Table S1. Information of exposure and outcome data sources.

Study/Consortium	Exposure/Outcome	Cases	Controls	Sample size	Population	First author (Year)
UK biobank	Total-BCAA	NA	NA	115047	European	Borges CM (2020)
UK biobank	Valine	NA	NA	115048	European	Borges CM (2020)
UK biobank	Leucine	NA	NA	115074	European	Borges CM (2020)
UK biobank	Isoleucine	NA	NA	115075	European	Borges CM (2020)
FinnGen biobank	Peripheral artery disease	7098	206541	213639	European	2021
FinnGen biobank	Transient ischemic attack	8835	202223	211058	European	2021
EBI databases	Small vessel stroke	5386	192662	198048	European	Malik R (2018)
EBI databases	Large artery stroke	4373	406111	410484	European	Malik R (2018)
EBI databases	Cardioembolic stroke	7193	406111	413304	European	Malik R (2018)
EBI databases	Ischemic stroke	34217	406111	440328	European	Malik R (2018)
FinnGen biobank	Subarachnoid hemorrhage	1338	201230	202568	European	2021
FinnGen biobank	Intracerebral hemorrhage	1687	201146	202833	European	2021
FinnGen biobank	Stroke	18661	162201	180862	European	2021
FinnGen biobank	Heart failure	13087	195091	208178	European	2021
EBI databases	Coronary artery disease	42096	361	42457	European	Nikpay M (2015)
MRC-IEU	Angina	18168	187840	206008	European	2021
EBI databases	Myocardial infarction	2680	14125	16805	European	2021

Table S2. The total BCAA-related genetic variants used for the MR analyses.

Exposure	SNP	Chr	Position	Effect allele	Other allele	EAF	Beta	SE	*P* value	Nearby gene	R^2	F-statistic
BCAA	rs1128249	2	165528624	T	G	0.3920	-0.0348	0.0041	2.00E-17	COBLL1	0.000627	72.15
BCAA	rs10018448	4	89225171	G	A	0.5353	0.6965	0.0040	7.29E-128	PPM1K-DT	0.005030	578.67
BCAA	rs2977929	8	76454025	T	C	0.1968	0.0289	0.0050	1.10E-8	HNF4G	0.000284	32.71
BCAA	rs17096421	10	88820592	T	A	0.0564	0.0537	0.0088	9.70E-10	GLUD1	0.000325	37.38
BCAA	rs2638315	12	56865056	C	G	0.1825	0.0439	0.0052	1.80E-17	GLS2, SPRYD4	0.000629	72.36
BCAA	rs36181536	12	122528263	C	T	0.6735	-0.0263	0.0043	7.00E-10	MLXIP	0.000331	38.03
BCAA	rs6499561	16	72148404	G	A	0.3621	0.0239	0.0042	1.30E-08	NA	0.000280	32.26
BCAA	rs117643180	17	7185779	A	C	0.0259	-0.1494	0.0127	3.80E-32	SLC2A4	0.001211	139.29
BCAA	rs12974412	19	14151809	G	A	0.7800	-0.0280	0.0050	1.80E-08	IL27RA	0.000276	31.73
BCAA	rs4801776	19	49304215	T	C	0.2992	-0.0393	0.0045	1.30E-18	BCAT2	0.000674	77.55
BCAA	rs5747934	22	18915282	T	C	0.0423	-0.0050	0.0100	1.20E-09	PRODH	0.000321	36.96

Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; EAF, effect allele frequency; SE, standard error.

Table S3. The Valine-related genetic variants used for the MR analyses.

Exposure	SNP	Chr	Position	Effect allele	Other allele	EAF	Beta	SE	*P* value	Nearby gene	R^2	F-statistic
Valine	rs1128249	2	165528624	T	G	0.3920	-0.0351	0.0041	1.50E-17	NA	0.000631	72.65
Valine	rs10018448	4	89225171	G	A	0.5353	0.1046	0.0040	2.30E-148	PPM1K-DT	0.005849	672.97
Valine	rs12648408	4	89244131	A	G	0.0508	-0.0509	0.0093	4.20E-08	PPM1K-DT	0.000261	30.04
Valine	rs61587941	5	55814890	A	G	0.0512	-0.0502	0.0091	3.40E-08	C5orf67	0.000265	30.45
Valine	rs6941263	6	109162094	A	T	0.1878	-0.0285	0.0052	3.40E-08	NA	0.000265	30.46
Valine	rs17096421	10	88820592	T	A	0.0564	0.0625	0.0088	1.40E-12	GLUD1	0.000436	50.15
Valine	rs36181536	12	122528263	C	T	0.6735	-0.0318	0.0043	1.30E-13	MLXIP	0.000476	54.81
Valine	rs2638315	12	56865056	C	G	0.1825	0.0426	0.0052	2.20E-16	GLS2,SPRYD4	0.000586	67.39
Valine	rs2274815	14	102718052	A	G	0.2050	0.0280	0.0050	1.80E-08	MOK	0.000275	31.68
Valine	rs117643180	17	7185779	A	C	0.0259	-0.1748	0.0127	6.30E-43	SLC2A4	0.001640	188.64
Valine	rs8071084	17	79634162	G	T	0.1617	-0.0323	0.0055	3.10E-09	OXLD1,CCDC137	0.000305	35.11
Valine	rs35230038	19	49300431	A	G	0.0454	-0.0984	0.0098	1.10E-23	BCAT2	0.000875	100.62
Valine	rs117048185	19	49309776	C	G	0.0173	0.1899	0.0154	8.70E-35	BCAT2,LOC105372432	0.001316	151.37
Valine	rs12974412	19	14151809	G	A	0.7800	-0.0272	0.0050	4.80E-08	IL27RA	0.000259	29.81
Valine	rs837616	19	49365588	G	A	0.2915	-0.0250	0.0044	1.60E-08	PLEKHA4	0.000278	31.96
Valine	rs2238732	22	18915347	T	C	0.0423	-0.0621	0.0100	5.80E-10	PRODH	0.000334	38.38

Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; EAF, effect allele frequency; SE, standard error.

Table S4. The leucine-related genetic variants used for the MR analyses.

