (18%)	460 (21%)	
3	64,275 (26%)	78 (32%)	583 (26%)	
4	27,505 (11%)	41 (17%)	215 (9.7%)	
5	28,042 (11%)	28 (11%)	278 (13%)	
6	19,501 (7.9%)	25 (10%)	198 (8.9%)	
Smoking				<0.001
0	134,082 (55%)	144 (58%)	1,122 (51%)	
1	84,882 (35%)	64 (26%)	895 (40%)	
2	25,643 (10%)	39 (16%)	197 (8.9%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 10 Hyperlipidemia				
	Disease-free, N[1] = 185,110	Early-onset, N[1] = 2,688	Other-onset, N[1] = 24,192	p-value[2]
Met Score	-45.10 (-45.42, -44.74)	-45.03 (-45.38, -44.65)	-44.89 (-45.24, -44.50)	<0.001
Age	56 (48, 62)	46 (43, 49)	61 (57, 65)	<0.001
Sex				<0.001
0	106,392 (57%)	1,109 (41%)	11,341 (47%)	
1	78,718 (43%)	1,579 (59%)	12,851 (53%)	
BMI	26.3 (23.8, 29.4)	28.5 (25.6, 31.9)	27.6 (25.0, 30.7)	<0.001
SBP	136 (124, 150)	136 (125, 148)	144 (131, 158)	<0.001
Deprivation	-2.28 (-3.72, 0.25)	-1.02 (-3.08, 2.35)	-2.09 (-3.61, 0.69)	<0.001
Alcohol				<0.001
1	36,134 (20%)	402 (15%)	5,280 (22%)	
2	43,991 (24%)	566 (21%)	5,298 (22%)	
3	49,466 (27%)	662 (25%)	6,071 (25%)	
4	21,228 (11%)	364 (14%)	2,455 (10%)	
5	20,317 (11%)	378 (14%)	2,910 (12%)	
6	13,645 (7.4%)	307 (11%)	2,115 (8.8%)	
Smoking				<0.001
0	106,064 (58%)	1,400 (52%)	11,510 (48%)	
1	59,692 (32%)	690 (26%)	9,769 (41%)	
2	18,538 (10%)	582 (22%)	2,768 (12%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson’s Chi-squared test

Supplementary table 11 Hypertension				
	Disease-free, N[1] = 148,546	Early-onset, N[1] = 3,449	Other-onset, N[1] = 31,032	p-value[2]
Met Score	-45.15 (-45.46, -44.81)	-45.02 (-45.36, -44.64)	-44.89 (-45.23, -44.52)	<0.001
Age	55 (48, 61)	45 (43, 48)	61 (56, 65)	<0.001
Sex				<0.001
0	86,703 (58%)	1,621 (47%)	15,310 (49%)	
1	61,843 (42%)	1,828 (53%)	15,722 (51%)	
BMI	25.8 (23.5, 28.6)	28.8 (25.7, 32.5)	27.5 (24.9, 30.5)	<0.001
SBP	132 (121, 144)	143 (131, 155)	147 (134, 161)	<0.001
Deprivation	-2.31 (-3.73, 0.19)	-1.14 (-3.20, 2.09)	-2.18 (-3.66, 0.48)	<0.001
Alcohol				<0.001
1	28,371 (19%)	509 (15%)	6,668 (22%)	
2	36,356 (25%)	684 (20%)	6,690 (22%)	
3	40,256 (27%)	960 (28%)	7,790 (25%)	
4	17,232 (12%)	421 (12%)	3,306 (11%)	
5	15,644 (11%)	492 (14%)	3,737 (12%)	
6	10,437 (7.0%)	365 (11%)	2,759 (8.9%)	
Smoking				<0.001
0	86,109 (58%)	1,912 (56%)	14,955 (49%)	
1	46,417 (31%)	924 (27%)	12,141 (39%)	
2	15,403 (10%)	597 (17%)	3,721 (12%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 12 Hypertensive heart disease				
	Disease-free, N[1] = 249,794	Early-onset[1], N = 49	Other-onset[1], N = 435	p-value[2]
Met Score	-45.02 (-45.36, -44.63)	-44.64 (-45.05, -44.31)	-44.46 (-44.92, -44.01)	<0.001
Age	58 (50, 63)	48 (44, 51)	63 (59, 67)	<0.001
Sex				<0.001
0	134,784 (54%)	16 (33%)	132 (30%)	
1	115,010 (46%)	33 (67%)	303 (70%)	
BMI	26.8 (24.2, 29.9)	30.3 (28.4, 35.6)	29.6 (26.6, 33.9)	<0.001
