

Supplementary Materials of

Causal effects of cardiovascular health on five epigenetic clocks

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Table S1. The 74 SNPs associated with the total cholesterol (TC) score ($p < 5E-8$)

CHR	SNP	A1	A2	MAF	BP	BETA	SE	p-value
1	rs10782936	A	G	0.08	92576349	0.0296	0.0052	1.03E-08
1	rs2495500	T	A	0.43	55021995	0.0176	0.0028	5.50E-10
1	rs3832016	C	CT	0.07	109275536	0.1020	0.0055	1.15E-75
1	rs486142	G	A	0.22	234712862	0.0219	0.0034	6.24E-11
1	rs557211	G	T	0.19	55048542	0.0282	0.0036	2.85E-15
1	rs565436	G	A	0.10	55058928	0.0258	0.0046	2.03E-08
1	rs6661533	G	A	0.27	25445224	-0.0215	0.0032	1.11E-11
1	rs867772	A	G	0.19	220799001	0.0282	0.0036	2.61E-15
1	rs998403	A	G	0.21	62462878	0.0424	0.0034	4.32E-35
2	rs10164853	G	A	0.31	157625480	0.0207	0.0030	6.94E-12
2	rs11687710	C	T	0.08	21148196	-0.0622	0.0051	2.54E-34
2	rs13384733	C	G	0.01	43726614	-0.0763	0.0130	4.07E-09
2	rs57825321	A	T	0.15	21024193	0.0834	0.0040	2.77E-98
2	rs6547692	G	A	0.49	27512105	-0.0372	0.0028	3.32E-40
2	rs6727888	T	C	0.27	62660749	0.0302	0.0031	6.67E-22
2	rs77401561	G	T	0.09	21311543	-0.0291	0.0049	2.86E-09
4	rs35502934	A	G	0.17	99547078	-0.0215	0.0038	1.13E-08
4	rs9994887	A	G	0.42	68671757	0.0163	0.0029	1.28E-08
5	rs28735189	C	T	0.27	156967082	0.0354	0.0032	4.14E-29
5	rs3064191	CTT-GTA	C	0.49	75343719	0.0410	0.0028	1.33E-48
6	rs144194669	C	G	0.01	160375171	-0.1032	0.0130	1.74E-15
6	rs2859078	G	A	0.04	32734672	-0.0455	0.0072	2.94E-10
6	rs73596816	A	G	0.05	160596331	-0.0636	0.0063	4.04E-24
6	rs9380151	C	T	0.11	30052051	0.0247	0.0045	3.26E-08
7	rs4917129	C	T	0.26	50283578	-0.0186	0.0032	5.07E-09
8	rs112784971	T	C	0.23	58493931	0.0274	0.0033	2.49E-16
8	rs2737246	C	G	0.31	115647351	0.0216	0.0031	1.31E-12
8	rs4921915	A	G	0.48	18414956	0.0195	0.0028	3.19E-12
8	rs6982502	C	T	0.44	125467120	-0.0301	0.0028	1.52E-26
9	rs11789603	T	C	0.06	104884738	-0.0434	0.0057	3.18E-14
9	rs13289095	T	G	0.08	128704210	0.0318	0.0052	1.13E-09
9	rs1883025	T	C	0.23	104902020	0.0491	0.0033	3.39E-50
9	rs2519093	T	C	0.18	133266456	-0.0525	0.0036	2.22E-47
9	rs2740480	G	A	0.42	104800276	0.0204	0.0028	6.35E-13
9	rs4149307	C	T	0.26	104827463	0.0328	0.0032	6.57E-25
9	rs79638982	G	T	0.22	127963460	-0.0236	0.0034	3.21E-12
10	rs2001737	T	C	0.39	112236289	0.0201	0.0029	2.68E-12
10	rs2297991	T	C	0.28	112153464	-0.0233	0.0031	6.77E-14
10	rs4919594	G	C	0.18	93063839	-0.0204	0.0037	3.00E-08
11	rs12718464	A	G	0.04	116836685	0.0463	0.0070	2.98E-11
11	rs174570	C	T	0.41	61829740	-0.0324	0.0029	1.10E-29
11	rs2342387	C	G	0.36	5671209	-0.0173	0.0030	6.41E-09
11	rs662799	G	A	0.27	116792991	-0.0580	0.0031	2.05E-76
11	rs7130876	G	A	0.14	48029443	-0.0263	0.0042	3.21E-10
11	rs72085277	T	TTCTG	0.36	126371957	-0.0179	0.0029	9.18E-10
12	rs10846744	G	C	0.42	124827879	0.0175	0.0028	7.17E-10
12	rs11066222	T	G	0.33	112263014	-0.0228	0.0033	4.03E-12
12	rs1568428	C	T	0.30	123254329	-0.0242	0.0031	2.17E-15
12	rs2373355	A	G	0.29	100528401	-0.0187	0.0031	1.47E-09
13	rs9567609	G	A	0.37	32371580	0.0173	0.0029	2.56E-09
14	rs2296651	A	G	0.10	69778476	0.0399	0.0048	7.71E-17
15	rs2070895	A	G	0.38	58431740	-0.0376	0.0029	4.25E-39
15	rs261291	C	T	0.41	58387979	-0.0365	0.0028	1.58E-37
15	rs6493996	T	C	0.19	58284097	0.0292	0.0036	3.73E-16
16	rs117891475	T	C	0.03	72113517	-0.1012	0.0086	5.17E-32
16	rs183130	T	C	0.16	56957451	-0.0414	0.0038	1.67E-27
16	rs201375854	A	AAGTT	0.20	72862845	0.0202	0.0035	1.09E-08
16	rs6499560	C	A	0.24	72113767	-0.0231	0.0033	1.71E-12
17	rs4794047	T	A	0.34	47685639	-0.0211	0.0030	1.17E-12

CHR	SNP	A1	A2	MAF	BP	BETA	SE	p-value
17	rs8077252	C	T	0.43	69088921	-0.0225	0.0029	3.74E-15
18	rs11082764	G	A	0.41	49593209	-0.0373	0.0029	5.44E-39
18	rs1943973	G	A	0.19	49653146	0.0313	0.0036	1.83E-18
19	rs141622900	A	G	0.07	44923535	0.1743	0.0053	3.34E-232
19	rs143020224	G	C	0.01	11076648	0.1056	0.0138	2.38E-14
19	rs148673297	A	ATTTTATTTTAT	0.06	11068052	-0.0491	0.0060	2.75E-16
19	rs2278426	T	C	0.26	11239812	0.0543	0.0032	8.47E-65
19	rs2738464	G	C	0.28	11131631	0.0523	0.0031	2.06E-62
19	rs4802607	C	G	0.41	49456107	0.0212	0.0029	2.25E-13
19	rs58542926	T	C	0.07	19268740	0.0310	0.0056	3.80E-08
19	rs6857	T	C	0.08	44888997	-0.0892	0.0051	2.56E-69
20	rs2328223	C	A	0.20	17865277	-0.0201	0.0035	1.01E-08
20	rs6124341	G	A	0.24	41325964	0.0272	0.0033	7.05E-17
20	rs6129629	G	A	0.45	40556638	-0.0172	0.0028	9.63E-10
22	rs2106430	T	C	0.11	30201146	-0.0246	0.0045	3.19E-08
1	rs10782936	A	G	0.08	92576349	0.0296	0.0052	1.03E-08

Table S2. The 37 SNPs associated with the fasting glucose (FG) score ($p < 5E-8$)

CHR	SNP	A1	A2	MAF	BP	BETA	SE	p-value
2	rs1402837	T	C	0.40	168900844	-0.0235	0.0021	4.49E-28
2	rs243021	G	A	0.34	60357684	0.0123	0.0022	2.83E-08
2	rs340515	G	T	0.44	44961231	-0.0247	0.0021	1.97E-31
2	rs6547692	G	A	0.49	27512105	0.0231	0.0021	4.27E-28
2	rs75536691	G	A	0.04	164525008	0.0320	0.0056	9.48E-09
2	rs78910115	T	C	0.47	172685102	0.0163	0.0021	8.95E-15
3	rs140691790	T	C	0.20	152700541	-0.0159	0.0026	1.90E-09
3	rs34782298	A	G	0.24	185803208	-0.0159	0.0025	1.18E-10
3	rs7639266	C	T	0.30	23432840	0.0139	0.0023	1.24E-09
4	rs72501962	T	A	0.34	1252250	0.0162	0.0022	2.93E-13
5	rs465002	C	T	0.47	56512648	0.0124	0.0021	3.28E-09
6	rs35261542	A	C	0.35	20675561	-0.0318	0.0022	4.52E-47
6	rs3765467	A	G	0.24	39065819	0.0148	0.0025	2.04E-09
7	rs17168486	T	C	0.48	14858657	-0.0213	0.0021	2.84E-24
7	rs2191996	G	C	0.28	15117604	0.0128	0.0023	4.37E-08
7	rs2908290	A	G	0.46	44176538	-0.0180	0.0021	1.43E-17
7	rs2971670	T	C	0.19	44186502	-0.0282	0.0027	3.14E-26
7	rs6967891	T	C	0.31	15025449	0.0242	0.0023	1.55E-26
7	rs7778167	A	G	0.13	128211575	-0.0236	0.0032	1.45E-13
8	rs13262861	A	C	0.13	41651058	0.0192	0.0032	1.36E-09
8	rs35859536	T	C	0.46	117179236	0.0275	0.0021	3.89E-39
9	rs10811660	A	G	0.41	22134069	0.0304	0.0021	2.76E-46
9	rs16920619	C	T	0.27	590735	-0.0159	0.0024	2.05E-11
9	rs4237150	C	G	0.45	4290085	-0.0214	0.0021	2.52E-24
10	rs10882106	C	T	0.19	92720577	-0.0187	0.0027	2.40E-12
10	rs10906100	C	T	0.44	12218020	0.0191	0.0021	1.05E-19
10	rs7923442	G	A	0.27	26208775	0.0131	0.0024	2.85E-08
11	rs10830963	G	C	0.43	92975544	-0.0312	0.0021	1.66E-49
11	rs17244499	G	A	0.06	72918901	0.0277	0.0043	1.91E-10
11	rs2283228	C	A	0.36	2828300	0.0307	0.0022	5.82E-45
11	rs231361	G	A	0.19	2670270	0.0173	0.0027	1.18E-10
11	rs28456	A	G	0.42	61822009	-0.0154	0.0021	6.98E-13
13	rs2067296	AAGAC	A	0.22	32979946	-0.0197	0.0025	1.07E-14
15	rs16968809	C	T	0.42	77379776	-0.0128	0.0021	1.59E-09
15	rs8037894	C	G	0.34	62102065	0.0201	0.0022	9.76E-20
16	rs8063057	C	T	0.12	53778521	-0.0206	0.0032	9.00E-11
20	rs11477526	A	AT	0.13	22574444	0.0226	0.0031	2.44E-13

Table S3. The 31 SNPs associated with the blood pressure (BP) score ($p < 5E-8$)

CHR	SNP	A1	A2	MAF	BP	BETA	SE	p-value
2	chr2:61296261_AAAAT_A	AAAAT	A	0.37	61296261	0.0174	0.0029	2.00E-09
2	rs10200835	C	A	0.18	161831529	0.0205	0.0036	1.84E-08
2	rs35021474	G	C	0.26	26693976	0.0259	0.0032	9.86E-16
2	rs6547692	G	A	0.49	27512105	-0.0159	0.0028	1.53E-08
2	rs73029563	C	G	0.43	164151656	0.0367	0.0029	5.93E-38
2	rs77559470	G	T	0.46	163587846	0.0166	0.0029	7.42E-09
3	rs79991967	G	GT	0.27	53527269	-0.0219	0.0032	5.96E-12
4	rs16998073	T	A	0.42	80263187	-0.0473	0.0028	7.48E-62
4	rs3215177	G	GA	0.31	120268174	0.0177	0.0031	6.62E-09
4	rs6817516	A	C	0.39	110434534	-0.0208	0.0029	5.51E-13
5	rs1036190	G	A	0.27	149008049	0.0178	0.0032	1.82E-08
5	rs1173727	T	C	0.33	32830415	0.0204	0.0030	7.44E-12
5	rs17149944	G	A	0.50	123120403	0.0257	0.0028	8.77E-20
6	rs7692	A	C	0.30	43336269	-0.0216	0.0031	1.64E-12
7	rs13243033	T	C	0.38	27208754	0.0177	0.0029	1.47E-09
8	rs17054793	T	C	0.39	26038894	-0.0192	0.0029	5.33E-11
8	rs62525059	A	G	0.30	142901545	0.0170	0.0031	3.55E-08
10	chr10:94266427_CA_C	CA	C	0.45	94266427	-0.0198	0.0028	2.26E-12
10	rs11191548	C	T	0.29	103086421	0.0298	0.0031	3.74E-22
10	rs7075062	C	T	0.14	113967473	-0.0253	0.0041	4.64E-10
11	rs11230729	T	C	0.41	61511446	0.0208	0.0029	7.52E-13
11	rs415895	G	C	0.42	9748015	-0.0171	0.0028	1.80E-09
11	rs4754698	C	G	0.48	100761177	0.0190	0.0028	1.53E-11
11	rs7938342	T	A	0.22	1866576	0.0233	0.0034	5.54E-12
12	rs10850432	T	C	0.06	109593246	-0.0374	0.0062	1.23E-09
12	rs12579302	G	A	0.31	89656726	0.0341	0.0030	3.03E-29
12	rs2579290	G	A	0.44	20017604	-0.0172	0.0028	1.50E-09
15	rs1378940	A	C	0.18	74791153	0.0279	0.0037	3.61E-14
17	rs28406364	T	C	0.24	49377145	-0.0194	0.0033	5.36E-09
17	rs9905385	A	G	0.28	61420889	0.0193	0.0031	6.36E-10
20	rs6108787	T	G	0.45	10986566	0.0159	0.0028	1.91E-08

