SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Blood lead biomarker results from the Normative Aging Study (NAS)

An additional analysis was performed in a subset of the Normative Aging Study (N = 348) to examine the association between lead levels in blood with DNA methylation values (Table S1). Similar to the methodological approach for tibia and patella lead[12], an epigenome-wide robust linear regression was performed that accounted for outliers and heteroskedasticity in DNA methylation beta values. Covariates in the epigenome wide analysis were identified through principle-component analysis (Figure S1). Epigenome-wide analysis indicated no excess of false positive rates (Figure S2). An elastic net approach (Figure S3) was used to identify significant CpG sites ($p < 0.0001$), and 80% of participants were randomly assigned to the training dataset, while 20% were randomly selected for the test dataset. Elastic-net was performed on the training set with leave-one-out cross validation, and lead biomarkers for blood were estimated as the linear combination of regression coefficients and DNA methylation beta-values matrix of the test dataset (Table S2). There were 75 CpG sites associated with blood lead concentrations. Estimated blood lead concentrations were then compared to measured blood lead values in order to validate this biomarker in a subset of the NAS (Figures S4-S5). The Pearson's correlation coefficients between actual and estimated blood lead levels was moderate ($r = 0.49$), and the mean square error (MSE) was 0.40. Results from receiver operating characteristic (ROC) and area under the curve (AUC) indicated good accuracy (AUC: 0.82, 95% CI: 0.73-0.91). The difference in means between the estimated and measured blood lead concentrations were not significantly different ($p = 0.84$), and the Kolmogorov-Smirnov test ($p = 0.01$) indicated that these values likely came from the same distribution.

Table S1. Description of participants from the Normative Aging Study (NAS)

Variables	mean ± SD
Age (years)	76.25 ± 6.57
Education (years)	16 ± 3.02
Pack-years	33 ± 25.17
Smoking Status	
never	156 (0.3)
ever	360 (0.7)
Alcohol Consumption	
≤2 drinks per day	417 (0.81)
>2 drinks per day	99 (0.19)
Patella lead levels	27.36 ± 17.74
Tibia lead levels	21.05 ± 12.91
Blood lead levels	3.96 ± 2.32

Table S2. Identification of DNA methylation sites relative to blood lead exposure

CpG Name	Elastic Net Coeff	Chromosome	MAPINFO	UCSC_RefGene_Name	UCSC_RefGene_Group	Relation_to_UCSC_CpG_Island
(Intercept)	-10.0414	NA	NA	NA	NA	NA
cg10442735	0.428246	1	3062633	PRDM16;PRDM16	Body;Body	S_Shelf
cg10442251	-1.20932	1	18700625	IGSF21	Body	N_Shelf
cg07031996	-0.39012	1	38324738	MTF1	5'UTR	N_Shore
cg17791651	0.078059	1	38513489	POU3F1	TSS1500	Island
cg06408034	-3.93669	1	45671987	ZSWIM5	1stExon	Island
cg16005939	0.034461	1	91191990			Island
cg08122338	23.79213	1	243419530	CEP170;CEP170;CEP170;SDCCAG8	TSS1500;TSS1500;TSS1500;1stExon	S_Shore
cg16596470	0.133058	1	246451744	SMYD3;SMYD3	Body;Body	
cg19407717	0.175645	2	1544120	TPO;TPO;TPO;TPO	Body;Body;Body;Body	N_Shore
cg12416637	-0.77252	2	154333650			N_Shore
cg14844194	-0.40731	2	200524259			S_Shore
cg12346504	-4.03666	2	214148862	SPAG16;SPAG16	TSS1500;TSS1500	N_Shore
cg22753768	-0.03878	3	52443424	BAP1;PHF7;PHF7	Body;TSS1500;TSS1500	N_Shore
cg12226306	1.55914	3	105087718	ALCAM	Body	N_Shore

cg03552688	0.985584	3	138822369	BPESC1	TSS1500	
cg12958778	-0.85696	4	6912474	TBC1D14;TBC1D14	5'UTR;5'UTR	S_Shore
cg01411468	-0.30947	4	36283588	DTHD1;DTHD1	5'UTR;1stExon	
cg11761728	0.322849	4	111536679			N_Shelf
cg07799386	-0.12272	5	122430821	PRDM6	Body	Island
cg12532966	0.453348	5	178854202			
cg25511429	0.092361	6	6008125	NRN1	TSS1500	N_Shore
cg23646360	-0.56428	6	10886130	SYCP2L	TSS1500	N_Shore
cg17779289	12.63892	6	33272148	TAPBP;TAPBP;TAPBP	Body;Body;Body	
cg20566286	-2.04254	6	168785923			
cg10884288	0.18269	7	4922196	RADIL	5'UTR	N_Shore
cg17469978	1.736623	7	116164704	CAV1	TSS200	Island
cg03917158	0.279592	8	1381012			
cg22883125	-0.31365	8	11540758			S_Shore
cg01546563	-0.22378	8	11567189	GATA4	Body	Island
cg09430976	3.464535	8	25907314			N_Shore
cg02504902	-0.53933	8	53326922			

cg17099568	-0.19174	8	65284438			N_Shore
cg20413392	-0.38521	9	131155013	MIR219-2	TSS200	Island
cg01240049	0.597319	9	138068091			Island
cg20395881	0.396681	10	1759215	ADARB2	Body	
cg05453333	-0.64092	10	49731375	ARHGAP22	Body	N_Shore
cg19880462	0.219686	10	61468548	SLC16A9	5'UTR	N_Shore
cg24591300	-0.41475	10	100993025	HPSE2;HPSE2;HPSE2;HPSE2	Body;Body;Body;Body	N_Shore
cg22391400	-12.7911	10	105727767	SLK	Body	S_Shore
cg20639805	0.816579	10	112404997	RBM20	Body	S_Shore
cg22773555	5.800023	11	830233	EFCAB4A	Body	Island
cg03922337	-0.21862	11	14380918	RRAS2;RRAS2	TSS200;TSS1500	S_Shore
cg09867084	-3.20354	11	63912367	MACROD1	Body	
cg14235783	-1.53413	11	65420518			Island
cg04800788	2.362246	11	123396571	GRAMD1B;GRAMD1B	1stExon;5'UTR	
cg22063247	-0.37862	11	133994642	JAM3	Body	N_Shore
cg14121142	-1.12071	12	49391363	DDN	Body	Island
cg09287190	-0.17873	13	100640914			N_Shore