Exposure	SNP	Chr	Position	Effect allele	Other allele	EAF	Beta	SE	*P* value	Nearby gene	R^2	F-statistic
Leucine	rs11166420	1	100702216	A	T	0.9044	-0.0380	0.0067	1.70E-08	DBT	0.000276	31.77
Leucine	rs13389219	2	165528876	T	C	0.3925	-0.0321	0.0041	2.30E-15	COBLL1	0.000545	62.75
Leucine	rs150277164	4	89258580	A	G	0.0142	0.1159	0.0168	5.20E-12	PPM1K-DT	0.000414	47.62
Leucine	rs10018448	4	89225171	G	A	0.5353	0.0878	0.0040	4.30E-108	PPM1K-DT	0.004239	487.81
Leucine	rs2977929	8	76454025	T	C	0.1968	0.0282	0.0050	1.80E-08	HNF4G	0.000276	31.74
Leucine	rs2638315	12	56865056	C	G	0.1825	0.0409	0.0051	1.20E-15	GLS2,SPRYD4	0.000557	64.06
Leucine	rs9930957	16	72149923	T	C	0.1598	0.0525	0.0054	2.10E-22	NA	0.000824	94.76
Leucine	rs117643180	17	7185779	A	C	0.0259	-0.1184	0.0125	4.00E-21	SLC2A4	0.000773	89.00
Leucine	rs12974412	19	14151809	G	A	0.7800	-0.0291	0.0049	3.30E-09	IL27RA	0.000304	35.01
Leucine	rs4801776	19	49304215	T	C	0.2992	-0.0324	0.0044	2.40E-13	BCAT2	0.000466	53.61
Leucine	rs5747934	22	18915282	T	C	0.0423	-0.0568	0.0099	8.60E-09	PRODH	0.000288	33.14

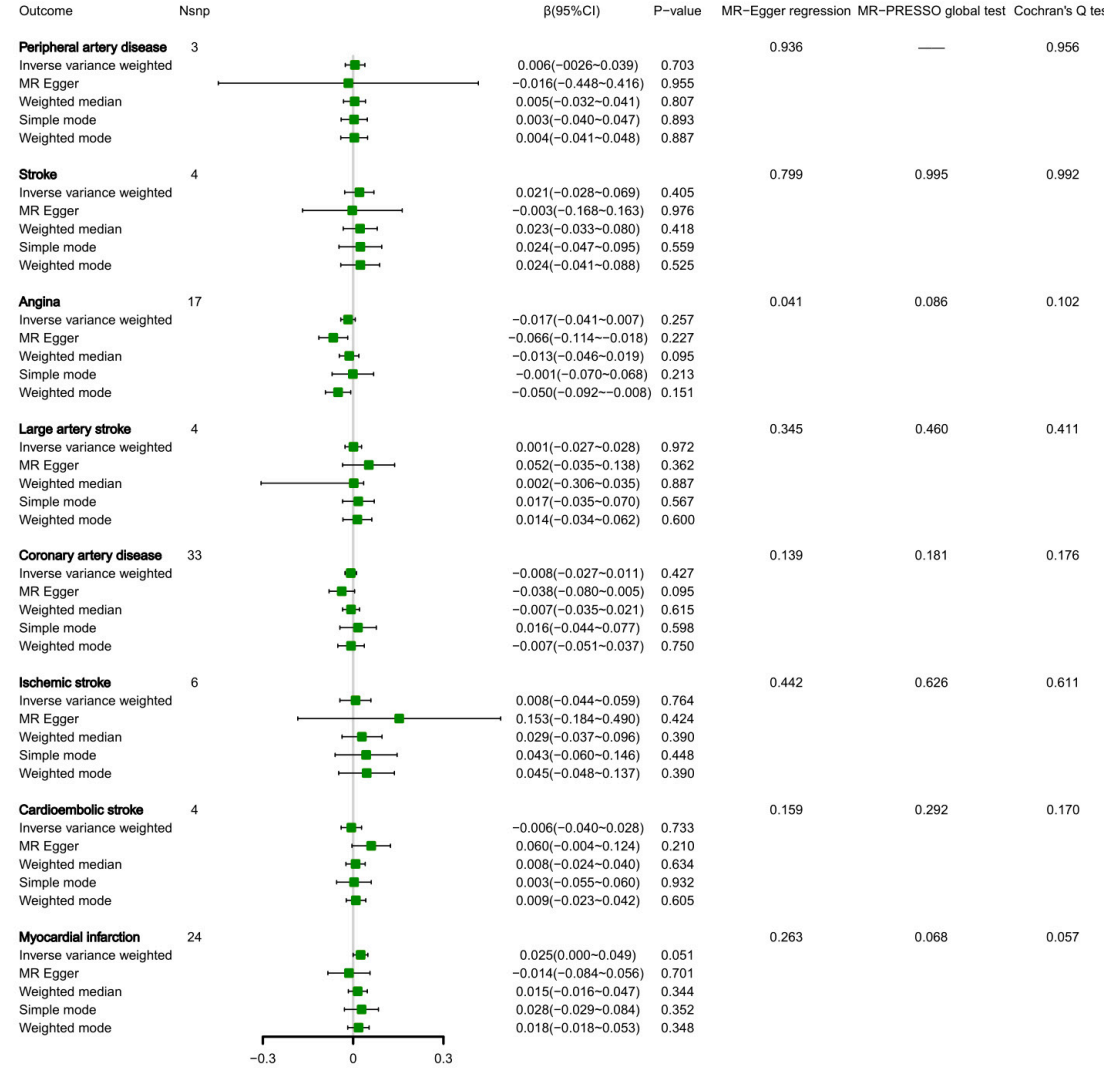
Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; EAF, effect allel frequency; SE, standard error.

Table S5. The Isoleucine-related genetic variants used for the MR analyses.