Table S4. The 34 SNPs associated with the BMI score ($p < 5E-8$)

CHR	SNP	A1	A2	MAF	BP	BETA	SE	p-value
1	rs543874	G	A	0.15	177920345	-0.0349	0.0044	4.03E-15
2	rs5829949	T	TC	0.41	24913321	-0.0263	0.0033	7.95E-16
2	rs71417307	G	T	0.17	104138509	-0.0237	0.0043	3.82E-08
2	rs7576224	G	A	0.25	51065295	0.0218	0.0038	7.27E-09
2	rs7585056	A	G	0.07	631528	0.0576	0.0062	1.94E-20
3	rs1543683	T	G	0.09	61668052	-0.0370	0.0056	3.88E-11
4	rs13130484	T	C	0.26	45173674	-0.0275	0.0036	4.58E-14
4	rs6839738	T	C	0.09	151682691	-0.0363	0.0055	4.75E-11
5	rs10063803	A	C	0.44	177240326	0.0179	0.0032	3.52E-08
5	rs34215404	C	T	0.40	96526002	-0.0233	0.0033	1.28E-12
6	rs10807036	G	A	0.09	28638620	0.0403	0.0056	7.80E-13
6	rs2744475	G	C	0.35	50817167	-0.0298	0.0034	7.83E-19
6	rs67131976	T	C	0.35	20686647	0.0191	0.0034	1.34E-08
9	rs10816778	T	C	0.24	109180729	0.0209	0.0038	2.87E-08
9	rs10993127	A	G	0.39	94266397	0.0185	0.0033	1.67E-08
9	rs5900713	C	CT	0.44	126636057	0.0219	0.0032	1.39E-11
10	rs11191531	C	G	0.29	103047141	-0.0224	0.0035	1.97E-10
10	rs9415676	G	A	0.34	63250866	0.0191	0.0034	1.89E-08
11	rs11030099	A	C	0.49	27656036	0.0177	0.0032	3.04E-08
12	rs7132908	A	G	0.21	49869365	-0.0219	0.0039	2.88E-08
13	rs4477562	T	C	0.24	53530833	-0.0204	0.0037	4.50E-08
14	rs57933514	A	G	0.07	35560917	0.0432	0.0064	1.19E-11
15	rs144047837	T	C	0.19	62084197	0.0266	0.0041	8.52E-11
15	rs6493202	A	G	0.33	46249093	-0.0202	0.0034	3.71E-09
15	rs80032853	CA	C	0.42	67835505	-0.0229	0.0033	3.12E-12
16	rs12599169	T	C	0.27	20237087	0.0300	0.0036	1.67E-16
16	rs1421085	C	T	0.13	53767042	-0.0678	0.0048	1.29E-45
16	rs2238435	G	C	0.32	3964281	-0.0195	0.0034	1.31E-08
17	rs7223643	A	G	0.34	67834166	0.0190	0.0034	2.20E-08
18	rs17066842	A	G	0.02	60373391	0.0707	0.0105	1.81E-11
18	rs6567160	C	T	0.18	60161902	-0.0419	0.0042	6.28E-24
19	rs2302382	A	C	0.06	45669311	-0.0434	0.0070	5.43E-10
19	rs4808136	A	G	0.23	18508057	-0.0218	0.0038	7.48E-09
21	rs13053080	T	C	0.43	38940283	-0.0228	0.0032	1.98E-12

Table S5. The SNP associated with the smoking (SMK) score ($p < 5E-8$)

CHR	SNP	A1	A2	MAF	BP	BETA	SE	p-value
12	rs11066132	T	C	0.28	112030402	-0.0238	0.0034	3.35E-12

Note: CHR: chromosome; SNP: single-nucleotide polymorphism; MAF: minor allele frequency; BP: base pair.

Table S6. Check for the MR assumption (2)

P-value in each cell denotes the correlation between wGRS and the confounding factor	Chronological age	SEX	Educational attainment	Drinking status
CVH-wGRS (15 SNPs)	0.0607	0.0176	0.7126	0.2292
CVH-wGRS (14 SNPs) (Checking assumption (2), we removed rs13306194 from the original 15 SNPs)	0.1258	0.0799	0.4984	0.2423
CVH-wGRS (13 SNPs) (Checking assumption (3), we removed rs662799 from the abovementioned 14 SNPs)	0.2098	0.0688	0.5149	0.3131
TC-wGRS (74 SNPs)	0.4193	0.0815	0.4703	0.4111
TC-wGRS (68 SNPs) (Checking assumption (3), we removed rs35502934, rs6982502, rs2297991, rs662799, rs2278426, and rs2106430 from the original 74 SNPs)	0.5222	0.0691	0.4444	0.3574
FG-wGRS (37 SNPs)	0.0130	0.2150	0.4360	0.1837
FG-wGRS (33 SNPs) (Checking assumption (2), we removed rs6547692, rs1402837, rs3765467, and rs8063057 from the original 37 SNPs)	0.0640	0.1254	0.2008	0.1683
FG-wGRS (32 SNPs) (Checking assumption (3), we removed rs6967891 from the abovementioned 33 SNPs)	0.0650	0.1540	0.1275	0.2484
BP-wGRS (31 SNPs)	0.6433	0.4017	0.7256	0.9667
BMI-wGRS (34 SNPs)	0.1421	0.0628	0.0071	0.7884
BMI-wGRS (32 SNPs) (Checking assumption (2), we removed rs67131976 and rs1421085 from the original 34 SNPs)	0.3905	0.1139	0.0749	0.5031
BMI-wGRS (28 SNPs) (Checking assumption (3), we removed rs4477562, rs6567160, rs17066842, and rs4808136 from the abovementioned 32 SNPs)	0.5023	0.1391	0.2520	0.9761

Note: wGRS: the weighted genetic risk score; CVH: cardiovascular health; TC: total cholesterol; FG: fasting glucose; BP: blood pressure; BMI: body mass index; SMK: smoking status; DS: diet type; Educational attainment: 1 represented no formal education and illiterate; 2 represented self-study and literate; 3 represented primary school; 4 represented junior high school; 5 represented senior high school; 6 represented undergraduate; 7 represented graduate or above; Bold fonts represent violations of the MR assumption (2).

The MR assumption (2) (the independence assumption) was tested using a two-sample t-test for known categorical confounders (sex and drinking status) and a Pearson correlation test for known continuous confounders (chronological age and educational attainment).

Table S7. Check for the MR assumption (3)

Exposure	Outcome	IV	Beta	SE	P-value
CVH Score	HannumEAA	CVH-wGRS (14 SNPs) (14 SNPs remaining through assumption (2))	-0.3204	0.5160	0.5347
CVH Score	IEAA	CVH-wGRS (14 SNPs) (14 SNPs remaining through assumption (2))	-0.0172	0.5262	0.9740
CVH Score	PhenoEAA	CVH-wGRS (14 SNPs) (14 SNPs remaining through assumption (2))	0.1359	0.6936	0.87447
CVH Score	GrimEAA	CVH-wGRS (14 SNPs) (14 SNPs remaining through assumption (2))	-0.4686	0.4362	0.2828
CVH Score	DNAmPAI-1	CVH-wGRS (14 SNPs) (14 SNPs remaining through assumption (2))	-0.2356	0.1195	0.0488
CVH Score	DNAmPAI-1	CVH-wGRS (13 SNPs) (rs662799 removed from the abovementioned 14 SNPs)	-0.1119	0.1262	0.3755
CVH Score	DunedinPACE	CVH-wGRS (14 SNPs) (14 SNPs remaining through assumption (2))	-0.0024	0.0143	0.8695
TC Score	HannumEAA	TC-wGRS (74 SNPs)	-0.0144	0.4626	0.9751
TC Score	IEAA	TC-wGRS (74 SNPs)	-0.3069	0.4662	0.5104
TC Score	PhenoEAA	TC-wGRS (74 SNPs)	-0.0728	0.6193	0.9064
TC Score	GrimEAA	TC-wGRS (74 SNPs)	-0.1285	0.3988	0.7473
TC Score	DNAmPAI-1	TC-wGRS (74 SNPs)	-0.3262	0.1104	0.0032
TC Score	DNAmPAI-1	TC-wGRS (68 SNPs) (rs35502934, rs6982502, rs2297991, rs662799, rs2278426, rs2106430 removed from the original 74 SNPs)	-0.2190	0.1149	0.0568
TC Score	DunedinPACE	TC-wGRS (74 SNPs)	0.0001	0.0131	0.9949
FG Score	HannumEAA	FG-wGRS (33 SNPs) (33 SNPs remaining through assumption (2))	0.9327	1.0050	0.3535
FG Score	IEAA	FG-wGRS (33 SNPs) (33 SNPs remaining through assumption (2))	1.0580	1.0220	0.3007
FG Score	PhenoEAA	FG-wGRS (33 SNPs) (33 SNPs remaining through assumption (2))	0.4450	1.3327	0.7385

Exposure	Outcome	IV	Beta	SE	P-value
FG Score	GrimEAA	FG-wGRS (33 SNPs) (33 SNPs remaining through assumption (2))	0.9434	0.8648	0.2754
FG Score	DNAmPAI-1	FG-wGRS (33 SNPs) (33 SNPs remaining through assumption (2))	0.4862	0.2383	0.0414
FG Score	DNAmPAI-1	FG-wGRS (32 SNPs) (rs6967891 removed from the abovementioned 33 SNPs)	0.3826	0.2456	0.1194
FG Score	DunedinPACE	FG-wGRS (33 SNPs) (33 SNPs remaining through assumption (2))	0.0111	0.0280	0.6920
BP Score	HannumEAA	BP-wGRS (31 SNPs)	0.2874	0.9055	0.7510
BP Score	IEAA	BP-wGRS (31 SNPs)	0.0941	0.9243	0.9189
BP Score	PhenoEAA	BP-wGRS (31 SNPs)	0.0011	1.2244	0.9993
BP Score	GrimEAA	BP-wGRS (31 SNPs)	0.0028	0.8024	0.9972
BP Score	DNAmPAI-1	BP-wGRS (31 SNPs)	0.1455	0.2198	0.5080
BP Score	DunedinPACE	BP-wGRS (31 SNPs)	0.0285	0.0260	0.2743
BMI Score	HannumEAA	BMI-wGRS (32 SNPs) (32 SNPs remaining through assumption (2))	-2.1039	0.8761	0.0164
BMI Score	HannumEAA	BMI-wGRS (28 SNPs) (rs4477562, rs6567160, rs17066842, rs4808136 removed from the abovementioned 32 SNPs)	-1.8540	0.9577	0.0530
BMI Score	IEAA	BMI-wGRS (32 SNPs) (32 SNPs remaining through assumption (2))	-0.5509	0.8896	0.5358
BMI Score	PhenoEAA	BMI-wGRS (32 SNPs) (32 SNPs remaining through assumption (2))	-1.9393	1.1783	0.1000
BMI Score	GrimEAA	BMI-wGRS (32 SNPs) (32 SNPs remaining through assumption (2))	-1.2663	0.7622	0.0968
BMI Score	DNAmPAI-1	BMI-wGRS (32 SNPs) (32 SNPs remaining through assumption (2))	0.0403	0.2059	0.8447
BMI Score	DunedinPACE	BMI-wGRS (32 SNPs) (32 SNPs remaining through assumption (2))	-0.0473	0.0244	0.0529

Note: wGRS: the weighted genetic risk score; CVH score: cardiovascular health score; TC score: ideal total cholesterol score; FG score: ideal fasting glucose score; BP score: ideal blood pressure score; BMI score: ideal body mass index score; SMK score: ideal smoking status score; DS score: ideal diet type score; HannumEAA: the Hannum clock's measurement of epigenetic-age acceleration; IEAA: the Horvath's clock's measurement of

Exposure	Outcome	IV	Beta	SE	P-value
<p>epigenetic-age acceleration; PhenoEAA: the PhenoAge clock's measurement of epigenetic-age acceleration; GrimEAA: the GrimAge clock's measurement of epigenetic-age acceleration; DNAm PAI-1: the DNA methylation proxies for plasminogen activator inhibitor-1; Bold fonts represent violations of the MR assumption (3).</p> <p>The MR assumption (3) (the exclusion restriction assumption) was tested by regressing the outcome (e.g., HannumEAA) on IV (e.g., CVH-wGRS) while adjusting for the exposure (e.g., the CVH score), chronological age, sex, drinking status, and educational attainment. Beta is the regression coefficient of IV, and P-value is the statistical significance of Beta.</p>					

Table S8. The p-values of testing the associations between sex, DNAmPAI-1, and the 15 SNPs constructing CVH-wGRS originally.