cg24670552	-0.03639	13	110436780	IRS2	1stExon	Island
cg16851425	0.606277	13	110437759	IRS2	1stExon	Island
cg04393471	-0.37513	13	111010255	COL4A2	Body	
cg26053975	1.858657	14	54973785			N_Shelf
cg09298014	-0.40781	14	97058864			N_Shore
cg26471610	0.968717	15	34640893	C15orf55	Body	
cg24956533	-0.45115	15	37173638	LOC145845	Body	S_Shore
cg03603381	0.106808	15	38857474	RASGRP1;RASGRP1	TSS1500;TSS1500	Island
cg17865114	-0.65723	16	3067759	CLDN6	5'UTR	Island
cg09981030	-3.41555	16	3179796			
cg16631088	-0.46834	16	15528133	C16orf45	TSS200	N_Shore
cg10137837	0.063332	17	6926742	BCL6B	5'UTR	Island
cg21969795	-0.20118	17	7759140	TMEM88	3'UTR	N_Shore
cg06418907	-0.30942	17	7982510	ALOX12B	Body	N_Shore
cg13718961	-0.00948	17	27939261	ANKRD13B	Body	N_Shore
cg05478824	-0.10059	17	79970135	ASPSCR1	Body	S_Shelf
cg23928512	-0.19177	17	79970192	ASPSCR1	Body	S_Shelf

cg27226927	-0.09136	17	79993863	DCXR	Body	N_Shore
cg13214542	-0.94023	18	33552019	C18orf21	TSS1500	N_Shore
cg26901714	1.01678	19	376152	THEG;THEG	TSS200;TSS200	S_Shore
cg19399220	-0.30309	19	10527588			Island
cg01397939	-0.31035	19	14583568	PTGER1	Body	Island
cg11571942	-0.68779	19	55610938	PPP1R12C	Body	S_Shore
cg12014753	-0.32942	20	50384822	ATP9A	Body	Island
cg24875593	-0.12506	21	45153009	PDXK	Body	S_Shelf
cg06911679	0.764272	22	22877746			
cg03938598	-1.51491	22	50699868	MAPK12	1stExon	Island

Table S3. Average beta values for each probe used in the Strong Heart Study analysis according to men and women

CpG_Name	Mean Beta Values Males	Mean Beta values Females	p-value
cg00056541	0.58496843	0.582887355	0.7659865
cg00118365	0.42868554	0.418396093	0.007774756
cg00178249	0.20722654	0.210491875	0.2397211
cg00284153	0.6291812	0.645383531	8.45281E-08
cg00295339	0.94771763	0.94751594	0.7659865
cg00380835	0.74041844	0.779700844	3.6853E-48
cg00549219	0.4402119	0.444518224	0.2673082
cg00616922	0.95090747	0.951576707	0.1768622
cg00668034	0.22873846	0.239005099	0.05562816
cg00697358	0.84656619	0.849918297	0.1747424
cg00779216	0.75719151	0.759914162	0.2300414
cg00788177	0.12906659	0.134293886	0.1870585
cg00815440	0.01045778	0.01044907	0.9305097
cg00845862	0.02946731	0.029652953	0.5630539
cg00846121	0.86361652	0.865733048	0.2228284
cg00964109	0.01183793	0.011724312	0.4473895
cg01154573	0.01352264	0.013559338	0.7659865
cg01198591	0.04118068	0.04318176	0.1551233
cg01240049	0.88363526	0.888104586	0.01057448
cg01283863	0.95507173	0.955521172	0.4072994
cg01330312	0.77391814	0.774935805	0.7440688
cg01397939	0.38810596	0.396766654	0.00011298
cg01411468	0.92257617	0.933420123	1.26968E-12
cg01502872	0.26467011	0.264038505	0.811521
cg01546563	0.1292038	0.125979448	0.1434667
cg01815833	0.0254163	0.025306478	0.8024407
cg02012703	0.11240353	0.112911434	0.8023217
cg02021288	0.8237959	0.820060127	0.1534882

cg02033302	0.71107632	0.717584688	0.006621538
cg02440976	0.01595504	0.016007914	0.6585425
cg02493604	0.07910375	0.079218722	0.9517672
cg02504902	0.86003648	0.875486897	7.55121E-13
cg02613380	0.94954078	0.952041939	1.57038E-05
cg02631879	0.01528417	0.015650696	0.4563141
cg02806322	0.75089225	0.760056177	1.31511E-05
cg02830714	0.94905328	0.949217764	0.8320486
cg03206925	0.95450323	0.956274081	0.006776076
cg03318593	0.94517853	0.945546979	0.7659865
cg03454705	0.94211574	0.941637977	0.2289362
cg03523835	0.17066817	0.174034979	0.1747424
cg03552688	0.95985134	0.962409335	2.09537E-05
cg03591798	0.03447532	0.034326159	0.7952533
cg03603381	0.55829467	0.571340473	5.20594E-11
cg03612522	0.02987886	0.029775071	0.8469719
cg03764965	0.84014945	0.847386484	0.004543919
cg03791150	0.92590865	0.931427581	4.13411E-10
cg03897712	0.02738225	0.028314977	0.001660234
cg03917158	0.85410775	0.854560929	0.8291399
cg03922337	0.15495776	0.163709336	1.6947E-16
cg03938598	0.02645677	0.026315627	0.8024407
cg04276508	0.07283903	0.074651596	0.1932282
cg04300684	0.53469052	0.505786098	7.08008E-08
cg04338871	0.6741962	0.683706213	0.002612561
cg04379155	0.01805047	0.017804687	0.3354398
cg04393471	0.94511639	0.945218367	0.9305097
cg04427735	0.00864506	0.008458977	0.1100234
cg04456892	0.91369662	0.912503997	0.4936289
cg04458670	0.02299539	0.025273104	5.89511E-05
cg04730882	0.35418876	0.359704605	0.003470847