Exposure	SNP	Chr	Position	Effect allele	Other allele	EAF	Beta	SE	*P* value	Nearby gene	R^2	F-statistic
Isoleucine	rs10184004	2	165508389	T	C	0.4061	-0.0299	0.0041	4.00E-13	NA	0.000457	52.64
Isoleucine	rs10018448	4	89225171	G	A	0.5353	0.0666	0.0041	4.10E-60	PPM1K-DT	0.002324	267.44
Isoleucine	rs2941456	8	76443463	A	G	0.1985	0.0293	0.0051	9.10E-09	HNF4G	0.000287	33.02
Isoleucine	rs7302925	12	56861458	G	A	0.8011	-0.0413	0.0051	3.60E-16	SPRYD4	0.000577	66.43
Isoleucine	rs12325419	16	70368909	A	G	0.1153	-0.0743	0.0063	1.10E-31	DDX19B,DDX19A-DT	0.001192	137.21
Isoleucine	rs117643180	17	7185779	A	C	0.0259	-0.1014	0.0128	2.90E-15	SLC2A4	0.000542	62.34
Isoleucine	rs545587	19	49319664	C	A	0.5148	0.0366	0.0041	2.30E-19	HSD17B14	0.000704	80.99

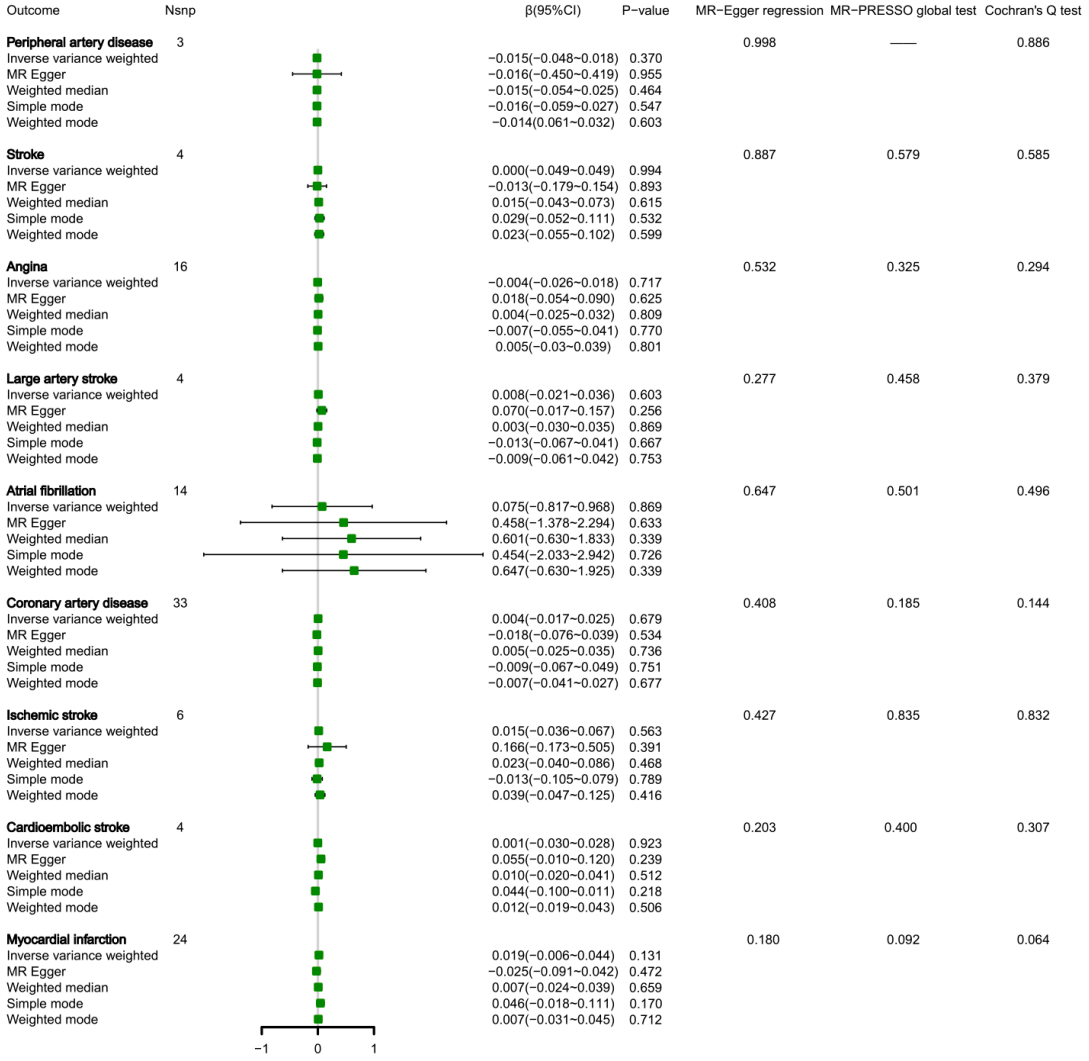
Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; EAF, effect allele frequency; SE, standard error.

Figure S1. Forest plot of cardiovascular diseases causally associated with circulating total BCAAs levels.