SNP	Sex	DNAmPAI-1
rs629301	0.7840 ¹	0.9950 ²
rs13306194	0.0091	0.3799
rs4709395	0.6594	0.4745
rs73596816	0.2813	0.0457
rs2908286	0.9810	0.3694
rs2519093	0.8540	0.4497
rs72643557	0.7384	0.9384
rs662799	0.8661	0.0008
rs10550903	0.5722	0.1375
rs72805612	0.0694	0.0292
rs11082764	0.1695	0.5024
rs3745683	0.4366	0.0743
rs12972970	0.2846	0.0732
rs141622900	0.4149	0.4596
rs7246757	0.4331	0.9103
<i>Note: Bold fonts represent SNPs that were eliminated from CVH-wGRS.</i>		

¹ 0.7840 was the p-value of Cochran-Armitage test between rs629301 and sex.

² 0.9950 was the p-value of regressing DNAmPAI-1 on rs629301 while adjusting for the CVH score, chronological age, sex, drinking status, and educational attainment.

Table S9. The p-values of testing the associations between DNAmPAI1 and the 74 SNPs constructing TC-wGRS originally.

SNP	DNAmPAI1
rs6661533	0.4736 ¹
rs2495500	0.8410
rs557211	0.1984
rs565436	0.7776
rs998403	0.4603
rs10782936	0.7207
rs3832016	0.7975
rs867772	0.6294
rs486142	0.0617
rs57825321	0.2295
rs11687710	0.2119
rs77401561	0.6362
rs6547692	0.0347
rs13384733	0.5119
rs6727888	0.7637
rs10164853	0.5055
rs9994887	0.0277
rs35502934	0.0032
rs3064191	0.8089
rs28735189	0.6944
rs9380151	0.1005
rs2859078	0.9155
rs144194669	0.4758
rs73596816	0.0950
rs4917129	0.2849
rs4921915	0.8831
rs112784971	0.0237
rs2737246	0.5376
rs6982502	0.0114
rs2740480	0.1861
rs4149307	0.7192
rs11789603	0.2609
rs1883025	0.6471
rs79638982	0.5756
rs13289095	0.2256
rs2519093	0.4577
rs4919594	0.5153
rs2297991	0.0158
rs2001737	0.1471
rs2342387	0.6010
rs7130876	0.7078
rs174570	0.2309
rs662799	0.0024
rs12718464	0.3767
rs72085277	0.4481
rs2373355	0.5535
rs11066222	0.8459
rs1568428	0.3789
rs10846744	0.2359
rs9567609	0.2694
rs2296651	0.5084
rs6493996	0.3204
rs261291	0.2852
rs2070895	0.1595
rs183130	0.2676
rs117891475	0.1309

SNP	DNAmPAI1
rs6499560	0.8684
rs201375854	0.7441
rs4794047	0.4340
rs8077252	0.3726
rs11082764	0.5458
rs1943973	0.8475
rs148673297	0.7095
rs143020224	0.5484
rs2738464	0.1565
rs2278426	0.0165
rs58542926	0.4878
rs6857	0.1320
rs141622900	0.1798
rs4802607	0.4943
rs2328223	0.6949
rs6129629	0.0919
rs6124341	0.3345
rs2106430	0.0114
Note: Bold fonts represent SNPs that were eliminated from TC-wGRS.	

¹ 0.4736 was the p-value of regressing DNAmPAI-1 on rs6661533 while adjusting for the TC score, chronological age, sex, drinking status, and educational attainment.

Table S10. The p-values of testing the associations between chronological age, DNAmPAI-1 and the 37 SNPs constructing FG-wGRS originally.

SNP	Chronological age	DNAmPAI-1
rs6547692	0.0099 ¹	0.0071 ²
rs340515	0.8566	0.5350
rs243021	0.2702	0.8509
rs75536691	0.5160	0.7453
rs1402837	0.0400	0.4783
rs78910115	0.1217	0.1840
rs7639266	0.0959	0.3239
rs140691790	0.9463	0.6520
rs34782298	0.5807	0.2183
rs72501962	0.3174	0.0955
rs465002	0.3997	0.8333
rs35261542	0.4578	0.3361
rs3765467	0.0499	0.4524
rs17168486	0.2660	0.2489
rs6967891	0.3650	0.0248
rs2191996	0.2733	0.2134
rs2908290	0.7282	0.8178
rs2971670	0.5555	0.1613
rs7778167	0.4459	0.1460
rs13262861	0.7318	0.7238
rs35859536	0.4378	0.8643
rs16920619	0.6637	0.3293
rs4237150	0.0530	0.5662
rs10811660	0.9275	0.1072
rs10906100	0.0838	0.9903
rs7923442	0.4945	0.6842
rs10882106	0.1264	0.5409
rs231361	0.0700	0.6726
rs2283228	0.4070	0.4954
rs28456	0.7820	0.2271
rs17244499	0.6308	0.5887
rs10830963	0.8579	0.2326
rs2067296	0.5662	0.9240
rs8037894	0.9532	0.4764
rs16968809	0.0886	0.9365
rs8063057	0.0370	0.0401
rs11477526	0.5672	0.4892

Note: Bold fonts represent SNPs that were eliminated from FG-wGRS.

¹ 0.0099 was the p-value of regressing chronological age on rs6547692.

² 0.0071 was the p-value of regressing DNAmPAI-1 on rs6547692 while adjusting for the FG score, chronological age, sex, drinking status, and educational attainment.

Table S11. The p-values of testing the associations between educational attainment, HannumEAA and 34 SNPs constructing BMI-wGRS originally.

SNP	Educational attainment	HannumEAA
rs543874	0.9857 ¹	0.2120 ²
rs7585056	0.1200	0.3179
rs5829949	0.0644	0.1007
rs7576224	0.8862	0.7733
rs71417307	0.7315	0.6229
rs1543683	0.4439	0.4787
rs13130484	0.9155	0.8828
rs6839738	0.3273	0.1498
rs34215404	0.4745	0.7527
rs10063803	0.9817	0.1677
rs67131976	0.0192	0.1505
rs10807036	0.6567	0.4529
rs2744475	0.8881	0.7310
rs10993127	0.8944	0.1001
rs10816778	0.3383	0.5754
rs5900713	0.6132	0.4381
rs9415676	0.1877	0.8365
rs11191531	0.4074	0.9805
rs11030099	0.6160	0.7722
rs7132908	0.6575	0.3105
rs4477562	0.9471	0.0264
rs57933514	0.1314	0.3505
rs6493202	0.0769	0.1058
rs144047837	0.5458	0.8307
rs80032853	0.1137	0.1836
rs2238435	0.2093	0.6287
rs12599169	0.2710	0.2098
rs1421085	0.0246	0.2084
rs7223643	0.4596	0.6985
rs6567160	0.1846	0.0402
rs17066842	0.9762	0.0430
rs4808136	0.2729	0.0047
rs2302382	0.9737	0.1456
rs13053080	0.8184	0.9204

Note: Bold fonts represent SNPs that were eliminated from BMI-wGRS.

¹ 0.9857 was the p-value of regressing educational attainment on rs543874.

² 0.2120 was the p-value of regressing HannumEAA on rs543874 while adjusting for the BMI score, chronological age, sex, drinking status, and educational attainment.

Table S12. Test for heterogeneity and pleiotropy in the causal inference of the CVH score on epigenetic markers in EUR

	Pleiotropy test		Heterogeneity test	
	MR-Egger intercept	p-value	Q statistic	p-value
CVH score				
HannumEAA (years)	-0.412	0.304	3.927	0.951
IEAA (years)	-0.003	0.930	9.582	0.478
PhenoEAA (years)	-0.050	0.359	11.415	0.326
GrimEAA (years)	0.011	0.840	17.804	0.058
DNAmPAI-1 (pg/ml)	0.090	0.520	11.678	0.307
CVH score (without CVD)				
HannumEAA (years)	-0.038	0.286	4.059	0.945
IEAA (years)	-0.004	0.907	9.590	0.477
PhenoEAA (years)	-0.050	0.306	11.657	0.310
GrimEAA (years)	0.004	0.941	17.893	0.057
DNAmPAI-1 (pg/ml)	0.061	0.621	11.707	0.305
<i>Note: IEAA: Horvath's intrinsic epigenetic age acceleration; CVH: cardiovascular health; CVD: cardiovascular disease; Bold font indicates the possible presence of heterogeneity or pleiotropy.</i>				

Table S13. Definitions of the CVH factors in the two-sample MR analysis

CVH factor	GWAS ID	Sample size	Unit	P threshold	Population	Authors
Clinical Factor						
Diastolic blood pressure	ieu-b-39	757,601	mm Hg	$P < 5 \times 10^{-8}$	European	Evangelou, E et al [1]
Systolic blood pressure	ieu-b-38	757,601	mm Hg	$P < 5 \times 10^{-8}$	European	Evangelou, E et al [1]
Total cholesterol	ieu-a-301	187,365	SD (mg/dL)	$P < 5 \times 10^{-8}$	European (82%), African (9%), Asian (9%)	Willer CJ et al [2]
Fasting glucose	ebi-a-GCST90002232	200,622	SD (1mmol/L)	$P < 5 \times 10^{-8}$	European	Chen J et al [3]
Lifestyle Factor						
Body mass index	ieu-b-40	681,275	SD (kg/m ²)	$P < 5 \times 10^{-8}$	European	Yengo, L et al [4]
Smoking status						
Current	ukb-a-225	case 33,928 control 302,096	logOR	$P < 5 \times 10^{-8}$	European	Neale lab ¹
Previous	ukb-a-224	case 118,419 control 217,605	logOR	$P < 5 \times 10^{-8}$	European	Neale lab ¹
Never	ukb-d-20116_0	case 195,068 control 164,638	logOR	$P < 5 \times 10^{-8}$	European	Neale lab ¹
Amount of smoking						
Packyears	ukb-b-10831	142,387	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Number of days/week of physical activity 10+ minutes						
Moderate	ukb-b-4710	440,266	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Vigorous	ukb-b-151	440,512	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Types of physical activity in last 4 weeks						
Heavy DIY	ukb-b-13184	case 197,006 control 263,370	logOR	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Light DIY	ukb-b-11495	case 236,244 control 224,132	logOR	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Strenuous sports	ukb-b-7663	case 47,468 control 412,908	logOR	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Walking for pleasure	ukb-b-7337	case 329,755 control 130,621	logOR	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Other physical activity	ukb-b-8764	case 222,470 control 237,906	logOR	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
No physical activity	ukb-b-15869	case 28,040 control 432,336	logOR	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Food intake						
Dried fruit	ukb-b-16576	421,764	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Fresh fruit	ukb-b-3881	446,462	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Salad	ukb-b-1996	435,435	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Cooked vegetable	ukb-b-8089	448,651	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Oily fish	ukb-b-2209	460,443	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Non oily fish	ukb-b-17627	460,800	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Cereal	ukb-b-15926	441,640	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Bacon	ukb-b-4414	64,949	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
Processed meat	ukb-b-6324	461,981	SD	$P < 5 \times 10^{-8}$	European	Ben Elsworth et al [5]
<p><i>Note:</i> Heavy DIY = e.g.: weeding, lawn mowing, carpentry, digging; Light DIY = e.g.: pruning, watering the lawn; Walking = Walking for pleasure (not as a means of transport); Other PA = Other physical activity, e.g.: swimming, cycling, keep fit, bowling; No PA = None of the above physical activity.</p> <p>¹ Rapid GWAS of thousands of phenotypes for 337.000 samples in the UK Biobank — Neale lab</p>						

Table S14. EUR MR analysis result: the causal effects of the CVH factors on HannumEAA