SBP	138 (126, 152)	144 (130, 161)	149 (138, 165)	<0.001
Deprivation	-2.21 (-3.68, 0.42)	2.10 (-2.06, 5.17)	-1.37 (-3.11, 1.77)	<0.001
Alcohol				<0.001
1	49,652 (20%)	6 (13%)	103 (24%)	
2	58,036 (23%)	3 (6.3%)	85 (20%)	
3	65,326 (26%)	11 (23%)	112 (26%)	
4	27,944 (11%)	9 (19%)	38 (8.8%)	
5	28,503 (11%)	8 (17%)	51 (12%)	
6	19,847 (8.0%)	11 (23%)	43 (10.0%)	
Smoking				<0.001
0	136,184 (55%)	25 (51%)	164 (38%)	
1	86,412 (35%)	10 (20%)	192 (45%)	
2	25,970 (10%)	14 (29%)	75 (17%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 13 Ischemic heart disease				
	Disease-free, N[1] = 222,053	Early-onset, N[1] = 2,008	Other-onset, N[1] = 18,067	p-value[2]
Met Score	-45.06 (-45.39, -44.69)	-44.93 (-45.28, -44.54)	-44.72 (-45.09, -44.30)	<0.001
Age	57 (49, 63)	47 (44, 50)	63 (59, 66)	<0.001
Sex				<0.001
0	125,974 (57%)	603 (30%)	6,388 (35%)	
1	96,079 (43%)	1,405 (70%)	11,679 (65%)	
BMI	26.6 (24.0, 29.7)	28.5 (25.5, 32.1)	28.1 (25.4, 31.3)	<0.001
SBP	137 (125, 151)	138 (127, 150)	145 (133, 159)	<0.001
Deprivation	-2.25 (-3.70, 0.32)	-0.80 (-3.01, 2.54)	-2.01 (-3.56, 0.85)	<0.001
Alcohol				<0.001
1	44,002 (20%)	288 (14%)	3,905 (22%)	
2	52,363 (24%)	389 (19%)	3,719 (21%)	
3	58,482 (26%)	528 (26%)	4,441 (25%)	
4	25,061 (11%)	243 (12%)	1,872 (10%)	
5	24,950 (11%)	306 (15%)	2,265 (13%)	
6	16,773 (7.6%)	246 (12%)	1,821 (10%)	
Smoking				<0.001
0	124,777 (56%)	981 (49%)	7,736 (43%)	
1	74,156 (34%)	496 (25%)	7,723 (43%)	
2	22,090 (10.0%)	520 (26%)	2,480 (14%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson’s Chi-squared test

Supplementary table 14 Fibrosis and cirrhosis of liver				
	Disease-free, N[1] = 248,910	Early-onset[1], N = 108	Other-onset[1], N = 965	p-value[2]
Met Score	-45.02 (-45.36, -44.64)	-44.68 (-45.22, -44.21)	-44.37 (-44.84, -43.86)	<0.001
Age	58 (50, 63)	45 (43, 48)	61 (56, 65)	<0.001
Sex				<0.001
0	134,314 (54%)	47 (44%)	414 (43%)	
1	114,596 (46%)	61 (56%)	551 (57%)	
BMI	26.7 (24.2, 29.9)	29.4 (25.8, 32.8)	29.9 (26.3, 34.3)	<0.001
SBP	138 (126, 152)	127 (119, 139)	144 (131, 157)	<0.001
Deprivation	-2.22 (-3.68, 0.41)	0.49 (-2.42, 4.88)	-0.76 (-3.12, 2.42)	<0.001
Alcohol				<0.001
1	49,473 (20%)	15 (14%)	252 (26%)	
2	57,948 (23%)	16 (15%)	136 (14%)	
3	65,181 (26%)	24 (22%)	201 (21%)	
4	27,872 (11%)	9 (8.4%)	87 (9.1%)	
5	28,356 (11%)	14 (13%)	135 (14%)	
6	19,597 (7.9%)	29 (27%)	149 (16%)	
Smoking				<0.001
0	135,823 (55%)	46 (43%)	381 (40%)	
1	86,043 (35%)	38 (35%)	417 (44%)	
2	25,825 (10%)	24 (22%)	156 (16%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 15 Disease of oral cavity				
	Disease-free, N[1] = 227,986	Early-onset, N[1] = 1,193	Other-onset, N[1] = 10,729	p-value[2]
Met Score	-45.02 (-45.37, -44.64)	-45.15 (-45.46, -44.78)	-44.91 (-45.28, -44.51)	<0.001
Age	58 (50, 63)	43 (42, 46)	59 (53, 64)	<0.001
Sex				<0.001