cg04800788	0.92392269	0.928567365	5.29813E-08
cg04804542	0.86811638	0.872293814	0.04984412
cg04827747	0.0120057	0.012142951	0.06104231
cg04929736	0.02632464	0.026226671	0.805865
cg05005659	0.94775253	0.951312908	0.000210125
cg05347216	0.61562419	0.607575812	0.000496259
cg05453333	0.31287689	0.310320094	0.4473895
cg05459971	0.35325474	0.372120463	2.5017E-06
cg05478824	0.62652694	0.625713873	0.837371
cg05499853	0.01782655	0.017866197	0.8214504
cg06100461	0.06666467	0.066981879	0.8024407
cg06155303	0.29759262	0.334689604	2.37168E-18
cg06376277	0.88733509	0.892669751	0.000400618
cg06382254	0.94982495	0.953266852	0.000006456
cg06408034	0.02705669	0.026694588	0.4473587
cg06418907	0.38295105	0.384082316	0.8024407
cg06436673	0.96246947	0.964520213	0.1363552
cg06773604	0.02771975	0.029220305	0.000217691
cg06890950	0.76827007	0.769505077	0.7783067
cg06911679	0.923253	0.926617845	0.0006456
cg07015663	0.84660682	0.848419866	0.2477632
cg07031996	0.1455926	0.14512796	0.8300571
cg07105947	0.13450664	0.147806192	0.000108698
cg07122529	0.72713874	0.731313517	0.2300414
cg07361385	0.96913929	0.970529982	5.89511E-05
cg07513561	0.96262694	0.963626463	0.007907952
cg07545743	0.30837788	0.320011077	0.02597441
cg07764113	0.84288543	0.840901313	0.5121869
cg07799386	0.09218271	0.094209988	0.1741885
cg07846297	0.14843267	0.150739046	0.12105
cg08069883	0.8084274	0.815907877	0.000402556

cg08122338	0.02539538	0.025325591	0.8811339
cg08220084	0.03895264	0.040035359	0.1845172
cg08421126	0.25305366	0.255224475	0.2585871
cg08570458	0.95446321	0.95664953	0.000235253
cg08615567	0.08744007	0.091646716	0.006008831
cg08693172	0.14543769	0.147709499	0.4473895
cg08790487	0.91713536	0.919099112	0.1119232
cg09062550	0.11324341	0.113864512	0.8024407
cg09135656	0.76687302	0.762111709	0.3354398
cg09178385	0.82794409	0.836735747	3.15403E-05
cg09264065	0.48855514	0.52139771	6.994E-23
cg09284949	0.22763095	0.19635569	1.27103E-16
cg09287190	0.41326462	0.416510742	0.24748
cg09298014	0.06879225	0.077160597	1.27711E-08
cg09430976	0.02326638	0.023384074	0.8214504
cg09436495	0.79545639	0.798029022	0.2603782
cg09463656	0.06354496	0.063660055	0.9326718
cg09741221	0.04794629	0.048743499	0.2857081
cg09867084	0.90759998	0.910090956	0.005631067
cg09981030	0.02118936	0.02118163	0.9863333
cg10042319	0.02970335	0.031895207	2.152E-07
cg10086141	0.02469616	0.024244482	0.2476225
cg10137837	0.32732382	0.338338996	5.68263E-08
cg10197862	0.01962838	0.019735399	0.4065568
cg10442251	0.52114124	0.535732908	7.12466E-06
cg10442735	0.89969056	0.902355832	0.1183124
cg10521014	0.53174386	0.533214412	0.7915947
cg10716862	0.90709192	0.908609051	0.53531
cg10845249	0.12378774	0.126648879	0.2300414
cg10884288	0.04859265	0.050792374	0.00160119
cg11352369	0.91263601	0.914790372	0.04890909

cg11571942	0.89022465	0.891443684	0.2567727
cg11728928	0.29951645	0.303285247	0.4434066
cg11753765	0.0274747	0.029409776	8.12604E-05
cg11761728	0.32048304	0.325056358	0.01069886
cg11888571	0.01762917	0.017541554	0.8193292
cg11990334	0.0733973	0.075752209	0.2399189
cg12063795	0.24392602	0.243865421	0.9826113
cg12153668	0.81991514	0.830428023	3.14394E-06
cg12226306	0.14751235	0.14949392	0.2289362
cg12346504	0.01551764	0.01568627	0.6181827
cg12416637	0.04044338	0.039561378	0.2289362
cg12532966	0.84560692	0.850668008	0.03147872
cg12841525	0.8517187	0.85660277	0.047075
cg12858300	0.0163708	0.016530306	0.329689
cg12903529	0.85671824	0.866156656	4.88683E-05
cg12920180	0.09328164	0.095989235	0.2289362
cg12958778	0.7257577	0.734699749	0.000178471
cg13214542	0.09717336	0.097668665	0.8024407
cg13251292	0.87232593	0.875138183	0.2566928
cg13257129	0.86239076	0.868595301	0.008351512
cg13415073	0.10183125	0.107537822	0.003673877
cg13446622	0.91100134	0.915060704	0.00267394
cg13448092	0.59668003	0.590516236	0.2300414
cg13463245	0.81078363	0.807887931	0.3623588
cg13580008	0.02582386	0.025374774	0.2231704
cg13718961	0.90134212	0.909583663	8.4466E-22
cg13807056	0.89878117	0.90485048	0.001336323
cg14074486	0.69496203	0.705761845	2.56941E-07
cg14121142	0.04100012	0.04490217	0.008351512
cg14133708	0.04817508	0.048690267	0.7388203
cg14235783	0.03490175	0.034300926	0.2673082