CVH Factor	No. of SNPs	IVW				Weighted Median			MR-Egger			MR-PRESSO			
		F	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	No. of outliers	β (SE), years	p Value	q Value
Clinical Factor															
Total cholesterol (1SD)	117	125	-0.083 (0.073)	2.51E-01	5.44E-01	-0.060 (0.114)	5.96E-01	8.41E-01	-0.112 (0.120)	3.53E-01	8.61E-01	2	-0.051 (0.065)	4.42E-01	7.12E-01
Fasting glucose (1SD)	85	109	-0.191 (0.200)	3.40E-01	6.31E-01	0.515 (0.319)	1.06E-01	5.60E-01	0.951 (0.372)	1.23E-02	3.21E-01	0	0.191 (0.200)	3.42E-01	7.12E-01
DBP (1mmHg)	793	65	0.002 (0.009)	8.58E-01	9.09E-01	-0.017 (0.013)	1.88E-01	6.94E-01	-0.020 (0.022)	3.59E-01	8.61E-01	3	0.004 (0.008)	6.24E-01	8.14E-01
SBP (1mmHg)	755	64	0.001 (0.005)	8.26E-01	9.09E-01	-0.005 (0.008)	5.05E-01	8.41E-01	-0.013 (0.013)	3.38E-01	8.61E-01	5	-0.001 (0.005)	8.73E-01	9.09E-01
Lifestyle Factor															
BMI (1SD)	941	58	0.200 (0.079)	1.12E-02	2.92E-01	0.212 (0.128)	9.79E-02	5.60E-01	0.462 (0.243)	5.77E-02	7.50E-03	2	0.184 (0.078)	1.82E-02	2.28E-01
Smoking status															
Current	16	40	2.016 (1.630)	2.16E-01	5.28E-01	3.481 (2.313)	1.32E-01	5.73E-01	-5.379 (7.309)	4.74E-01	8.61E-01	0	2.016 (1.517)	2.04E-01	5.39E-01
Previous	20	38	-0.335 (1.004)	7.38E-01	9.09E-01	0.222 (1.322)	8.67E-01	9.39E-01	2.271 (5.885)	7.04E-01	8.61E-01	0	-0.335 (1.004)	7.42E-01	8.43E-01
Never	76	41	0.205 (0.488)	6.74E-01	9.09E-01	0.162 (0.693)	8.15E-01	9.22E-01	1.425 (2.161)	5.12E-01	8.61E-01	0	0.205 (0.488)	6.75E-01	8.14E-01
Amount of smoking															
Packyears (1SD)	11	73	-0.067 (0.361)	8.53E-01	9.09E-01	-0.195 (0.388)	6.15E-01	8.41E-01	-0.464 (0.870)	6.70E-01	8.61E-01	0	-0.067 (0.361)	8.56E-01	9.09E-01
Number of days/week of physical activity 10+ minutes															
Moderate (1SD)	16	36	-0.252 (0.278)	3.65E-01	6.33E-01	-0.440 (0.364)	2.27E-01	6.94E-01	-2.292 (1.737)	2.08E-01	8.61E-01	0	-0.252 (0.278)	3.80E-01	7.12E-01
Vigorous (1SD)	11	40	-0.494 (0.350)	1.59E-01	4.86E-01	-0.485 (0.430)	2.59E-01	6.94E-01	-1.070 (2.798)	7.11E-01	8.61E-01	0	-0.494 (0.222)	5.03E-02	3.14E-01
Types of physical activity in last 4 weeks															
Heavy DIY	19	35	1.664 (1.170)	1.55E-01	4.86E-01	2.522 (1.567)	1.08E-01	5.60E-01	-3.771 (7.623)	6.27E-01	8.61E-01	0	1.664 (1.014)	1.18E-01	3.86E-01
Light DIY	12	41	-0.930 (1.599)	5.61E-01	8.58E-01	-1.738 (1.840)	3.45E-01	7.55E-01	3.759 (6.498)	5.76E-01	8.61E-01	0	-0.930 (1.599)	5.73E-01	7.95E-01
Strenuous sports	6	39	-7.449 (5.405)	1.68E-01	4.86E-01	-5.039 (4.539)	2.67E-01	6.94E-01	-9.138 (28.190)	7.62E-01	8.61E-01	1	-2.745 (3.169)	4.35E-01	7.12E-01
Walking	21	34	-1.196 (1.215)	3.25E-01	6.31E-01	-1.596 (1.703)	3.49E-01	7.55E-01	-7.121 (12.611)	5.79E-01	8.61E-01	0	-1.196 (0.982)	2.37E-01	5.39E-01
Other physical activity	14	38	-1.959 (1.239)	1.14E-01	4.86E-01	-3.043 (1.733)	7.91E-02	5.60E-01	-17.217 (9.376)	9.12E-02	7.90E-01	0	-1.959 (1.155)	1.14E-01	3.86E-01
No physical activity	5	33	-18.028 (11.960)	1.32E-01	4.86E-01	-13.894 (7.124)	5.11E-02	5.60E-01	-144.64 (149.341)	4.99E-01	8.61E-01	2	-14.010 (0.154)	1.21E-04	3.04E-03
Food intake															
Dried fruit (1SD)	43	42	-0.595 (0.489)	2.33E-01	5.28E-01	-0.068 (0.620)	9.13E-01	9.49E-01	0.002 (2.239)	9.99E-01	9.99E-01	0	-0.595 (0.489)	2.30E-01	5.39E-01
Fresh fruit (1SD)	56	45	0.797 (0.487)	1.02E-01	4.86E-01	0.579 (0.748)	4.39E-01	8.41E-01	0.936 (1.814)	6.08E-01	8.61E-01	0	0.797 (0.468)	9.39E-02	3.86E-01
Salad (1SD)	17	37	-0.199 (1.252)	8.74E-01	9.09E-01	0.830 (1.292)	5.21E-01	8.41E-01	-1.079 (6.496)	8.70E-01	9.25E-01	1	0.750 (0.980)	4.56E-01	7.12E-01
Cooked vegetable (1SD)	17	38	0.561 (0.860)	5.14E-01	8.36E-01	0.331 (1.099)	7.63E-01	9.22E-01	3.145 (9.667)	7.49E-01	8.61E-01	0	0.561 (0.860)	5.24E-01	7.70E-01
Oily fish (1SD)	69	44	-0.454 (0.291)	1.19E-01	4.86E-01	-0.017 (0.425)	9.67E-01	9.67E-01	-1.037 (1.269)	4.17E-01	8.61E-01	0	-0.454(0.291)	1.24E-01	3.86E-01
Non oily fish (1SD)	12	44	-0.073 (0.919)	9.37E-01	9.37E-01	0.306 (1.147)	7.90E-01	9.22E-01	-2.040 (4.687)	6.73E-01	8.61E-01	0	0.073 (0.919)	9.38E-01	9.38E-01
Cereal (1SD)	39	45	-0.840 (0.404)	3.78E-02	4.86E-01	-0.308 (0.595)	6.04E-01	8.41E-01	-0.755 (1.742)	6.64E-01	8.61E-01	0	-0.840 (0.402)	4.34E-02	3.14E-01
Bacon (1SD)	3	32	0.261 (0.805)	7.46E-01	9.09E-01	0.304 (0.934)	7.45E-01	9.22E-01	-2.929 (1.663)	8.89E-01	9.25E-01	-	-	-	-
Processed meat (1SD)	23	39	0.196 (0.485)	6.86E-01	9.09E-01	0.355 (0.690)	6.07E-01	8.41E-01	-0.755 (2.460)	7.56E-01	8.61E-01	0	0.196 (0.475)	6.84E-01	8.14E-01

Note: DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Bold font indicates that the MR results are significant after FDR correction ($q < 0.05$).

Table S15. EUR MR analysis result: the causal effects of the CVH factors on IEAA

CVH Factor	No. of SNPs	IVW				Weighted Median			MR-Egger			MR-PRESSO			
		F	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	No. of outliers	β (SE), years	p Value	q Value
Clinical factor															
Total cholesterol (1SD)	117	12	-0.036 (0.066)	5.85E-01	9.50E-01	0.005 (0.121)	9.69E-01	9.89E-01	0.020 (0.108)	8.53E-01	9.55E-01	0	-0.036 (0.061)	5.61E-01	9.36E-01
Fasting glucose (1SD)	85	10	0.026 (0.191)	8.91E-01	9.58E-01	-0.020 (0.291)	9.46E-01	9.89E-01	0.759 (0.360)	3.83E-02	5.38E-01	0	0.026 (0.191)	8.91E-01	9.58E-01
DBP (1mmHg)	793	65	0.008 (0.009)	3.68E-01	8.25E-01	0.002 (0.012)	8.73E-01	9.89E-01	-0.023 (0.023)	3.20E-01	8.33E-01	7	0.012 (0.009)	1.65E-01	9.36E-01
SBP (1mmHg)	756	64	0.004 (0.005)	4.15E-01	8.25E-01	-0.005 (0.008)	4.98E-01	9.89E-01	0.001 (0.014)	9.17E-01	9.55E-01	5	0.003 (0.005)	5.49E-01	9.36E-01
Lifestyle factor															
BMI (1SD)	941	58	0.258 (0.083)	1.83E-03	4.77E-02	0.144 (0.127)	2.58E-01	9.89E-01	0.270 (0.256)	2.29E-01	8.33E-01	3	0.250 (0.082)	2.29E-03	5.74E-02
Smoking status															
Current	16	40	0.896 (1.877)	6.33E-01	9.58E-01	-0.542 (2.189)	8.04E-01	9.89E-01	-3.762 (8.678)	6.71E-01	9.55E-01	0	0.896 (1.887)	6.40E-01	9.58E-01
Previous	20	38	-1.443 (1.013)	1.54E-01	8.25E-01	-1.853 (1.371)	1.76E-01	9.89E-01	2.514 (5.924)	6.76E-01	9.55E-01	0	-1.443 (1.013)	1.71E-01	9.36E-01
Never	76	41	0.773 (0.507)	1.48E-01	8.25E-01	0.890 (0.736)	2.26E-01	9.89E-01	1.255 (2.254)	5.79E-01	9.55E-01	0	0.733 (0.507)	1.52E-01	9.36E-01
Amount of smoking															
Packyears (1SD)	11	73	0.467 (0.436)	2.84E-01	8.25E-01	0.259 (0.437)	5.53E-01	9.89E-01	0.370 (1.065)	7.36E-01	9.55E-01	0	0.467 (0.436)	3.09E-01	9.36E-01
Number of days/week of physical activity 10+ minutes															
Moderate (1SD)	16	36	0.113 (0.319)	7.23E-01	9.58E-01	0.061 (0.361)	8.66E-01	9.89E-01	1.244 (2.070)	5.57E-01	9.55E-01	0	0.113 (0.319)	7.28E-01	9.58E-01
Vigorous (1SD)	11	40	-0.502 (0.458)	2.73E-01	8.25E-01	-0.526 (0.527)	3.18E-01	9.89E-01	2.438 (3.753)	5.32E-01	9.55E-01	0	-0.502 (0.458)	2.99E-01	9.36E-01
Types of physical activity in last 4 weeks															
Heavy DIY	19	35	0.113 (1.342)	9.33E-01	9.58E-01	-0.113 (1.749)	9.49E-01	9.89E-01	2.547 (8.981)	7.80E-01	9.55E-01	0	0.113 (1.342)	9.34E-01	9.58E-01
Light DIY	13	40	0.179 (1.349)	8.95E-01	9.58E-01	-0.434 (1.808)	8.10E-01	9.89E-01	-3.401 (5.482)	5.48E-01	9.55E-01	0	0.179 (1.254)	8.89E-01	9.58E-01
Strenuous sports	6	39	2.469 (3.706)	5.05E-01	8.76E-01	3.738 (3.960)	3.45E-01	9.89E-01	7.074 (19.262)	7.32E-01	9.55E-01	0	2.469 (3.706)	5.35E-01	9.36E-01
Walking	21	34	-1.202 (1.252)	3.37E-01	8.25E-01	-0.808 (1.746)	6.37E-01	9.89E-01	-18.275 (13.021)	1.77E-01	7.65E-01	0	-1.202 (1.220)	3.36E-01	9.36E-01
Other physical activity	14	38	-1.058 (1.275)	4.07E-01	8.25E-01	-1.716 (1.784)	3.36E-01	9.89E-01	-2.005 (9.629)	8.39E-01	9.55E-01	0	-1.058 (1.183)	3.87E-01	9.36E-01
No physical activity	5	33	-0.937 (4.966)	8.05E-01	9.58E-01	0.645 (6.163)	9.17E-01	9.89E-01	-75.506 (55.251)	2.65E-01	8.33E-01	0	-0.937 (4.966)	8.59E-01	9.58E-01
Food intake															
Dried fruit (1SD)	43	42	-0.349 (0.433)	4.31E-01	8.25E-01	-0.726 (0.623)	2.44E-01	9.89E-01	-3.288 (1.975)	1.04E-01	5.38E-01	0	-0.349 (0.443)	4.35E-01	9.36E-01
Fresh fruit (1SD)	56	45	0.453 (0.552)	4.12E-01	8.25E-01	0.191 (0.797)	8.11E-01	9.89E-01	2.509 (2.053)	2.27E-01	8.33E-01	0	0.453 (0.552)	4.16E-01	9.36E-01
Salad (1SD)	17	37	-0.233 (0.892)	8.02E-01	9.58E-01	-0.268 (1.211)	8.25E-01	9.89E-01	-0.001 (4.642)	9.99E-01	9.99E-01	0	-0.223 (0.892)	8.06E-01	9.58E-01
Cooked vegetable (1SD)	17	38	0.146 (0.792)	8.54E-01	9.58E-01	0.791 (1.134)	4.86E-01	9.89E-01	-17.119 (8.516)	6.28E-02	5.38E-01	0	0.146 (0.792)	8.56E-01	9.58E-01
Oily fish (1SD)	69	44	-0.087 (0.338)	7.97E-01	9.58E-01	0.006 (0.442)	9.89E-01	9.89E-01	-2.842 (1.436)	5.19E-02	5.38E-01	0	-0.087 (0.338)	7.98E-01	9.58E-01
Non oily fish (1SD)	12	44	-0.760 (0.993)	4.44E-01	8.25E-01	-0.959 (1.171)	4.13E-01	9.89E-01	-0.538 (5.111)	9.18E-01	9.55E-01	0	-0.760 (0.993)	4.60E-01	9.36E-01
Cereal (1SD)	39	45	0.457 (0.428)	2.86E-01	8.25E-01	-0.144 (0.620)	8.17E-01	9.89E-01	-0.936 (1.822)	6.10E-01	9.55E-01	0	0.457 (0.428)	2.93E-01	9.36E-01
Bacon (1SD)	3	32	-1.783 (0.835)	3.27E-02	4.26E-01	-1.550 (1.043)	1.38E-01	9.89E-01	-0.524 (1.729)	8.13E-01	9.55E-01	-	-	-	-
Processed meat (1SD)	23	39	-0.032 (0.596)	9.58E-01	9.58E-01	-0.486 (0.700)	4.87E-01	9.89E-01	5.010 (2.895)	9.82E-02	5.38E-01	0	-0.032 (0.596)	9.58E-01	9.58E-01

Note: DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Bold font indicates that the MR results are significant after FDR correction (q<0.05).