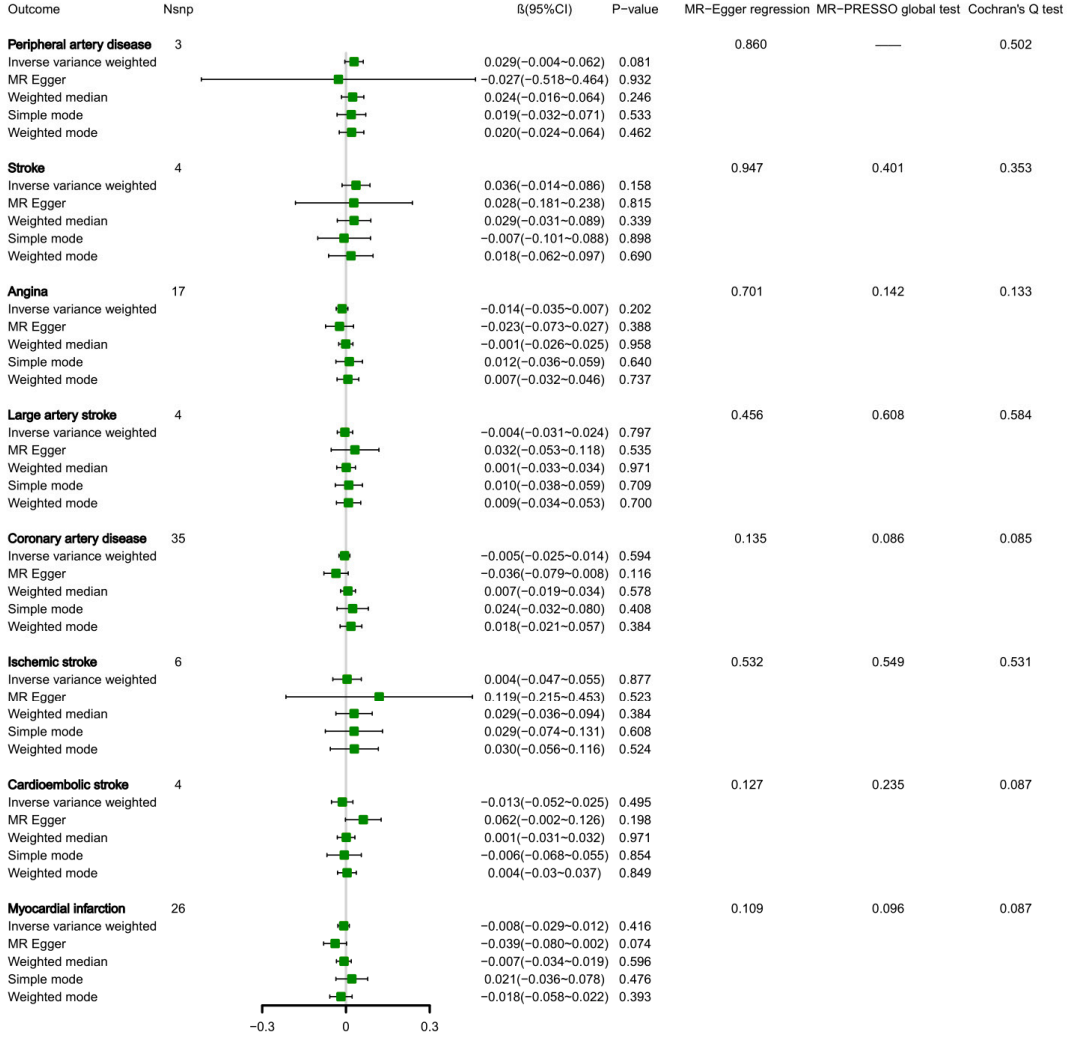
Abbreviations: β, beta value; CI, confidence interval, Nsnp, number of the SNPs.

Figure S2. Forest plot of cardiovascular diseases causally associated with circulating valine levels.



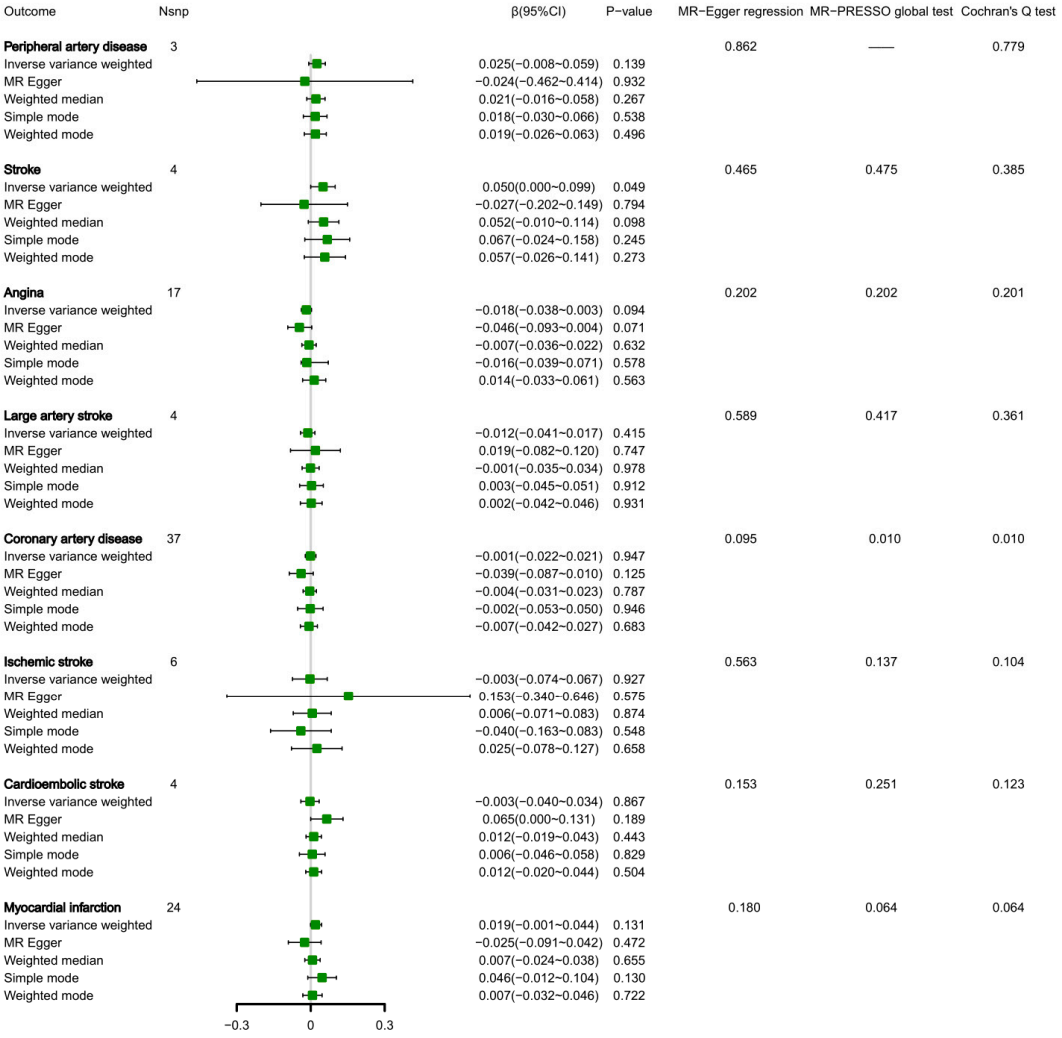
Abbreviations: β, beta value; CI, confidence interval, Nsnp, number of the SNPs.

Figure S3. Forest plot of cardiovascular diseases causally associated with circulating leucine levels.