0	122,039 (54%)	671 (56%)	6,043 (56%)	
1	105,947 (46%)	522 (44%)	4,686 (44%)	
BMI	26.7 (24.2, 29.8)	26.8 (23.8, 30.5)	27.2 (24.5, 30.6)	<0.001
SBP	138 (126, 152)	129 (118, 140)	139 (126, 153)	<0.001
Deprivation	-2.23 (-3.69, 0.37)	-0.75 (-3.01, 2.30)	-2.05 (-3.59, 0.80)	<0.001
Alcohol				<0.001
1	45,748 (20%)	140 (12%)	2,028 (19%)	
2	53,500 (24%)	261 (22%)	2,243 (21%)	
3	59,749 (26%)	303 (26%)	2,739 (26%)	
4	25,301 (11%)	175 (15%)	1,205 (11%)	
5	25,664 (11%)	175 (15%)	1,391 (13%)	
6	17,584 (7.7%)	134 (11%)	1,094 (10%)	
Smoking				<0.001
0	125,073 (55%)	660 (56%)	5,429 (51%)	
1	78,826 (35%)	279 (24%)	3,808 (36%)	
2	22,977 (10%)	243 (21%)	1,431 (13%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 16 Osteoporosis				
	Disease-free, N[1] = 236,103	Early-onset[1], N = 899	Other-onset, [1]N = 8,086	p-value[2]
Met Score	-45.02 (-45.37, -44.64)	-45.06 (-45.49, -44.64)	-44.90 (-45.28, -44.49)	<0.001
Age	57 (50, 63)	49 (46, 52)	63 (59, 66)	<0.001
Sex				<0.001
0	123,112 (52%)	752 (84%)	6,644 (82%)	
1	112,991 (48%)	147 (16%)	1,442 (18%)	
BMI	26.8 (24.3, 30.0)	24.6 (22.0, 28.2)	25.6 (23.0, 29.0)	<0.001
SBP	138 (126, 152)	128 (118, 142)	140 (127, 154)	<0.001
Deprivation	-2.22 (-3.68, 0.40)	-1.36 (-3.43, 2.05)	-2.04 (-3.57, 0.71)	<0.001
Alcohol				<0.001
1	47,253 (20%)	140 (16%)	1,504 (19%)	
2	55,444 (24%)	164 (18%)	1,543 (19%)	
3	62,137 (26%)	224 (25%)	1,885 (23%)	
4	26,401 (11%)	121 (13%)	896 (11%)	
5	26,339 (11%)	142 (16%)	1,252 (16%)	
6	18,084 (7.7%)	106 (12%)	980 (12%)	
Smoking				<0.001
0	128,860 (55%)	511 (57%)	4,199 (52%)	
1	81,642 (35%)	220 (25%)	2,944 (37%)	
2	24,470 (10%)	164 (18%)	884 (11%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 17 Parkinson's disease				
	Disease-free, N[1] = 248,047	Early-onset[1], N = 183	Other-onset, [1] N = 1,643	p-value[2]
Met Score	-45.02 (-45.36, -44.63)	-45.03 (-45.39, -44.68)	-44.79 (-45.16, -44.42)	<0.001
Age	58 (50, 63)	54 (49, 57)	65 (62, 67)	<0.001
Sex				<0.001
0	134,138 (54%)	76 (42%)	575 (35%)	
1	113,909 (46%)	107 (58%)	1,068 (65%)	
BMI	26.8 (24.2, 29.9)	26.8 (23.9, 30.4)	27.2 (24.8, 30.2)	<0.001
SBP	138 (126, 152)	136 (124, 148)	144 (131, 157)	<0.001
Deprivation	-2.21 (-3.68, 0.42)	-1.93 (-3.64, 0.87)	-2.39 (-3.75, 0.42)	0.2
Alcohol				<0.001
1	49,288 (20%)	26 (14%)	372 (23%)	
2	57,618 (23%)	45 (25%)	382 (23%)	
3	64,910 (26%)	57 (31%)	386 (24%)	
4	27,785 (11%)	13 (7.1%)	149 (9.1%)	
5	28,316 (11%)	19 (10%)	176 (11%)	
6	19,650 (7.9%)	22 (12%)	170 (10%)	
Smoking				<0.001
0	135,171 (55%)	123 (67%)	816 (50%)	
1	85,756 (35%)	44 (24%)	702 (43%)	
2	25,904 (10%)	16 (8.7%)	113 (6.9%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 18 Polyarthritis				
	Disease-free, N[1] = 241,791	Early-onset[1], N = 681	Other-onset, [1] N = 6,123	p-value[2]