Table S16. EUR MR analysis result: the causal effects of the CVH factors on PhenoEAA

CVH Factor	No. of SNPs	IVW				Weighted Median			MR-Egger			MR-PRESSO			
		F	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	No. of outliers	β (SE), years	p Value	q Value
Clinical Factor															
Total cholesterol (1SD)	117	125	-0.038 (0.092)	6.81E-01	7.76E-01	-0.013 (0.135)	9.25E-01	9.56E-01	-0.010 (0.152)	9.74E-01	9.85E-01	2	-0.034 (0.087)	6.92E-01	7.86E-01
Fasting glucose (1SD)	85	109	-0.224 (0.235)	3.41E-01	6.69E-01	0.245 (0.380)	5.19E-01	9.16E-01	1.002 (0.451)	2.90E-02	6.61E-01	0	-0.224 (0.234)	3.40E-01	6.54E-01
DBP (1mmHg)	793	65	0.035 (0.010)	6.77E-04	8.80E-03	0.030 (0.016)	6.17E-02	4.69E-01	0.039 (0.027)	1.45E-01	6.61E-01	2	0.036 (0.010)	4.45E-04	5.56E-03
SBP (1mmHg)	756	64	0.014 (0.006)	2.65E-02	1.38E-01	0.010 (0.010)	2.83E-01	7.36E-01	0.025 (0.017)	1.45E-01	6.61E-01	3	0.015 (0.006)	1.90E-02	1.03E-01
Lifestyle Factor															
BMI (1SD)	941	58	0.604 (0.104)	5.86E-09	1.52E-07	0.745 (0.157)	2.00E-06	5.20E-05	0.616 (0.321)	5.54E-02	6.61E-01	3	0.617 (0.102)	2.02E-09	5.05E-08
Smoking status															
Current	16	40	0.964 (2.097)	6.46E-01	7.76E-01	1.754 (2.937)	5.50E-01	9.16E-01	-6.623 (9.495)	4.97E-01	8.05E-01	0	0.964 (2.097)	6.52E-01	7.86E-01
Previous	20	38	-0.190 (1.571)	9.04E-01	9.73E-01	-0.126 (1.889)	9.47E-01	9.56E-01	6.692 (9.091)	4.71E-01	8.05E-01	0	-0.190 (1.571)	9.05E-01	9.43E-01
Never	76	41	-1.089 (0.766)	1.55E-01	4.46E-01	-0.768 (0.906)	3.97E-01	9.16E-01	2.125 (3.389)	5.33E-01	8.05E-01	2	-1.227 (0.690)	7.96E-02	2.84E-01
Amount of smoking															
Packyears (1SD)	11	73	0.596 (0.396)	1.32E-01	4.46E-01	0.304 (0.511)	5.52E-01	9.16E-01	0.217 (0.916)	8.18E-01	9.51E-01	0	0.596 (0.378)	1.46E-01	4.40E-01
Number of days/week of physical activity 10+ minutes															
Moderate (1SD)	16	36	0.132 (0.326)	6.87E-01	7.76E-01	-0.117 (0.411)	7.75E-01	9.16E-01	0.325 (2.067)	8.77E-01	9.51E-01	0	0.132 (0.228)	5.72E-01	7.86E-01
Vigorous (1SD)	11	40	-0.451 (0.644)	4.84E-01	6.99E-01	-0.212 (0.607)	7.27E-01	9.16E-01	-0.884 (5.440)	8.74E-01	9.51E-01	0	-0.113 (0.567)	8.46E-01	9.20E-01
Types of physical activity in last 4 weeks															
Heavy DIY	19	35	1.285 (1.503)	3.39E-01	6.99E-01	0.665 (2.114)	7.53E-01	9.16E-01	13.948 (9.837)	1.74E-01	6.61E-01	2	1.285 (1.501)	4.03E-01	6.62E-01
Light DIY	13	40	-2.283 (1.735)	1.88E-01	4.46E-01	-0.597 (2.488)	8.11E-01	9.16E-01	2.955 (7.260)	6.92E-01	9.47E-01	0	-2.283 (1.735)	2.13E-01	5.32E-01
Strenuous sports	6	39	0.619 (7.681)	9.36E-01	9.73E-01	2.726 (5.795)	6.38E-01	9.16E-01	56.448 (28.439)	1.18E-01	6.61E-01	0	1.850 (3.510)	6.35E-01	7.86E-01
Walking	21	34	-2.222 (1.559)	1.54E-01	4.46E-01	-3.603 (2.199)	1.01E-01	4.69E-01	13.664 (16.227)	4.10E-01	8.05E-01	0	-2.222 (1.516)	1.58E-01	4.40E-01
Other physical activity	14	38	-0.766 (1.716)	6.55E-01	7.76E-01	1.052 (2.250)	6.40E-01	9.16E-01	-9.080 (13.276)	5.07E-01	8.05E-01	0	-0.766 (1.716)	6.63E-01	7.86E-01
No physical activity	5	33	8.220 (6.255)	1.89E-01	4.46E-01	5.694 (8.203)	4.88E-01	9.16E-01	-64.740 (71.843)	4.34E-01	8.05E-01	0	8.220 (6.255)	2.59E-01	5.40E-01
Food intake															
Dried fruit (1SD)	43	42	-1.636 (0.596)	6.10E-03	5.28E-02	-0.923 (0.084)	2.51E-01	7.24E-01	-2.388 (2.725)	3.86E-01	8.05E-01	0	-1.636 (0.596)	8.92E-03	7.43E-02
Fresh fruit (1SD)	56	45	0.526 (0.625)	4.00E-01	6.69E-01	1.209 (0.910)	1.84E-01	6.66E-01	1.459 (2.321)	5.32E-01	8.05E-01	0	0.526 (0.601)	3.85E-01	6.62E-01
Salad (1SD)	17	37	-0.911 (1.110)	4.12E-01	6.68E-01	-0.479 (1.517)	7.52E-01	9.16E-01	-3.498 (5.832)	5.58E-01	8.05E-01	0	-0.911 (1.110)	4.24E-01	6.62E-01
Cooked vegetable (1SD)	17	38	1.477 (1.211)	2.22E-01	4.82E-01	0.078 (1.419)	9.56E-01	9.56E-01	-4.784 (13.539)	7.29E-01	9.47E-01	0	1.477 (1.211)	2.40E-01	5.40E-01
Oily fish (1SD)	69	44	-0.946 (0.399)	1.77E-02	1.15E-01	-0.964 (0.548)	7.85E-02	4.69E-01	-2.367 (1.739)	1.78E-01	6.61E-01	0	-0.946 (0.399)	2.05E-02	1.03E-01
Non oily fish (1SD)	12	44	1.656 (1.038)	1.10E-01	4.46E-01	2.309 (1.365)	9.06E-02	4.69E-01	-4.311 (5.102)	4.18E-01	8.05E-01	0	1.656 (0.842)	7.48E-02	2.84E-01
Cereal (1SD)	39	45	0.014 (0.518)	9.78E-01	9.78E-01	-0.242 (0.717)	7.35E-01	9.16E-01	-1.480 (2.194)	5.04E-01	8.05E-01	0	0.014 (0.418)	9.73E-01	9.73E-01
Bacon (1SD)	3	32	-1.025 (1.645)	5.33E-01	7.30E-01	-2.222 (1.383)	1.08E-01	4.69E-01	1.068 (4.335)	8.46E-01	9.51E-01	-	-	-	-
Processed meat (1SD)	23	39	-0.525 (0.691)	4.47E-01	6.84E-01	1.177 (0.928)	2.05E-01	6.66E-01	0.027 (3.653)	9.94E-01	9.41E-01	0	-0.525 (0.691)	4.55E-01	6.69E-01

Note: DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Bold font indicates that the MR results are significant after FDR correction (q<0.05).

Table S17. EUR MR analysis result: the causal effects of the CVH factors on DNAmPAI-1

CVH Factor	IVW					Weighted Median			MR-Egger			N o. of ou tli er s	MR-PRESSO		
	No. of SNPs	F	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value	β (SE), year	p Value	q Value		β (SE), years	p Value	q Value
Clinical Factor															
Total cholesterol (1SD)	117	125	-0.126 (0.159)	4.28E-01	8.59E-01	-0.074 (0.271)	7.86E-01	9.70E-01	0.092 (0.261)	7.26E-01	7.83E-01	0	-0.126 (0.140)	3.85E-01	7.62E-01
Fasting glucose (1SD)	83	111	-0.068 (0.469)	8.85E-01	9.20E-01	0.691 (0.735)	3.47E-01	9.70E-01	1.565 (0.913)	9.05E-02	7.28E-01	0	-0.068 (0.440)	8.79E-01	9.16E-01
DBP (1mmHg)	791	65	0.022 (0.019)	2.41E-01	8.59E-01	0.011 (0.032)	7.39E-01	9.70E-01	-0.018 (0.051)	7.29E-01	7.83E-01	0	0.022 (0.019)	2.37E-01	7.62E-01
SBP (1mmHg)	753	64	0.009 (0.012)	4.17E-01	8.59E-01	0.005 (0.018)	7.96E-01	9.70E-01	-0.011 (0.032)	7.25E-01	7.83E-01	0	0.009 (0.011)	4.17E-01	7.62E-01
Lifestyle Factor															
BMI (1SD)	937	58	0.566 (0.192)	3.21E-03	8.34E-02	0.367 (0.309)	2.35E-01	9.70E-01	0.940 (0.599)	1.17E-01	7.28E-01	0	0.566 (0.187)	3.29E-03	8.22E-01
Smoking status															
Current	16	40	1.805 (3.987)	6.51E-01	8.59E-01	0.620 (5.663)	9.13E-01	9.70E-01	25.371 (17.470)	1.68E-01	7.28E-01	0	1.805 (3.980)	6.57E-01	7.82E-01
Previous	20	38	-2.384 (2.372)	3.15E-01	8.59E-01	-0.704 (3.173)	8.24E-01	9.70E-01	19.724 (13.017)	1.47E-01	7.28E-01	0	-2.684 (2.243)	3.28E-01	7.62E-01
Never	75	41	-0.778 (1.284)	5.45E-01	8.59E-01	-1.203 (1.816)	5.08E-01	9.70E-01	4.465 (5.753)	4.40E-01	7.83E-01	0	-0.778 (1.240)	5.46E-01	7.62E-01
Amount of smoking															
Packyears (1SD)	11	73	0.569 (0.756)	4.52E-01	8.59E-01	-0.279 (1.006)	7.82E-01	9.70E-01	0.133 (1.736)	9.41E-01	9.41E-01	0	0.569 (0.672)	4.32E-01	7.62E-01
Number of days/week of physical activity 10+ minutes															
Moderate (1SD)	16	36	-0.099 (0.624)	8.74E-01	9.20E-01	0.081 (0.792)	9.19E-01	9.70E-01	-1.262 (3.933)	7.53E-01	7.83E-01	0	-0.099 (0.550)	8.60E-01	9.16E-01
Vigorous (1SD)	11	40	0.791 (0.863)	3.59E-01	8.59E-01	0.653 (1.141)	5.67E-01	9.70E-01	-4.534 (6.752)	5.19E-01	7.83E-01	0	0.791 (0.734)	3.06E-01	7.62E-01
Types of physical activity in last 4 weeks															
Heavy DIY	19	35	1.599 (2.924)	5.84E-01	8.59E-01	2.528 (3.826)	5.09E-01	9.70E-01	26.939 (19.163)	1.78E-01	7.28E-01	0	1.599 (2.205)	4.78E-01	7.62E-01
Light DIY	13	40	-1.894 (4.807)	6.94E-01	8.59E-01	-3.211 (4.555)	4.81E-01	9.70E-01	-13.300 (22.486)	5.66E-01	7.83E-01	2	-1.847 (3.180)	5.74E-01	7.62E-01
Strenuous sports	6	39	5.162 (8.105)	5.24E-01	8.59E-01	2.686 (10.011)	7.88E-01	9.70E-01	32.040 (40.159)	4.70E-01	7.83E-01	0	5.162 (5.418)	3.84E-01	7.62E-01
Walking	21	34	-0.590 (3.240)	8.55E-01	9.20E-01	-1.901 (4.311)	6.59E-01	9.70E-01	-15.067 (34.654)	6.69E-01	7.83E-01	0	-0.590 (3.240)	8.57E-01	9.16E-01
Other physical activity	14	38	-5.706 (3.029)	5.96E-02	4.87E-01	-6.677 (4.041)	9.85E-02	9.70E-01	8.952 (22.536)	6.98E-01	7.83E-01	0	-5.706 (1.899)	1.48E-02	1.85E-01
No physical activity	5	33	-4.694 (11.453)	6.82E-01	8.59E-01	-0.992 (14.351)	9.45E-01	9.70E-01	61.318 (131.547)	6.73E-01	7.83E-01	0	-4.694 (7.783)	5.79E-01	7.62E-01
Food intake															
Dried fruit (1SD)	43	42	-2.320 (1.080)	3.16E-02	4.11E-01	-2.326 (1.463)	1.12E-01	9.70E-01	-3.966 (4.842)	4.18E-01	7.83E-01	0	-2.320 (0.596)	3.74E-02	3.12E-01
Fresh fruit (1SD)	56	45	0.736 (1.198)	5.39E-01	8.59E-01	0.344 (1.789)	8.48E-01	9.70E-01	1.926 (4.417)	6.65E-01	7.83E-01	0	0.736 (0.601)	5.38E-01	7.62E-01
Salad (1SD)	17	37	-1.821 (2.206)	4.09E-01	8.59E-01	-0.117 (3.087)	9.70E-01	9.70E-01	-14.302 (13.193)	2.95E-01	7.68E-01	0	-1.821 (1.110)	3.99E-01	7.62E-01
Cooked vegetable (1SD)	17	38	1.838 (1.885)	3.29E-01	8.59E-01	2.212 (2.654)	4.05E-01	9.70E-01	26.004 (20.504)	2.24E-01	7.28E-01	0	1.838 (1.211)	2.90E-01	7.62E-01
Oily fish (1SD)	69	44	0.054 (0.728)	9.41E-01	9.41E-01	0.536 (1.027)	6.01E-02	9.70E-01	4.060 (3.260)	2.17E-01	7.28E-01	0	0.054 (0.399)	9.41E-01	9.41E-01
Non oily fish (1SD)	12	44	3.052 (2.010)	1.29E-01	6.70E-01	2.845 (2.746)	3.00E-02	9.70E-01	4.223 (9.955)	6.80E-01	7.83E-01	0	3.052 (0.842)	6.77E-02	4.15E-01
Cereal (1SD)	39	45	1.896 (1.065)	7.50E-02	4.87E-01	1.808 (1.399)	1.96E-01	9.70E-01	-8.921 (4.156)	3.85E-02	7.28E-01	0	1.896 (0.418)	8.30E-02	4.15E-01
Bacon (1SD)	3	32	1.372 (4.944)	7.81E-01	9.20E-01	1.382 (3.282)	6.74E-01	9.70E-01	-2223.237 (996.878)	2.68E-01	7.68E-01	-	-	-	-
Processed meat (1SD)	23	39	0.559 (1.220)	6.47E-01	8.59E-01	1.596 (1.744)	3.60E-01	9.70E-01	-2.286 (7.168)	7.53E-01	7.83E-01	0	0.559 (0.691)	6.47E-01	7.82E-01