Abbreviations: β, beta value; CI, confidence interval, Nsnp, number of the SNPs.

Figure S4. Forest plot of cardiovascular diseases causally associated with circulating isoleucine levels.



Abbreviations: β, beta value; CI, confidence interval, Nsnp, number of the SNPs.

Table S6. Baseline characteristics of UK Biobank participants of serum total-BCAA levels.

Values are means (SD) or % unless otherwise specified.

	Serum Total-BCAAs levels（mmol/L）			
Characteristics	**Tertile 1 (<0.346)**	**Tertile 2 (0.346~0.416)**	**Tertile 3 (>0.416)**	***P*-value**
N	2842	2845	2845	
Age, y	59.45±7.47	59.37±7.12	59.98±7.13	0.031
Male, (%)	26.60	35.20	38.20	<0.001
Drinking status, (%)				0.393
Current	33.10	33.40	33.60	
Previous	34.90	31.00	34.00	
Never	35.00	36.40	28.60	
Missing	40.00	30.00	30.00	
Smoking status, (%)				<0.001
Current	40.50	33.20	26.40	
Previous	30.70	34.00	35.30	
Never	33.70	32.80	33.50	
Missing	33.90	32.10	33.90	
Physical activity, (%)				0.037
Low	33.30	32.90	33.80	
Medium	30.50	33.80	35.70	
High	34.70	34.30	31.00	
Household income (€)				<0.001
<18,000	38.50	31.10	30.40	
18,000~30,999	31.80	33.30	34.90	
31,000~51,999	29.10	35.00	35.90	
52,000~100,000	30.10	35.60	34.30	
>100,000	21.80	37.40	40.80	
Missing	35.40	33.10	31.50	
Qualification				0.049
College or	32.30	33.90	33.80	
University	30.30	33.30	36.40	
A levels/AS levels	33.80	33.10	33.10	
O levels/GCSEs	30.20	31.90	37.90	
CSEs or equivalent	31.30	34.50	34.20	
NVQ/HND/HNC	35.60	33.00	31.40	
None of the above				
BMI, kg/m^2	30.20±5.76	31.77±5.73	32.33±5.42	<0.001
TG, mmol/L	1.30±0.58	1.54±0.61	1.75±0.72	<0.001
TC, mmol/L	4.06±0.97	3.99±0.97	3.92±0.97	<0.001
HDL, mmol/L	1.21±0.32	1.11±0.25	1.09±0.24	<0.001
LDL, mmol/L	1.49±0.45	1.51±0.46	1.48±0.46	0.034
HbA1c, mmol/mol	46.44±12.20	47.88±12.73	50.59±14.32	<0.001
Glucose, mmol/L	6.35±2.41	6.68±2.53	7.59±3.45	<0.001
Creatinine, umol/L	66.36±23.63	69.50±15.25	73.43±15.23	<0.001
Urate, umol/L	320.60±83.62	345.45±80.79	350.62±80.10	<0.001
SBP, mmHg	144.70±18.59	145.00±17.75	144.97±17.69	0.795
DBP, mmHg	82.35±10.66	83.90±10.33	83.64±10.29	<0.001

Abbreviations: BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; SBP, systolic pressure; DBP, diastolic pressure.

Table S7. Baseline characteristics of UK Biobank participants of serum valine levels.

	Serum Valine levels（mmol/L）			
Characteristics	**Tertile 1 (<0.203)**	**Tertile 2 (0.203~0.238)**	**Tertile 3 (>0.238)**	***P*-value**
N	2844	2844	2843	
Age, y	59.28±7.52	59.58±7.13	58.93±7.06	0.003
Male, (%)	28.20	34.50	37.20	<0.001
Drinking status, (%)				0.130
Current	33.20	33.40	33.40	
Previous	34.90	29.80	35.30	
Never	33.80	37.60	28.60	
Missing	50.00	30.00	20.00	
Smoking status, (%)				<0.001
Current	41.50	32.10	26.40	
Previous	30.70	34.20	35.10	
Never	33.50	32.70	33.80	
Missing	30.40	41.10	28.60	
Physical activity, (%)				0.117
Low	33.60	32.80	33.60	
Medium	31.90	32.50	35.60	
High	33.40	35.10	31.50	
Household income (€)				<0.001
<18,000	38.10	32.30	29.70	
18,000~30,999	31.20	34.50	34.30	
31,000~51,999	30.10	33.20	36.70	
52,000~100,000	30.50	34.20	35.30	
>100,000	22.30	36.30	41.30	
Missing	35.60	32.50	31.90	
Qualification				0.032
College or	32.30	32.70	35.00	
University	29.60	34.30	36.10	
A levels/AS levels	33.90	33.00	33.10	
O levels/GCSEs	32.70	30.70	36.60	
CSEs or equivalent	31.60	35.10	33.30	
NVQ/HND/HNC	35.40	33.60	31.10	
None of the above				
BMI, kg/m^2	29.96±5.64	31.80±5.67	32.56±5.50	<0.001
TG, mmol/L	1.27±0.55	1.54±0.58	1.80±0.74	<0.001
TC, mmol/L	4.02±0.95	3.98±0.99	3.97±0.97	0.116
HDL, mmol/L	1.21±0.32	1.11±0.26	1.10±0.24	<0.001
LDL, mmol/L	1.47±0.44	1.51±0.46	1.50±0.46	0.014
HbA1c, mmol/mol	46.21±11.96	47.95±12.57	50.76±14.61	<0.001
Glucose, mmol/L	6.36±2.41	6.72±2.62	7.54±3.40	<0.001
Creatinine, umol/L	66.71±23.87	69.70±15.08	72.89±15.22	<0.001
Urate, umol/L	320.82±83.52	344.82±80.78	351.06±80.26	<0.001
SBP, mmHg	144.31±18.56	145.14±17.56	145.22±17.90	0.110
DBP, mmHg	82.27±10.71	83.62±10.26	84.00±10.30	<0.001

Values are means (SD) or % unless otherwise specified.

Abbreviations: BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; SBP, systolic pressure; DBP, diastolic pressure.

Table S8. Baseline characteristics of UK Biobank participants of serum leucine levels.