cg14312661	0.94709223	0.94740029	0.751726
cg14727952	0.02366804	0.02361159	0.8811339
cg14762973	0.06256058	0.063904141	0.5035128
cg14821507	0.02071654	0.020803245	0.6926121
cg14844194	0.1527787	0.158403321	0.02327435
cg14923295	0.01548794	0.015543837	0.6832347
cg15081825	0.76421339	0.768065598	0.4710984
cg15349474	0.94768242	0.948792569	0.04721224
cg15364504	0.84316391	0.850931172	0.002143723
cg15739944	0.02172167	0.021367435	0.5163719
cg15825186	0.0216944	0.021919112	0.7185787
cg15996769	0.32133988	0.337130398	2.97636E-06
cg16005939	0.18548533	0.190787977	0.01121337
cg16218705	0.88664416	0.890462077	0.3649591
cg16520800	0.02074738	0.021019908	0.2397211
cg16596470	0.97268657	0.972950518	0.341485
cg16619425	0.05512619	0.059504217	5.79247E-05
cg16631088	0.82325635	0.841250428	4.94288E-12
cg16851425	0.1020518	0.102712251	0.7867655
cg16937735	0.60400759	0.620827609	2.73483E-10
cg16944026	0.95926577	0.959454336	0.7783067
cg16961545	0.02480515	0.024711424	0.862952
cg16978871	0.01349794	0.013510411	0.9451073
cg17099568	0.14696479	0.151779387	0.048958
cg17331296	0.07388515	0.072352709	0.538
cg17469978	0.04744632	0.045549368	0.007229375
cg17531889	0.93830515	0.939070663	0.3858229
cg17584477	0.95487962	0.955672452	0.2604331
cg17779289	0.966167	0.966380222	0.5847826
cg17791651	0.57487655	0.595586109	1.6409E-15
cg17825384	0.02365016	0.023782885	0.6532857

cg17865114	0.95143862	0.953281848	0.000057835
cg17884698	0.95781925	0.958107423	0.5512512
cg17886028	0.01777533	0.017791895	0.9451073
cg18086761	0.06642791	0.068131302	0.4473895
cg18207091	0.02494037	0.025356759	0.5745631
cg18598900	0.07088687	0.072099249	0.5050612
cg18605120	0.93271021	0.932714301	0.997
cg18766080	0.02251333	0.022392814	0.7952533
cg18916055	0.87493137	0.874835272	0.9696274
cg19246761	0.08484054	0.082469422	0.175704
cg19399220	0.28103753	0.265107892	1.32507E-07
cg19407717	0.8723388	0.877941395	0.00060639
cg19531536	0.45638608	0.48506147	8.9039E-37
cg19615017	0.66761604	0.670326365	0.6512632
cg19880462	0.11121461	0.108836595	0.2289362
cg20100987	0.73623035	0.747374251	5.95939E-14
cg20326704	0.06693369	0.080600025	2.70537E-18
cg20395881	0.64511559	0.653942524	0.04714433
cg20413392	0.85533839	0.852730889	0.4186124
cg20506843	0.53583564	0.542926044	0.329689
cg20566286	0.92798539	0.928975282	0.2437248
cg20606555	0.76190802	0.764352055	0.538
cg20639805	0.32798408	0.372460976	3.29077E-31
cg20844771	0.01543032	0.015102398	0.1440746
cg20922251	0.03211064	0.032654739	0.01303615
cg21244880	0.01571983	0.0158056	0.5065939
cg21365094	0.04850061	0.046962078	0.2103459
cg21371809	0.26956099	0.265685871	0.4473895
cg21531679	0.94099427	0.94298578	0.1605107
cg21558508	0.01339452	0.013466776	0.4453934
cg21587066	0.09330338	0.092772035	0.8300571

cg21616420	0.95669641	0.958222857	0.01282233
cg21969795	0.74956769	0.757652125	0.002899662
cg21994822	0.66081969	0.655212663	0.1274826
cg21996068	0.54517711	0.556029723	0.003326507
cg22063247	0.37974464	0.371364492	0.003243371
cg22391400	0.011535	0.011303061	0.1085872
cg22691824	0.7133124	0.720137557	0.00298629
cg22753768	0.16210773	0.161696145	0.8755896
cg22773555	0.01821075	0.017697478	0.329689
cg22784964	0.01311743	0.013208519	0.3769128
cg22883125	0.02760152	0.02767862	0.8320486
cg22908581	0.42664251	0.426491765	0.975125
cg23028436	0.06785963	0.069812587	0.04984412
cg23087931	0.96034556	0.960969909	0.2235074
cg23483656	0.10846348	0.109980304	0.4434066
cg23497569	0.94859057	0.950157554	0.2058258
cg23528492	0.77355495	0.774005914	0.9240941
cg23646360	0.2809995	0.297255569	2.73828E-05
cg23832388	0.64937939	0.652115089	0.5745631
cg23928512	0.85352002	0.853044957	0.8193292
cg23931558	0.10526118	0.109975864	0.08198095
cg24036116	0.81175374	0.821037861	4.02844E-05
cg24362016	0.57194556	0.588801689	5.51137E-05
cg24526433	0.01472322	0.014601141	0.3818563
cg24591300	0.45479133	0.472695179	2.15424E-15
cg24612305	0.02026427	0.021223631	0.04077474
cg24670552	0.88373103	0.889265878	0.006008831
cg24731731	0.58343984	0.611364315	7.8279E-09
cg24792682	0.05809228	0.058568899	0.7031535
cg24875593	0.84606152	0.837244819	0.2841313
cg24915508	0.94497843	0.946390852	0.1857977

cg24956533	0.07698776	0.077341201	0.8811339
cg24958687	0.31670006	0.30776088	0.1100234
cg25055120	0.94731815	0.94354373	0.001142148
cg25511429	0.0931265	0.092088066	0.4637448
cg25566285	0.95055679	0.952678922	0.09578411
cg25774020	0.92609292	0.931161217	0.1001278
cg25884854	0.01495966	0.014253054	0.000113402
cg25926515	0.36105646	0.384927735	8.0969E-16
cg25987408	0.82365331	0.833793407	1.68736E-08
cg25994470	0.01603081	0.016155502	0.3485858
cg26053975	0.93120769	0.933078806	0.008351512
cg26070426	0.23242671	0.229498579	0.4434066
cg26234034	0.01852287	0.018515323	0.984985
cg26471610	0.94765203	0.949957743	7.12466E-06
cg26607429	0.95421099	0.955775788	0.1747424
cg26901714	0.86566625	0.86992686	0.007306173
cg26937798	0.01846308	0.017875041	0.08780566
cg26955337	0.98254318	0.982459595	0.3818563
cg27111925	0.35220067	0.355807776	0.344256
cg27226927	0.78542235	0.786589855	0.656564
cg27425146	0.96754543	0.967870615	0.4473895
cg27532331	0.96654603	0.966543031	0.9946978
cg27585878	0.9619612	0.962014053	0.9326718
cg27622405	0.01253221	0.012636875	0.4207821

Bonferroni corrected p-values are reported.