Note: DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Bold font indicates that the MR results are significant after FDR correction ($q < 0.05$).

Table S18. Test for heterogeneity and pleiotropy in the causal inference of the CVH factors on HannumEAA in

EUR

	Pleiotropy test		Heterogeneity test	
	MR-Egger intercept	p-value	Cochran's Q statistic	p-value
Clinical Factor				
TC (1SD)	0.002	0.765	151.490	0.015
FG (1SD)	-0.020	0.019	100.579	0.105
DBP (1mmHg)	0.004	0.284	1015.977	1.07E-07
SBP (1mmHg)	0.004	0.261	960.581	4.41E-07
Lifestyle Factor				
BMI (1SD)	-0.004	0.254	1017.274	0.040
Smoking status				
Current	0.039	0.317	13.000	0.602
Previous	-0.021	0.658	22.084	0.280
Never	-0.011	0.564	82.292	0.264
Amount of smoking				
Packyears (1SD)	0.015	0.625	13.710	0.187
Number of days/week of physical activity 10+ minutes				
Moderate (1SD)	0.068	0.254	18.009	0.262
Vigorous (1SD)	0.017	0.840	4.016	0.947
Types of physical activity in last 4 weeks				
Heavy DIY	0.037	0.480	13.529	0.759
Light DIY	-0.037	0.473	15.800	0.149
Strenuous sports	0.008	0.954	14.915	0.011
Walking	0.035	0.642	13.075	0.874
Other PA	0.115	0.127	11.303	0.585
No PA	0.295	0.562	26.409	2.62E-05
Food intake				
Dried fruit (1SD)	-0.007	0.786	56.475	0.067
Fresh fruit (1SD)	-0.001	0.937	50.600	0.643
Salad (1SD)	0.009	0.892	33.915	0.006
Cooked vegetable (1SD)	-0.027	0.792	20.542	0.197
Oily fish (1SD)	0.009	0.638	69.343	0.432
Non oily fish (1SD)	0.026	0.655	14.261	0.219
Cereal (1SD)	-0.001	0.960	37.549	0.490
Bacon (1SD)	0.022	0.769	0.192	0.908
Processed meat (1SD)	-0.009	0.816	21.159	0.511
<p><i>Note:</i> TC: total cholesterol; FG: fasting glucose; DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Other PA: other physical activity, e.g., swimming, cycling, keep fit, bowling; No PA: none of the above physical activity; Bold font indicates the possible presence of heterogeneity or pleiotropy.</p>				

Table S19. Test for heterogeneity and pleiotropy in the causal inference of the CVH factors on IEAA in EUR

	Pleiotropy test		Heterogeneity test	
	MR-Egger intercept	p-value	Cochran's Q statistic	p-value
Clinical Factor				
TC (1SD)	-0.004	0.515	102.077	0.818
FG (1SD)	-0.019	0.019	86.303	0.410
DBP (1mmHg)	0.006	0.145	1065.003	2.55E-10
SBP (1mmHg)	0.001	0.825	1024.396	1.89E-10
Lifestyle Factor				
BMI (1SD)	0.000	0.960	1058.960	0.004
Smoking status				
Current	0.024	0.591	18.794	0.223
Previous	-0.031	0.506	21.135	0.329
Never	-0.005	0.813	83.757	0.229
Amount of smoking				
Packyears (1SD)	0.004	0.921	18.798	0.043
Number of days/week of physical activity 10+ minutes				
Moderate (1SD)	-0.038	0.589	22.323	0.100
Vigorous (1SD)	-0.085	0.450	16.150	0.095
Types of physical activity in last 4 weeks				
Heavy DIY	-0.016	0.787	22.321	0.218
Light DIY	0.028	0.514	10.369	0.584
Strenuous sports	-0.022	0.819	6.585	0.253
Walking	0.102	0.203	19.001	0.522
Other PA	0.007	0.923	11.184	0.595
No PA	0.228	0.269	4.320	0.364
Mineral and other dietary supplements				
Dried fruit (1SD)	0.037	0.135	43.594	0.403
Fresh fruit (1SD)	-0.019	0.303	66.545	0.137
Salad (1SD)	-0.002	0.962	16.451	0.434
Cooked vegetable (1SD)	0.178	0.060	88.324	0.422
Oily fish (1SD)	0.041	0.053	15.696	0.049
Non oily fish (1SD)	-0.003	0.966	40.257	0.153
Cereal (1SD)	0.020	0.436	0.714	0.371
Bacon (1SD)	-0.050	0.558	31.342	0.700
Processed meat (1SD)	-0.076	0.090	8.981	0.089

Note: TC: total cholesterol; FG: fasting glucose; DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Other PA: other physical activity, e.g., swimming, cycling, keep fit, bowling; No PA: none of the above physical activity; Bold font indicates the possible presence of heterogeneity or pleiotropy.

Table S20. Test for heterogeneity and pleiotropy in the causal inference of the CVH factors on PhenoEAA in

EUR

	Pleiotropy test		Heterogeneity test	
	MR-Egger intercept	p-value	Cochran's Q statistic	p-value
Clinical Factor				
TC (1SD)	-0.002	0.818	147.736	0.025
FG (1SD)	-0.031	0.002	82.846	0.515
DBP (1mmHg)	-0.001	0.875	872.917	0.024
SBP (1mmHg)	-0.003	0.502	938.414	5.39E-06
Lifestyle Factor				
BMI (1SD)	0.000	0.969	1070.162	0.002
Smoking status				
Current	0.040	0.426	15.158	0.440
Previous	-0.054	0.452	32.770	0.026
Never	-0.028	0.334	122.942	4.04E-04
Amount of smoking				
Packyears (1SD)	0.014	0.657	9.118	0.521
Number of days/week of physical activity 10+ minutes				
Moderate (1SD)	-0.006	0.926	7.312	0.948
Vigorous (1SD)	0.013	0.938	20.597	0.024
Types of physical activity in last 4 weeks				
Heavy DIY	-0.085	0.210	17.942	0.459
Light DIY	-0.041	0.473	12.798	0.384
Strenuous sports	-0.266	0.115	18.139	0.003
Walking	-0.095	0.338	18.894	0.529
Other PA	0.063	0.539	15.192	0.296
No PA	0.223	0.383	4.404	0.354
Mineral and other dietary supplements				
Dried fruit (1SD)	0.009	0.779	51.142	0.158
Fresh fruit (1SD)	-0.009	0.678	50.786	0.636
Salad (1SD)	0.027	0.658	16.087	0.447
Cooked vegetable (1SD)	0.064	0.649	24.672	0.076
Oily fish (1SD)	0.021	0.404	78.992	0.170
Non oily fish (1SD)	0.074	0.260	7.235	0.780
Cereal (1SD)	0.022	0.488	24.733	0.952
Bacon (1SD)	-0.080	0.681	4.623	0.099
Processed meat (1SD)	-0.008	0.879	26.892	0.215
<i>Note: TC: total cholesterol; FG: fasting glucose; DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Other PA: other physical activity, e.g., swimming, cycling, keep fit, bowling; No PA: none of the above physical activity; Bold font indicates the possible presence of heterogeneity or pleiotropy.</i>				

Table S21. Test for heterogeneity and pleiotropy in the causal inference of the CVH factors on GrimEAA in

EUR

	Pleiotropy test		Heterogeneity test	
	MR-Egger intercept	p-value	Cochran's Q statistic	p-value
Clinical Factor				
TC (1SD)	-0.007	0.347	196.015	4.96E-06
FG (1SD)	-0.013	0.165	124.245	0.003
DBP (1mmHg)	0.002	0.579	918.263	0.001
SBP (1mmHg)	0.005	0.150	860.464	0.004
Lifestyle Factor				
BMI (1SD)	-0.005	0.183	1036.000	0.015
Smoking status				
Current	-0.017	0.664	12.140	0.668
Previous	-0.131	0.028	38.896	0.005
Never	0.033	0.094	91.801	0.091
Amount of smoking				
Packyears (1SD)	-0.035	0.311	17.166	0.071
Number of days/week of physical activity 10+ minutes				
Moderate (1SD)	0.037	0.546	17.193	0.307
Vigorous (1SD)	0.074	0.497	15.189	0.125
Types of physical activity in last 4 weeks				
Heavy DIY	0.011	0.838	14.007	0.729
Light DIY	-0.107	0.080	26.896	0.008
Strenuous sports	-0.028	0.822	11.404	0.044
Walking	-0.037	0.637	19.408	0.495
Other PA	-0.001	0.989	15.738	0.264
No PA	0.225	0.300	5.327	0.255
Mineral and other dietary supplements				
Dried fruit (1SD)	0.020	0.473	58.237	0.049
Fresh fruit (1SD)	-0.019	0.420	80.505	0.014
Salad (1SD)	-0.047	0.477	31.079	0.013
Cooked vegetable (1SD)	0.008	0.949	30.351	0.016
Oily fish (1SD)	-0.001	0.971	77.300	0.206
Non oily fish (1SD)	0.062	0.235	10.123	0.519
Cereal (1SD)	0.033	0.190	34.750	0.621
Bacon (1SD)	-0.016	0.833	0.635	0.728
Processed meat (1SD)	0.020	0.616	24.278	0.333
<i>Note: TC: total cholesterol; FG: fasting glucose; DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Other PA: other physical activity, e.g., swimming, cycling, keep fit, bowling; No PA: none of the above physical activity; Bold font indicates the possible presence of heterogeneity or pleiotropy.</i>				

Table S22. Test for heterogeneity and pleiotropy in the causal inference of the CVH factors on DNAmPAI-1 in