Met Score	-45.02 (-45.37, -44.64)	-45.03 (-45.41, -44.61)	-44.82 (-45.18, -44.42)	<0.001
Age	58 (50, 63)	48 (44, 51)	62 (58, 66)	<0.001
Sex				<0.001
0	129,247 (53%)	503 (74%)	3,993 (65%)	
1	112,544 (47%)	178 (26%)	2,130 (35%)	
BMI	26.7 (24.1, 29.8)	29.1 (25.6, 33.7)	28.7 (25.7, 32.3)	<0.001
SBP	138 (126, 152)	131 (120, 144)	142 (129, 155)	<0.001
Deprivation	-2.22 (-3.68, 0.40)	-0.92 (-2.97, 2.66)	-2.12 (-3.62, 0.84)	<0.001
Alcohol				<0.001
1	48,349 (20%)	84 (12%)	1,076 (18%)	
2	56,462 (23%)	118 (17%)	1,256 (21%)	
3	63,237 (26%)	171 (25%)	1,573 (26%)	
4	27,049 (11%)	91 (13%)	683 (11%)	
5	27,255 (11%)	132 (19%)	881 (14%)	
6	18,969 (7.9%)	84 (12%)	642 (11%)	
Smoking				<0.001
0	132,181 (55%)	368 (55%)	2,990 (49%)	
1	83,197 (35%)	187 (28%)	2,535 (42%)	
2	25,241 (10%)	117 (17%)	550 (9.1%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 19 Gastro-oesophageal reflux disease

	Disease-free, N[1] = 208,125	Early-onset, N[1] = 2,340	Other-onset, N[1] = 21,059	p-value[2]
Met Score	-45.04 (-45.38, -44.66)	-45.13 (-45.44, -44.76)	-44.90 (-45.25, -44.50)	<0.001
Age	57 (50, 63)	44 (42, 47)	61 (55, 65)	<0.001
Sex				<0.001
0	111,907 (54%)	1,287 (55%)	11,857 (56%)	
1	96,218 (46%)	1,053 (45%)	9,202 (44%)	
BMI	26.6 (24.0, 29.7)	27.4 (24.7, 31.0)	27.5 (24.9, 30.7)	<0.001
SBP	138 (125, 152)	129 (120, 141)	140 (128, 154)	<0.001
Deprivation	-2.24 (-3.70, 0.36)	-1.29 (-3.30, 1.59)	-2.14 (-3.61, 0.58)	<0.001
Alcohol				<0.001
1	42,003 (20%)	277 (12%)	4,078 (19%)	
2	49,298 (24%)	484 (21%)	4,411 (21%)	
3	54,559 (26%)	701 (30%)	5,401 (26%)	
4	23,179 (11%)	334 (14%)	2,382 (11%)	
5	22,937 (11%)	309 (13%)	2,751 (13%)	
6	15,749 (7.6%)	230 (9.9%)	1,994 (9.5%)	
Smoking				<0.001
0	115,427 (56%)	1,330 (57%)	10,413 (50%)	
1	70,115 (34%)	618 (27%)	8,360 (40%)	
2	21,621 (10%)	377 (16%)	2,139 (10%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Supplementary table 20 Stroke				
	Disease-free, N[1] = 245,035	Early-onset, N[1] = 170	Other-onset, N[1] = 1,522	p-value[2]
Met Score	-45.03 (-45.37, -44.64)	-44.94 (-45.24, -44.47)	-44.63 (-45.04, -44.18)	<0.001
Age	58 (50, 63)	48 (44, 52)	64 (60, 67)	<0.001
Sex				<0.001
0	132,850 (54%)	63 (37%)	598 (39%)	
1	112,185 (46%)	107 (63%)	924 (61%)	
BMI	26.7 (24.2, 29.9)	28.0 (24.5, 31.1)	27.5 (24.8, 30.6)	<0.001
SBP	138 (126, 152)	140 (124, 153)	148 (135, 160)	<0.001
Deprivation	-2.22 (-3.69, 0.39)	-0.89 (-2.83, 1.85)	-1.83 (-3.45, 1.02)	<0.001
Alcohol				<0.001
1	48,717 (20%)	26 (15%)	351 (23%)	
2	57,163 (23%)	40 (24%)	314 (21%)	
3	64,201 (26%)	42 (25%)	361 (24%)	
4	27,468 (11%)	26 (15%)	121 (8.0%)	
5	27,835 (11%)	18 (11%)	201 (13%)	
6	19,173 (7.8%)	16 (9.5%)	173 (11%)	
Smoking				<0.001
0	134,138 (55%)	93 (55%)	675 (45%)	
1	84,486 (35%)	36 (21%)	596 (39%)	
2	25,227 (10%)	41 (24%)	240 (16%)	

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test