Table S4. Hazard ratios (95% confidence interval) for cardiovascular disease mortality and cardiovascular disease incidence by lead epigenetic biomarkers after adjustment for urinary cadmium (N = 2,321)

CVD Mortality

Epigenetic biomarker	Tertile 1	Tertile 2	Tertile 3	Per double increase
eTibia lead	< 3.6 µg/g	3.6 - 3.9 µg/g	> 3.9 µg/g	
	1.00 (Reference)	1.18 (0.94 - 1.49)	1.19 (0.94 - 1.52)	**1.42 (1.08- 1.88)**
ePatella lead	< 4.3µg/g	4.3 - 4.5 µg/g	> 4.5 µg/g	
	1.00 (Reference)	0.98 (0.77 - 1.23)	1.12 (0.88 - 1.43)	1.22 (0.93 - 1.59)
eBlood lead	< 1.4 µg/dL	1.4 - 1.7 µg/dL	> 1.7 µg/dL	
	1.00 (Reference)	1.17 (0.93 - 1.48)	**1.28 (1.00 – 1.64)**	**1.56 (1.16 - 2.11)**

CVD Incidence

Epigenetic biomarker	Tertile 1	Tertile 2	Tertile 3	Per double increase
eTibia lead	< 3.6 µg/g	3.6 - 3.9 µg/g	> 3.9 µg/g	
	1.00 (Reference)	0.96 (0.83 - 1.12)	1.03 (0.88 - 1.21)	0.99 (0.83 - 1.19)
ePatella lead	< 4.3µg/g	4.3 - 4.5 µg/g	> 4.5 µg/g	
	1.00 (Reference)	0.89 (0.77 - 1.05)	1.03 (0.88 - 1.21)	1.07 (0.89 - 1.28)
eBlood lead	< 1.4 µg/dL	1.4 - 1.7 µg/dL	> 1.7 µg/dL	
	1.00 (Reference)	1.07 (0.92 - 1.25)	1.00 (0.85 – 1.18)	1.06 (0.87 – 1.30)

All models adjusted for sex, smoking status (never, former, current), BMI (kg/m2), genetic PC's, immune cell types (CD8+, CD4+, NK, B cells, monocytes), LDL-cholesterol (mg/dL) HDL-cholesterol (mg/dL), diabetes status (yes/no), blood pressure (mmHg),

hypertension treatment (yes/no), and estimated glomerular filtration rate (ml/min/1.73m2) and urinary cadmium (expressed in micrograms per gram of urine creatinine). All models included center of recruitment as a strata term, and age was accounted for in the follow-up times of all models. Tertiles were calculated on log2-transformed lead epigenetic biomarker concentrations.

Figure S1. Principal Component Regression Analysis including blood lead exposure: univariate association *P*-values between covariates of interest and the top 25 principal components that explain 56% of the variance for the whole blood DNA methylation data.

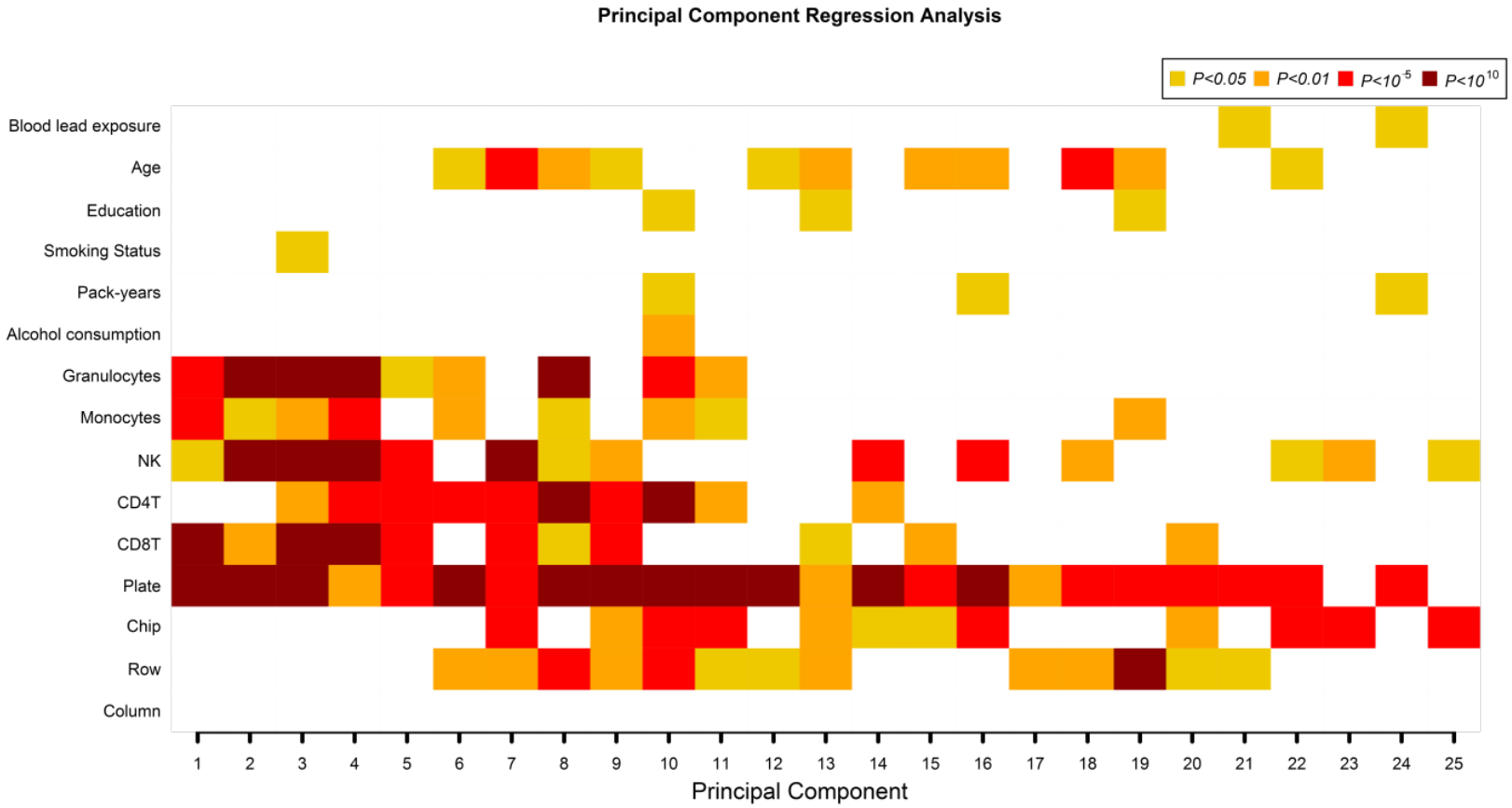


Figure S2. Quantile-Quantile plot and genomic inflation factor (lambda) for the Epigenome-Wide Association Analysis.