EUR

	Pleiotropy test		Heterogeneity test	
	MR-Egger intercept	p-value	Cochran's Q statistic	p-value
Clinical Factor				
TC (1SD)	-0.014	0.296	52.436	0.942
FG (1SD)	-0.041	0.040	74.663	0.705
DBP (1mmHg)	0.007	0.394	773.885	0.652
SBP (1mmHg)	0.006	0.486	765.188	0.361
Lifestyle Factor				
BMI (1SD)	-0.006	0.509	966.846	0.236
Smoking status				
Current	-0.125	0.188	14.944	0.455
Previous	-0.175	0.102	20.151	0.386
Never	-0.046	0.353	89.515	0.106
Amount of smoking				
Packyears (1SD)	0.017	0.787	8.447	0.585
Number of days/week of physical activity 10+ minutes				
Moderate (1SD)	0.039	0.769	11.639	0.706
Vigorous (1SD)	0.155	0.447	7.239	0.703
Types of physical activity in last 4 weeks				
Heavy DIY	-0.169	0.199	10.237	0.924
Light DIY	0.086	0.613	26.416	0.009
Strenuous sports	-0.126	0.532	2.234	0.816
Walking	0.086	0.679	23.172	0.280
Other PA	-0.111	0.524	5.849	0.951
No PA	-0.202	0.649	1.847	0.764
Mineral and other dietary supplements				
Dried fruit (1SD)	0.021	0.729	46.232	0.302
Fresh fruit (1SD)	-0.011	0.781	54.111	0.509
Salad (1SD)	0.128	0.352	14.520	0.560
Cooked vegetable (1SD)	-0.249	0.255	12.700	0.695
Oily fish (1SD)	-0.059	0.212	69.216	0.436
Non oily fish (1SD)	-0.014	0.907	6.175	0.861
Cereal (1SD)	0.158	0.011	44.307	0.223
Bacon (1SD)	54.070	0.268	5.259	0.072
Processed meat (1SD)	0.042	0.691	21.348	0.499
<i>Note: TC: total cholesterol; FG: fasting glucose; DBP: diastolic blood pressure; SBP: systolic blood pressure; BMI: body mass index; Moderate: number of days/week of moderate physical activity 10+ minutes; Vigorous: Number of days/week of vigorous physical activity 10+ minutes; Heavy DIY: e.g., weeding, lawn mowing, carpentry, digging; Light DIY: e.g., pruning, watering the lawn; Walking: walking for pleasure (not as a means of transport); Other PA: other physical activity, e.g., swimming, cycling, keep fit, bowling; No PA: none of the above physical activity; Bold font indicates the possible presence of heterogeneity or pleiotropy.</i>				

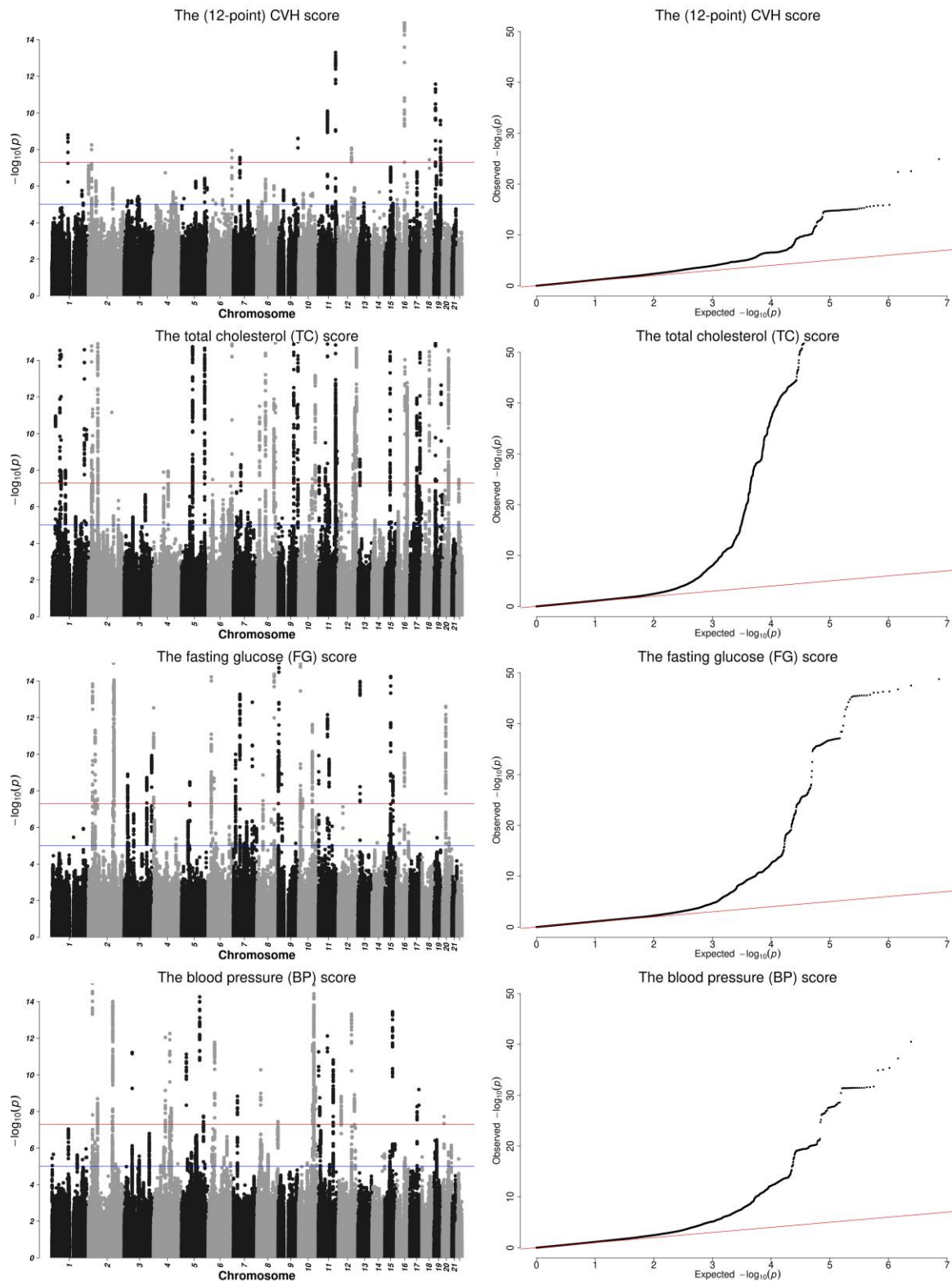


Figure S1. The Manhattan plots and the quantile-quantile (Q-Q) plots of the (12-point) CVH score, the total cholesterol (TC) score, the fasting glucose (FG) score, and the blood pressure (BP) score. In the Manhattan plots (left column), the horizontal red and blue lines mark the genome-wide significance level ($5E-8$) and the suggestive significance level ($1E-5$). The red lines in the Q-Q plots (right column) depict that the observed p-values match the expected p-values.

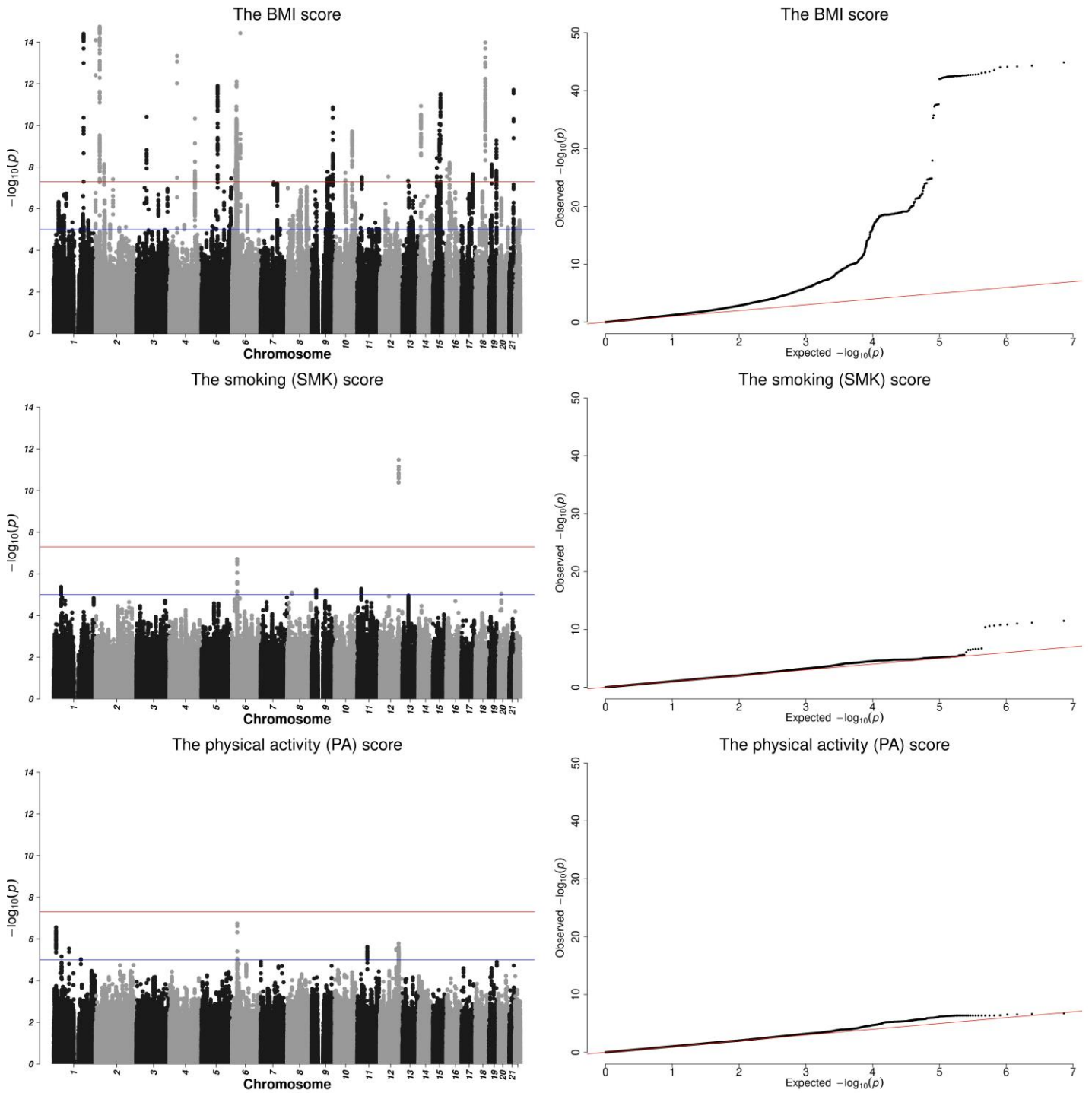


Figure S2. The Manhattan plots and the quantile-quantile (Q-Q) plots of the BMI score, the smoking (SMK) score, and the physical activity (PA) score

In the Manhattan plots (left column), the horizontal red and blue lines mark the genome-wide significance level ($5E-8$) and the suggestive significance level ($1E-5$). The red lines in the Q-Q plots (right column) depict that the observed p-values match the expected p-values.

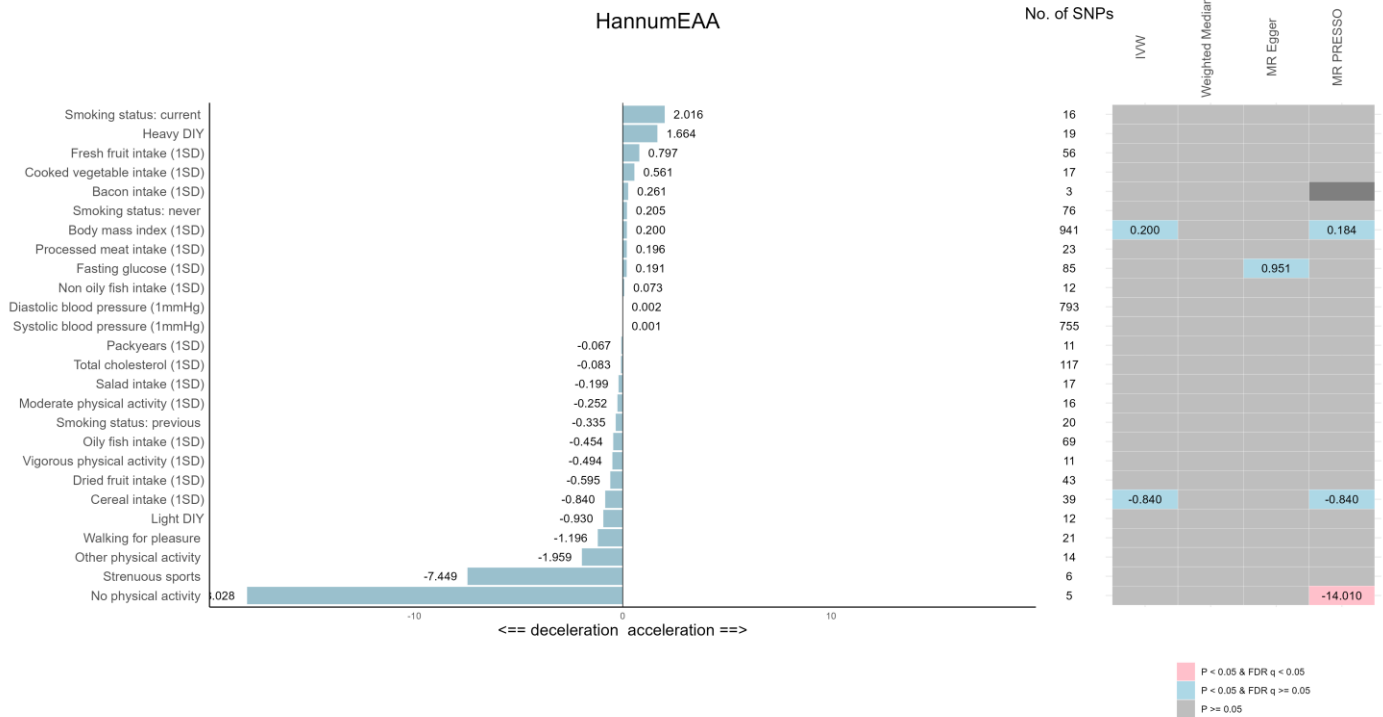


Figure S3. The causal effects of CVH factors on HannumEAA in EUR.