	Serum Leucine levels（mmol/L）			
Characteristics	**Tertile 1 (<0.096)**	**Tertile 2 (0.096~0.119)**	**Tertile 3 (>0.119)**	***P*-value**
N	2843	2842	2846	
Age, y	59.62±7.35	59.26±7.21	58.92±7.16	0.001
Male, (%)	25.30	35.10	39.60	<0.001
Drinking status, (%)				0.195
Current	32.90	33.40	33.70	
Previous	36.00	31.40	32.60	
Never	37.90	33.80	28.30	
Missing	30.00	30.00	40.00	
Smoking status, (%)				<0.001
Current	38.60	34.10	27.40	
Previous	31.10	33.40	35.50	
Never	34.00	33.00	33.00	
Missing	36.80	35.70	37.50	
Physical activity, (%)				0.206
Low	33.10	33.20	33.70	
Medium	31.60	33.10	35.30	
High	34.70	33.70	31.60	
Household income (€)				<0.001
<18,000	38.00	32.40	29.60	
18,000~30,999	31.60	33.40	35.00	
31,000~51,999	29.90	33.40	36.70	
52,000~100,000	29.90	35.30	34.80	
>100,000	25.10	31.30	43.60	
Missing	35.40	33.50	31.10	
Qualification				0.010
College or	33.60	33.60	32.70	
University	31.10	32.40	36.50	
A levels/AS levels	34.70	31.50	33.80	
O levels/GCSEs	28.00	33.70	38.40	
CSEs or equivalent	29.50	35.90	34.60	
NVQ/HND/HNC	34.70	33.70	31.60	
None of the above				
BMI, kg/m^2	30.54±5.96	31.74±5.73	32.03±5.30	<0.001
TG, mmol/L	1.36±0.62	1.53±0.61	1.71±0.70	<0.001
TC, mmol/L	4.07±0.98	3.99±0.96	3.90±0.97	<0.001
HDL, mmol/L	1.21±0.32	1.12±0.26	1.09±0.24	<0.001
LDL, mmol/L	1.50±0.45	1.51±0.46	1.47±0.45	0.003
HbA1c, mmol/mol	46.92±12.39	47.81±12.23	50.19±13.80	<0.001
Glucose, mmol/L	6.39±2.41	6.65±2.61	7.58±3.40	<0.001
Creatinine, umol/L	66.36±23.63	69.51±15.39	73.42±15.09	<0.001
Urate, umol/L	322.21±83.73	344.47±82.05	350.00±79.22	<0.001
SBP, mmHg	145.19±18.54	144.89±18.17	144.59±18.01	0.450
DBP, mmHg	82.53±10.68	83.84±10.36	83.52±10.27	<0.001

Values are means (SD) or % unless otherwise specified.

Abbreviations: BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; SBP, systolic pressure; DBP, diastolic pressure.

Table S9. Baseline characteristics of UK Biobank participants of serum isoleucine levels.

	Serum Isoleucine levels（mmol/L）			
Characteristics	**Tertile 1 (<0.046)**	**Tertile 2 (0.046~0.060)**	**Tertile 3 (>0.060)**	***P*-value**
N	2843	2842	2846	
Age, y	59.47±7.37	59.28±7.23	59.05±7.12	0.092
Male, (%)	27.40	34.90	37.80	<0.001
Drinking status, (%)				0.292
Current	33.10	33.50	33.40	
Previous	36.00	29.30	34.70	
Never	34.30	36.00	29.80	
Missing	30.00	40.00	30.00	
Smoking status, (%)				<0.001
Current	38.90	33.60	27.50	
Previous	31.00	33.70	35.30	
Never	33.90	33.00	33.10	
Missing	37.50	26.80	35.70	
Physical activity, (%)				0.447
Low	33.20	33.20	33.60	
Medium	31.50	34.00	34.40	
High	34.60	33.30	32.10	
Household income (€)				<0.001
<18,000	36.90	32.40	30.80	
18,000~30,999	31.80	33.30	34.90	
31,000~51,999	30.80	33.60	35.60	
52,000~100,000	30.80	35.70	33.40	
>100,000	25.70	31.80	42.50	
Missing	35.30	33.10	31.60	
Qualification				0.011
College or	33.20	33.00	33.80	
University	29.60	34.80	35.60	
A levels/AS levels	35.90	30.00	34.10	
O levels/GCSEs	29.70	35.40	34.90	
CSEs or equivalent	31.30	35.00	33.70	
NVQ/HND/HNC	34.00	34.50	31.50	
None of the above				
BMI, kg/m^2	30.45±5.75	31.72±5.70	32.14±5.53	<0.001
TG, mmol/L	1.35±0.61	1.56±0.64	1.69±0.69	<0.001
TC, mmol/L	4.08±0.99	4.01±0.96	3.88±0.96	<0.001
HDL, mmol/L	1.21±0.32	1.12±0.26	1.09±0.24	<0.001
LDL, mmol/L	1.51±0.46	1.51±0.45	1.46±0.45	<0.001
HbA1c, mmol/mol	46.86±12.20	47.91±13.27	50.14±13.94	<0.001
Glucose, mmol/L	6.40±2.40	6.67±2.60	7.56±3.42	<0.001
Creatinine, umol/L	65.89±21.28	69.89±18.32	73.52±15.18	<0.001
Urate, umol/L	324.56±83.28	341.95±82.55	350.18±79.74	<0.001
SBP, mmHg	144.75±18.32	145.23±18.00	144.69±17.71	0.457
DBP, mmHg	82.78±10.52	83.85±10.64	83.25±10.16	0.001

Values are means (SD) or % unless otherwise specified.

Abbreviations: BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; SBP, systolic pressure; DBP, diastolic pressure.

Table S10. Association between baseline circulating BCAAs in relation to the prevalence of multiple cardiovascular diseases.