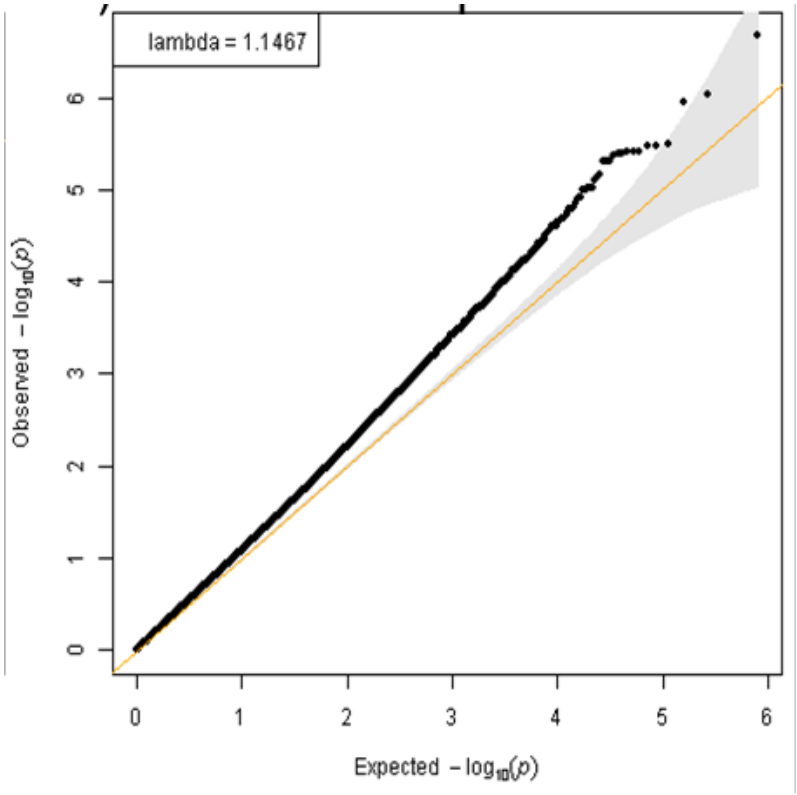


Figure S3. Alpha parameter selection (left) and Lambda parameter selection (right) of the elastic-net algorithm for methylation lead biomarkers in blood.

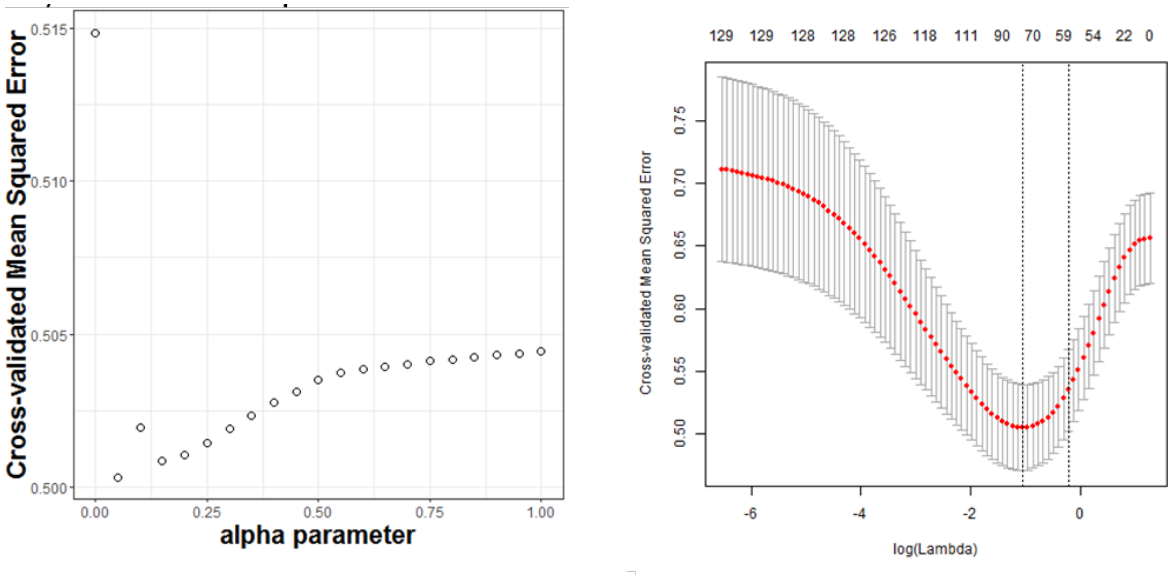
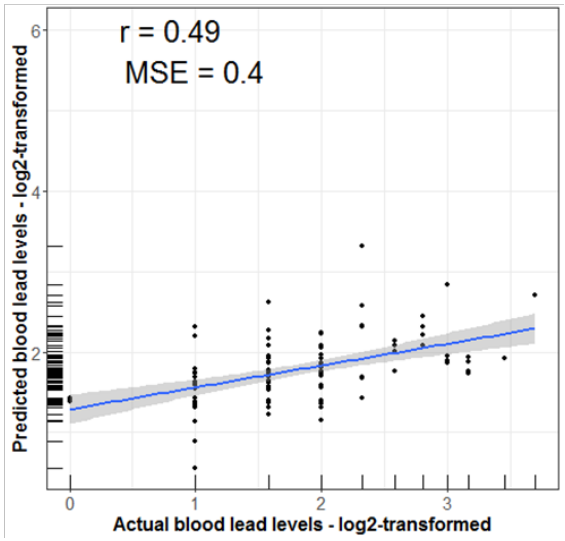
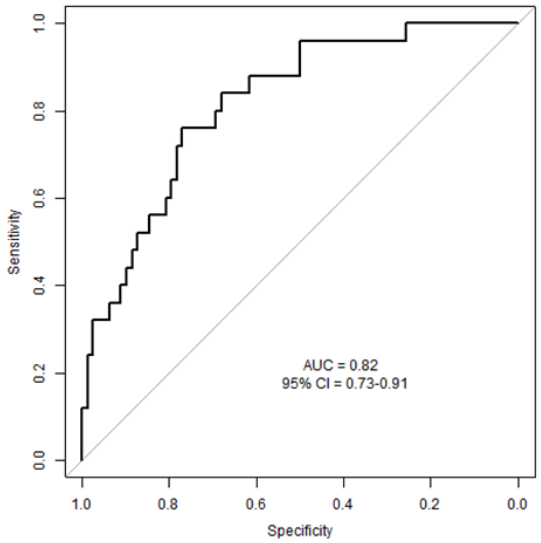