For the plot in the left panel, the numbers shown around the blue bars are the causal effect sizes. The number of SNPs between the two-panel plots represents the number of IVs. For the plot in the right panel, red boxes indicate significant causal effects (p-value < 0.05 & FDR q-value < 0.05). Blue boxes indicate suggestive causal effects (p-value < 0.05 & FDR q-value ≥ 0.05). Gray boxes indicate insignificant causal effects (p-value ≥ 0.05). The dark gray box indicates insufficient IVs for the MR analysis. The box numbers represent the causal effect sizes achieving significant or suggestive associations.

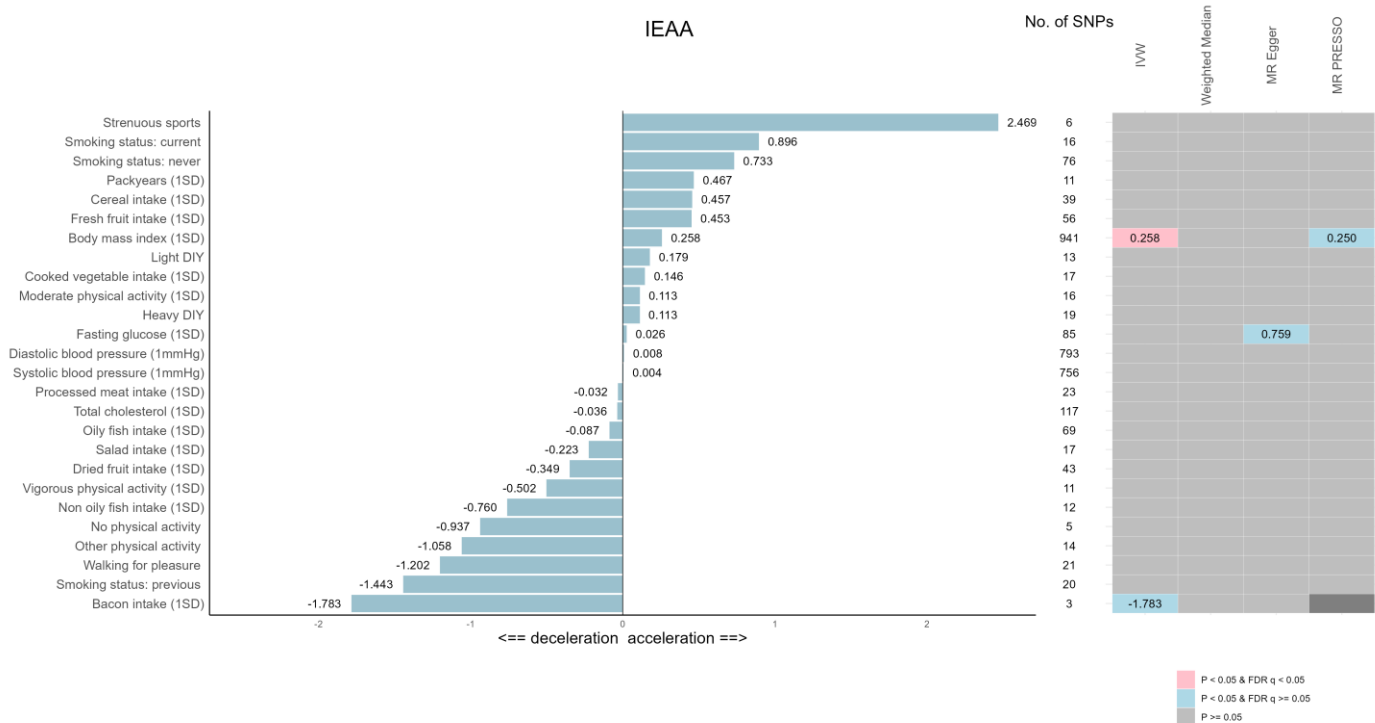


Figure S4. The causal effects of CVH factors on IEAA in EUR.

For the plot in the left panel, the numbers shown around the blue bars are the causal effect sizes. The number of SNPs between the two-panel plots represents the number of IVs. For the plot in the right panel, red boxes indicate significant causal effects (p -value < 0.05 & FDR q -value < 0.05). Blue boxes indicate suggestive causal effects (p -value < 0.05 & FDR q -value ≥ 0.05). Gray boxes indicate insignificant causal effects (p -value ≥ 0.05). The dark gray box indicates insufficient IVs for the MR analysis. The box numbers represent the causal effect sizes achieving significant or suggestive associations.

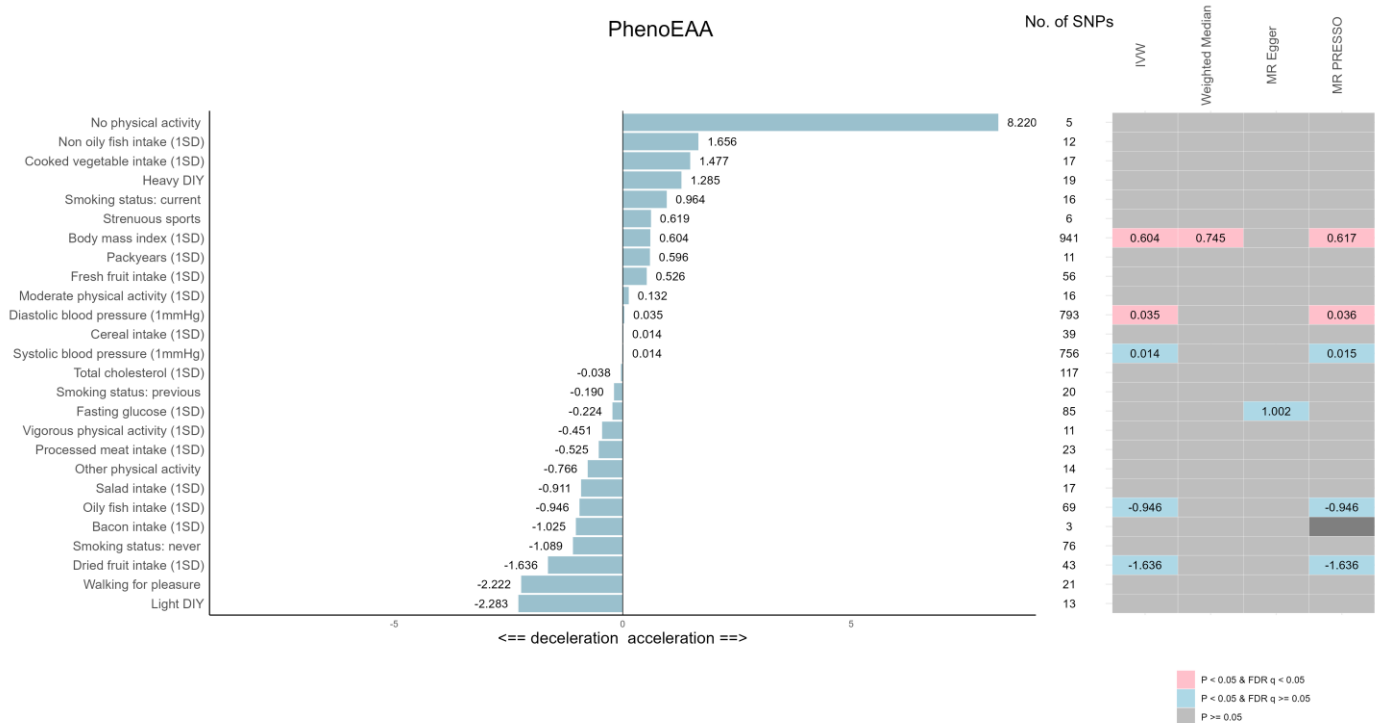


Figure S5. The causal effects of CVH factors on PhenoEAA in EUR.

For the plot in the left panel, the numbers shown around the blue bars are the causal effect sizes. The number of SNPs between the two-panel plots represents the number of IVs. For the plot in the right panel, red boxes indicate significant causal effects (p -value < 0.05 & FDR q -value < 0.05). Blue boxes indicate suggestive causal effects (p -value < 0.05 & FDR q -value \geq 0.05). Gray boxes indicate insignificant causal effects (p -value \geq 0.05). The dark gray box indicates insufficient IVs for the MR analysis. The box numbers represent the causal effect sizes achieving significant or suggestive associations.

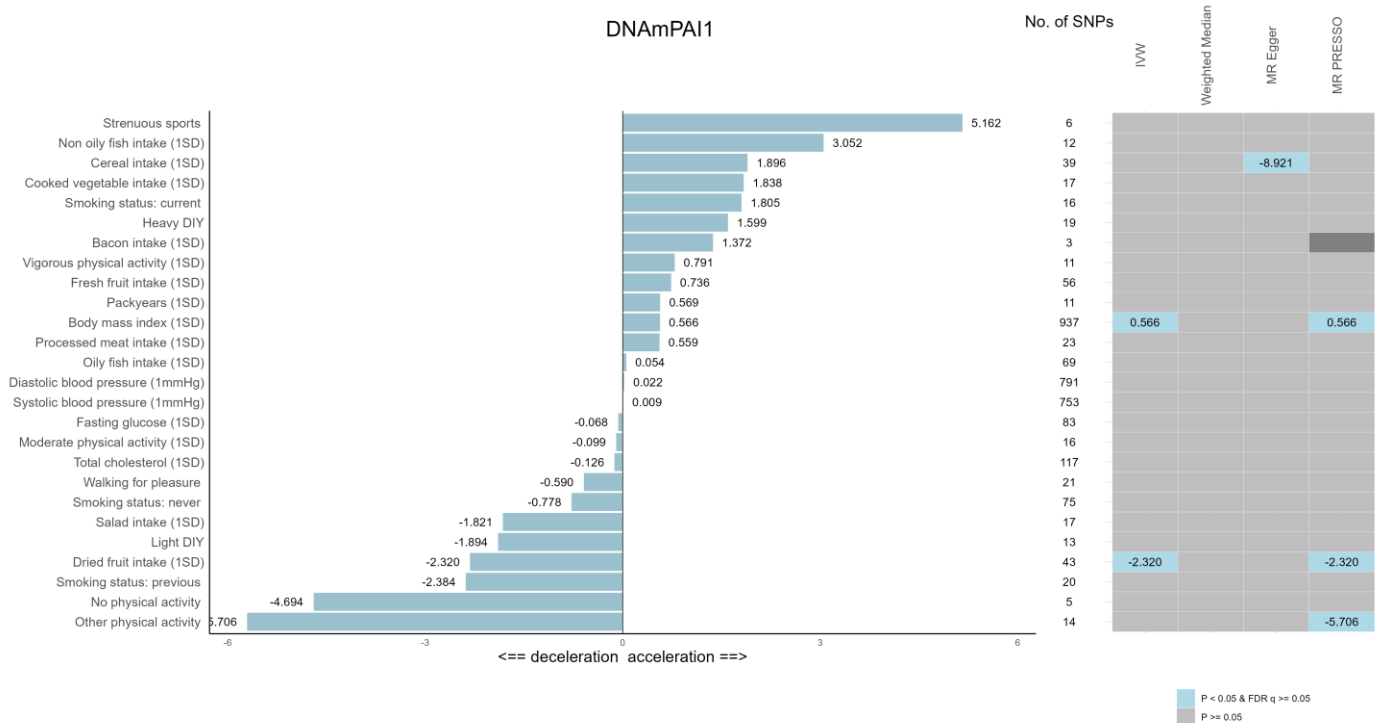


Figure S6. The causal effects of CVH factors on DNAmPAI-1 in EUR.

For the plot in the left panel, the numbers shown around the blue bars are the causal effect sizes. The number of SNPs between the two-panel plots represents the number of IVs. For the plot in the right panel, red boxes indicate significant causal effects (p -value < 0.05 & FDR q -value < 0.05). Blue boxes indicate suggestive causal effects (p -value < 0.05 & FDR q -value \geq 0.05). Gray boxes indicate insignificant causal effects (p -value \geq 0.05). The dark gray box indicates insufficient IVs for the MR analysis. The box numbers represent the causal effect sizes achieving significant or suggestive associations.

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