Serum Total BCAAs levels（mmol/L）				
	Tertile1 (<0.346)	Tertile2 (0.346~0.416)	Tertile3 (>0.416)	
Ischemic stroke	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	*p*-trend
Model 1	Reference	1.241 (0.919~1.676)	1.259 (0.931~1.703)	0.143
Model 2	Reference	1.251 (0.924~1.693)	1.267 (0.933~1.721)	0.139
Model 3	Reference	1.248 (0.922~1.689)	1.261 (0.929~1.712)	0.148
Subarachnoid hemorrhage				
Model 1	Reference	2.426 (0.440~13.374)	3.364 (0.639~17.693)	0.147
Model 2	Reference	2.338 (0.418~13.063)	3.212 (0.600~17.176)	0.169
Model 3	Reference	2.319 (0.414~12.942)	3.195 (0.596~17.116)	0.171
Intracerebral hemorrhage				
Model 1	Reference	1.010 (0.458~2.229)	1.671 (0.817~3.418)	0.132
Model 2	Reference	0.988 (0.445~2.194)	1.647 (0.796~3.407)	0.144
Model 3	Reference	0.998 (0.450~2.215)	1.643 (0.794~3.398)	0.147
Coronary artery disease				
Model 1	Reference	1.060 (0.928~1.212)	1.160 (1.015~1.324)	0.028*
Model 2	Reference	1.011 (0.883~1.157)	1.092 (0.954~1.251)	0.193
Model 3	Reference	1.009 (0.881~1.156)	1.083 (0.945~1.241)	0.240
Myocardial infarction				
Model 1	Reference	1.207 (0.939~1.551)	1.214 (0.943~1.563)	0.141
Model 2	Reference	1.186 (0.921~1.527)	1.185 (0.918~1.531)	0.207
Model 3	Reference	1.184 (0.920~1.525)	1.182 (0.915~1.527)	0.213
Peripheral arterial disease				
Model 1	Reference	1.019 (0.778~1.334)	0.800 (0.600~1.066)	0.130
Model 2	Reference	1.049 (0.798~1.378)	0.832 (0.621~1.113)	0.218
Model 3	Reference	1.047 (0.797~1.377)	0.826 (0.617~1.107)	0.202
Heart failure				
Model 1	Reference	1.000 (0.834~1.198)	1.000 (0.832~1.200)	0.996
Model 2	Reference	0.915 (0.761~1.101)	0.899 (0.746~1.085)	0.272
Model 3	Reference	0.912 (0.758~1.097)	0.894 (0.741~1.078)	0.246
Angina				
Model 1	Reference	1.080 (0.912~1.280)	1.130 (0.954~1.339)	0.160
Model 2	Reference	1.038 (0.875~1.232)	1.074 (0.905~1.276)	0.414
Model 3	Reference	1.036 (0.873~1.230)	1.067 (0.898~1.267)	0.464

Model 1 adjusted for sex, age, smoking, drinking. Model 2 adjusted for Model 1 and Townsend deprivation index, average total annual household income, physical activity, qualifications, BMI. Model 3 adjusted for Model 2 plus the history of high cholesterol, the history of hypertension.

Table S11. Association between baseline circulating Valine in relation to the prevalence of multiple cardiovascular diseases.

	Serum Valine levels（mmol/L）			
	Tertile1 (<0.203)	Tertile2 (0.203~0.238)	Tertile3 (>0.238)	
Ischemic stroke	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	*p*-trend
Model 1	Reference	1.346 (1.001~1.809)	1.213 (0.894~1.646)	0.233
Model 2	Reference	1.354 (1.004~1.827)	1.225 (0.898~1.672)	0.224
Model 3	Reference	1.353 (1.003~1.825)	1.226 (0.898~1.673)	0.223
Subarachnoid hemorrhage				
Model 1	Reference	2.348 (0.426~12.933)	3.244 (0.619~16.986)	0.159
Model 2	Reference	2.259 (0.403~12.654)	3.105 (0.579~16.661)	0.183
Model 3	Reference	2.219 (0.396~12.450)	3.068 (0.571~16.486)	0.188
Intracerebral hemorrhage				
Model 1	Reference	1.016 (0.462~2.237)	1.701 (0.835~3.467)	0.119
Model 2	Reference	1.003 (0.453~2.223)	1.677 (0.810~3.472)	0.133
Model 3	Reference	1.016 (0.458~2.252)	1.688 (0.815~3.495)	0.130
Coronary artery disease				
Model 1	Reference	1.064 (0.932~1.216)	1.183 (1.036~1.350)	0.012*
Model 2	Reference	1.002 (0.876~1.148)	1.099 (0.960~1.259)	0.161
Model 3	Reference	1.001 (0.874~1.147)	1.100 (0.960~1.260)	0.161
Myocardial infarction				
Model 1	Reference	1.109 (0.863~1.425)	1.217 (0.949~1.560)	0.121
Model 2	Reference	1.083 (0.841~1.394)	1.182 (0.918~1.523)	0.193
Model 3	Reference	1.080 (0.838~1.391)	1.181 (0.917~1.521)	0.195
Peripheral arterial disease				
Model 1	Reference	1.037 (0.793~1.356)	0.820 (0.615~1.092) ·	0.182
Model 2	Reference	1.068 (0.814~1.402)	0.858 (0.640~1.150)	0.312
Model 3	Reference	1.067 (0.812~1.402)	0.860 (0.641~1.154)	0.323
Heart failure				
Model 1	Reference	0.984 (0.820~1.180)	1.084 (0.904~1.299)	0.382
Model 2	Reference	0.880 (0.731~1.060)	0.950 (0.789~1.145)	0.621
Model 3	Reference	0.877 (0.728~1.057)	0.950 (0.788~1.146)	0.623
Angina				
Model 1	Reference	1.107 (0.935~1.312)	1.174 (0.992~1.390)	0.063
Model 2	Reference	1.054 (0.888~1.252)	1.105 (0.930~1.313)	0.257
Model 3	Reference	1.053 (0.887~1.250)	1.105 (0.929~1.313)	0.259

Model 1 adjusted for sex, age, smoking, drinking. Model 2 adjusted for Model 1 and Townsend deprivation index, average total annual household income, physical activity, qualifications, BMI. Model 3 adjusted for Model 2 plus the history of high cholesterol, the history of hypertension.

Table S12. Association between baseline circulating Leucine in relation to the prevalence of multiple cardiovascular diseases.