Figure S4. Relationship between actual and predicted (log_2-transformed) lead levels in whole blood (left), *Receiver Operating Characteristic, and* Area Under the Curve (AUC) *with* 95% Confidence Interval (95% CI) *(middle), and* box-plots and P-value for statistical difference between the means of actual and predicted (log_2-transformed) lead levels in blood (right).





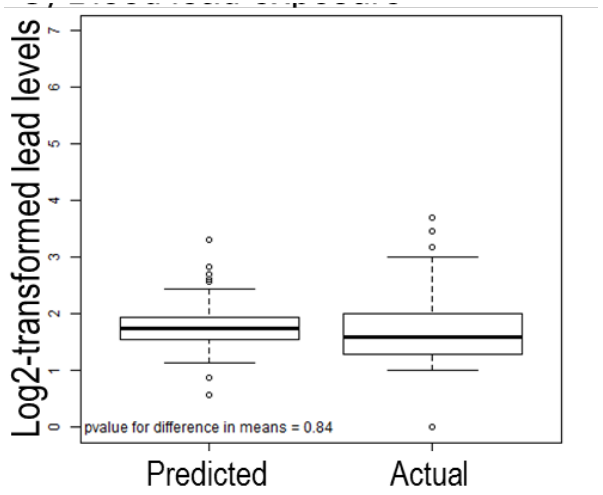


Figure S5. Empirical distribution function and Kolmogorov-Smirnov test of the actual and predicted lead levels in whole blood.

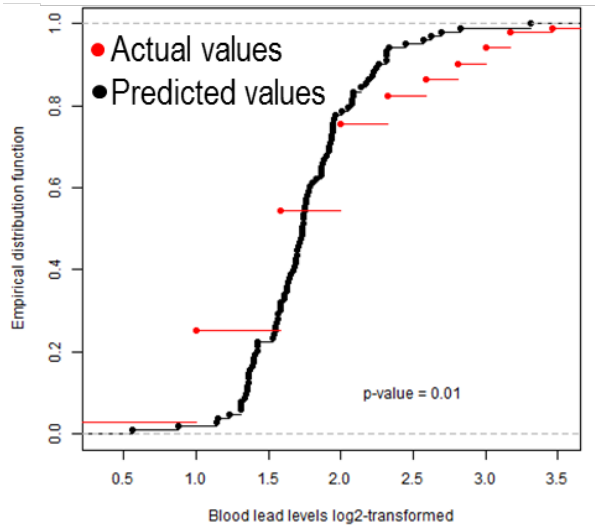


Figure S6. Distribution of tibia, patella, and blood epigenetic lead biomarkers in their native scale in the Strong Heart Study (n=2,231).

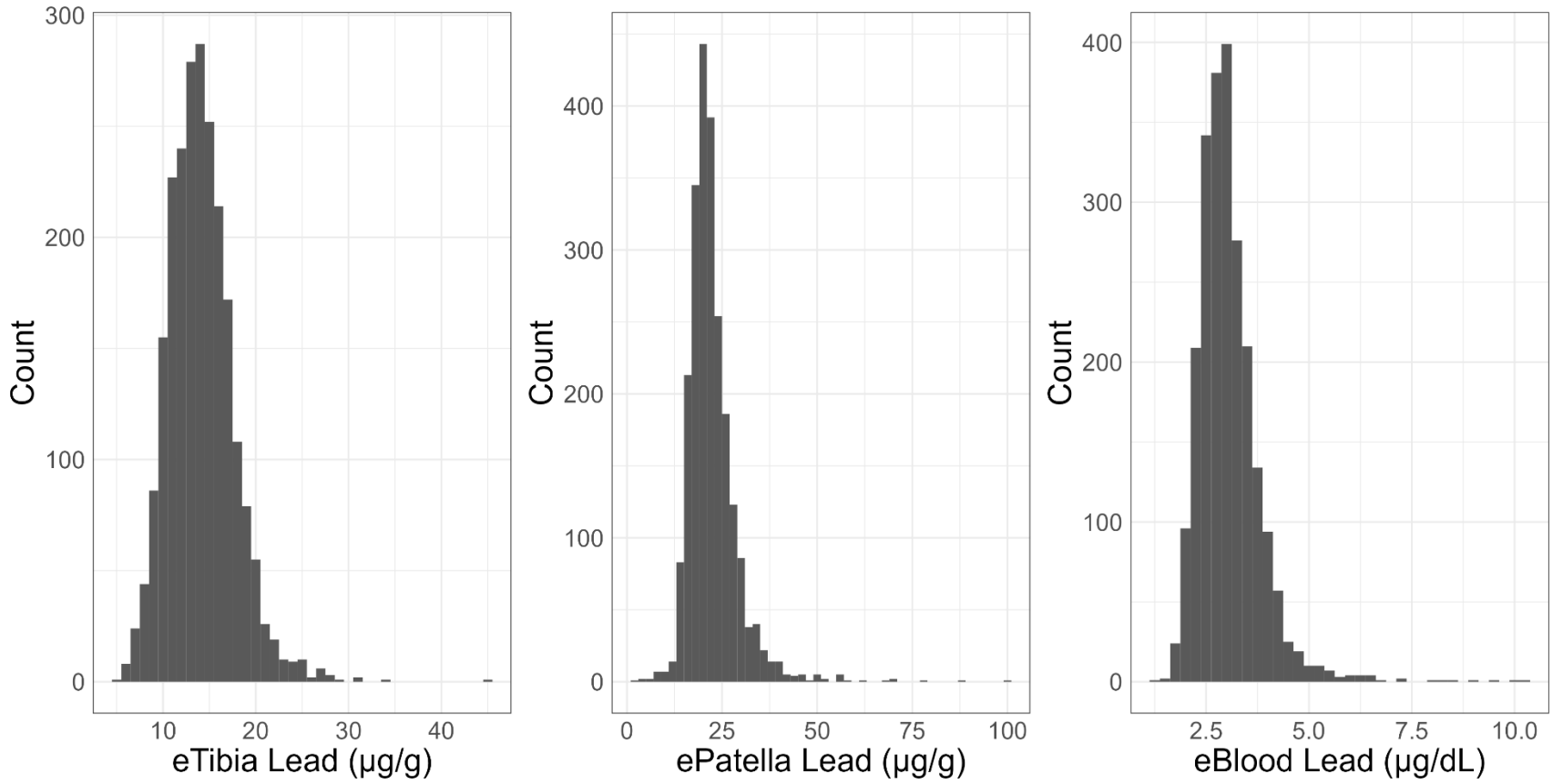
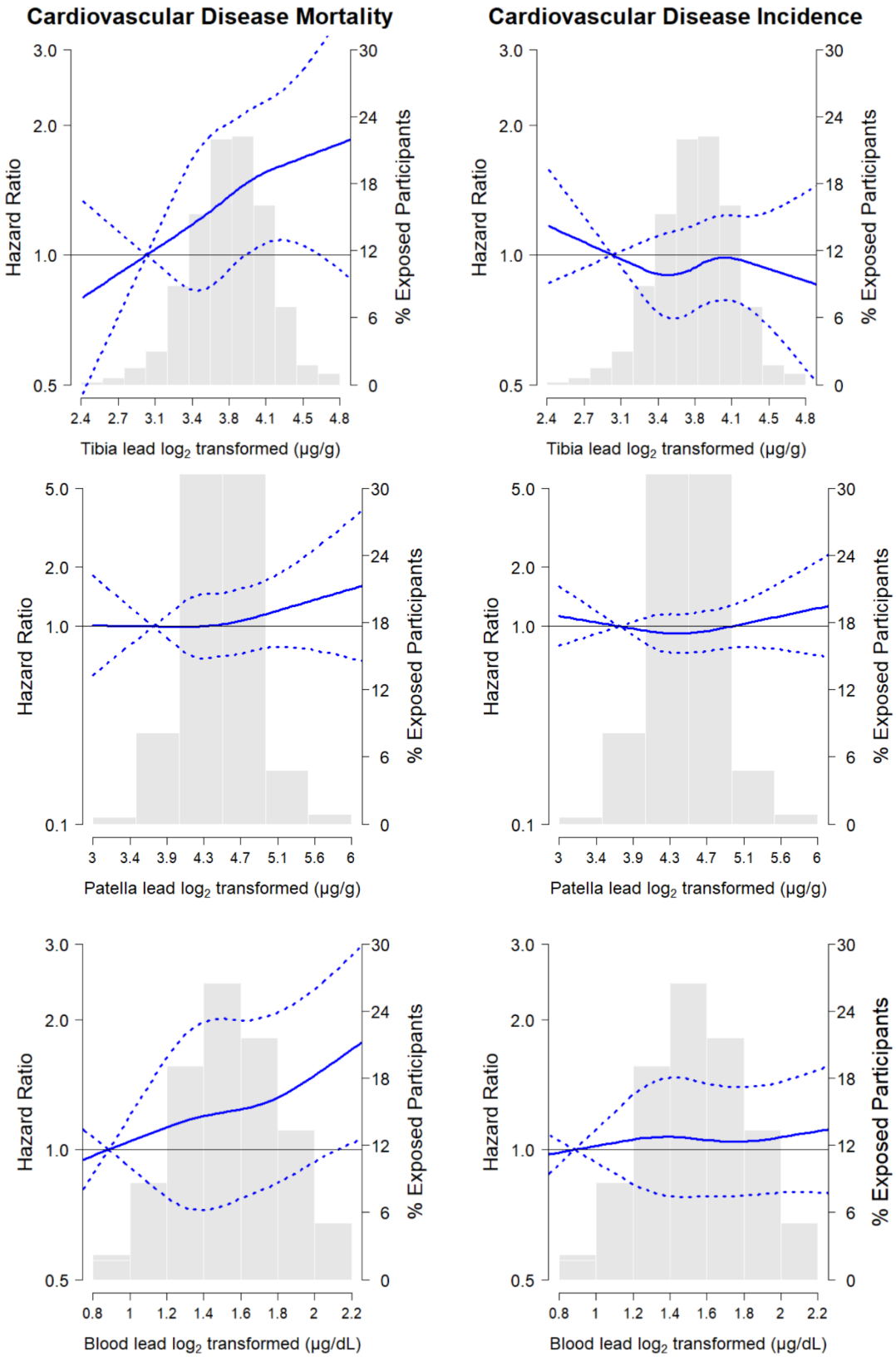


Figure S7. Associations between lead epigenetic biomarkers (eTibia, ePatella, eBlood) and cardiovascular disease mortality and incidence modeling lead epigenetic biomarkers using restricted quadratic splines (N = 2,321).



Hazard ratios incorporated restricted quadratic splines for epigenetic lead biomarkers with knots at the 10^{th}, 50^{th}, and 90^{th} percentiles, where the 10^{th} percentile was treated as the reference. Solid lines represent adjusted hazard ratios, and dotted lines represent 95% confidence intervals. All models were further adjusted for sex, smoking status (never, former, current), BMI (kg/m^2), genetic PCs, immune cell types (CD8+, CD4+, NK, B cells, Monocytes), LDL (mg/dL), HDL (mg/dL), diabetes status (yes/no), systolic blood pressure (mmHg), hypertension treatment (yes/no), and eGFR ($ml/min/1.73m^2$). All models included center of recruitment as a strata term, and age was accounted for in the follow-up times of all models.