Serum Leucine levels（mmol/L）				
	Tertile1 (<0.096)	Tertile2 (0.096~0.119)	Tertile3 (>0.119)	
Ischemic stroke	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	*p*-trend
Model 1	Reference	1.155 (0.858~1.554)	1.123 (0.831~1.519)	0.463
Model 2	Reference	1.150 (0.854~1.551)	1.124 (0.830~1.523)	0.464
Model 3	Reference	1.144 (0.848~1.541)	1.118 (0.825~1.515)	0.485
Subarachnoid hemorrhage				
Model 1	Reference	2.458 (0.445~13.574)	3.452 (0.653~18.253)	0.140
Model 2	Reference	2.352 (0.423~13.082)	3.385 (0.635~18.061)	0.148
Model 3	Reference	2.330 (0.419~12.963)	3.388 (0.634~18.114)	0.148
Intracerebral hemorrhage				
Model 1	Reference	0.783 (0.348~1.761)	1.589 (0.791~3.193)	0.143
Model 2	Reference	0.780 (0.346~1.761)	1.577 (0.780~3.186)	0.150
Model 3	Reference	0.783 (0.347~1.766)	1.564 (0.774~3.159)	0.157
Coronary artery disease				
Model 1	Reference	1.052 (0.919~1.203)	1.187 (1.039~1.357)	0.011*
Model 2	Reference	1.007 (0.879~1.154)	1.137 (0.993~1.301)	0.057
Model 3	Reference	0.999 (0.872~1.145)	1.126 (0.983~1.290)	0.077
Myocardial infarction				
Model 1	Reference	1.106 (0.862~1.419)	1.104 (0.859~1.420)	0.449
Model 2	Reference	1.080 (0.841~1.388)	1.081 (0.839~1.393)	0.555
Model 3	Reference	1.076 (0.838~1.383)	1.079 (0.838~1.391)	0.564
Peripheral arterial disease				
Model 1	Reference	1.219 (0.925~1.607)	0.976 (0.730~1.305)	0.837
Model 2	Reference	1.233 (0.933~1.629)	1.006 (0.750~1.350)	0.995
Model 3	Reference	1.219 (0.922~1.612)	1.004 (0.747~1.347)	0.984
Heart failure				
Model 1	Reference	1.070 (0.894~1.281)	0.947 (0.786~1.141)	0.562
Model 2	Reference	0.995 (0.829~1.195)	0.881 (1.055~1.066)	0.188
Model 3	Reference	0.988 (0.823~1.187)	0.877 (0.726~1.061)	0.173
Angina				
Model 1	Reference	1.112 (0.937~1.322)	1.240 (1.045~1.471)	0.013*
Model 2	Reference	1.073 (0.902~1.276)	1.194 (1.005~1.419)	0.041*
Model 3	Reference	1.066 (0.896~1.268)	1.185 (0.998~1.408)	0.051

Model 1 adjusted for sex, age, smoking, drinking. Model 2 adjusted for Model 1 and Townsend deprivation index, average total annual household income, physical activity, qualifications, BMI. Model 3 adjusted for Model 2 plus the history of high cholesterol, the history of hypertension.

Table S13. Association between baseline circulating Isoleucine in relation to the prevalence of multiple cardiovascular diseases.

Serum Isoleucine levels（mmol/L）				
	Tertile1 (<0.046)	Tertile2 (0.046~0.060)	Tertile3 (>0.060)	
Ischemic stroke	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	Prevalence ratio (95% CI)	*p*-trend
Model 1	Reference	1.017 (0.749~1.381)	1.320 (0.986~1.766)	0.055
Model 2	Reference	1.013 (0.745~1.377)	1.323 (0.986~1.775)	0.054
Model 3	Reference	1.012 (0.744~1.376)	1.313 (0.979~1.763)	0.061
Subarachnoid hemorrhage				
Model 1	Reference	7.026 (0.841~58.713)	5.120 (0.566~46.325)	0.165
Model 2	Reference	6.906 (0.822~58.059)	4.979 (0.546~45.382)	0.182
Model 3	Reference	6.883 (0.818~57.915)	4.988 (0.546~45.581)	0.182
Intracerebral hemorrhage				
Model 1	Reference	0.866 (0.380~1.973)	1.849 (0.915~3.736)	0.058
Model 2	Reference	0.863 (0.378~1.974)	1.831 (0.900~3.725)	0.063
Model 3	Reference	0.865 (0.378~1.978)	1.805 (0.888~3.670)	0.069
Coronary artery disease				
Model 1	Reference	1.085 (0.950~1.239)	1.148 (1.006~1.311)	0.042*
Model 2	Reference	1.041 (0.910~1.191)	1.094 (0.957~1.252)	0.188
Model 3	Reference	1.039 (0.908~1.190)	1.080 (0.943~1.236)	0.265
Myocardial infarction				
Model 1	Reference	1.190 (0.928~1.526)	1.147 (0.892~1.476)	0.299
Model 2	Reference	1.163 (0.906~1.492)	1.122 (0.870~1.446)	0.393
Model 3	Reference	1.163 (0.906~1.493)	1.119 (0.868~1.443)	0.403
Peripheral arterial disease				
Model 1	Reference	1.106 (0.837~1.463)	1.085 (0.818~1.440)	0.580
Model 2	Reference	1.113 (0.840~1.475)	1.116 (0.838~1.485)	0.460
Model 3	Reference	1.113 (0.840~1.476)	1.108 (0.832~1.476)	0.491
Heart failure				
Model 1	Reference	1.126 (0.941~1.346)	0.979 (0.813~1.178)	0.813
Model 2	Reference	1.050 (0.875~1.260)	0.901 (0.746~1.089)	0.272
Model 3	Reference	1.048 (0.873~1.258)	0.894 (0.740~1.080)	0.237
Angina				
Model 1	Reference	1.166 (0.985~1.380)	1.120 (0.945~1.329)	0.204
Model 2	Reference	1.125 (0.950~1.333)	1.075 (0.905~1.278)	0.432
Model 3	Reference	1.124 (0.949~1.333)	1.064 (0.896~1.265)	0.507

Model 1 adjusted for sex, age, smoking, drinking. Model 2 adjusted for Model 1 and Townsend deprivation index, average total annual household income, physical activity, qualifications, BMI. Model 3 adjusted for Model 2 plus the history of high cholesterol, the history of hypertension.