SUPPLEMENTARY FIGURES

Methods		PEND		B value
DNA methylation-estimated granulocyte prop	ortions	nsnp	OK(95% CI)	P value
MR Egger	+	4	1.005(0.994-1.016)	0.495
Weighted median	•	4	1.002(0.997-1.007)	0.400
Inverse variance weighted	•	4	1.002(0.998-1.007)	0.325
Simple mode	•	4	1.003(0.995-1.011)	0.484
Weighted mode	•	4	1.002(0.996-1.007)	0.545
DNA methylation GrimAge acceleration				
MR Egger	•	4	1.135(0.65-1.983)	0.699
Weighted median		4	1.193(0.974-1.461)	0.087
Inverse variance weighted	••	4	1.149(0.926-1.427)	0.207
Simple mode	•	4	1.283(0.907-1.815)	0.254
Weighted mode	••	4	1.209(0.946-1.543)	0.226
DNA methylation Hannum age acceleration				
MR Egger		4	1,248(0,858-1,816)	0.366
Weighted median	,	4	1.121(0.915-1.374)	0.270
Inverse variance weighted	•	4	1.118(0.933-1.338)	0.227
Simple mode	······•	4	1.084(0.813-1.446	0.622
Weighted mode	• • • • • • • • • • • • • • • • • • •	4	1.17(0.925-1.481)	0.282
Intrinsic epigenetic age acceleration				
MR Fager	•	1	1 708/1 0/1-2 801)	0 168
Weighted median		4	1 138(0 924-1 401)	0.100
Inverse variance weighted		4	1.013(0.696 - 1.474)	0.947
Simple mode		4	1.113(0.884-1.403)	0.430
Weighted mode	• • • • • • • • • • • • • • • • • • •	4	1.154(0.918-1.45)	0.307
DNA methylation-estimated plasminogen acti	vator inhibitor-1 levels		, , , , , , , , , , , , , , , , , , ,	
MR Egger		4	2 022/0 506 6 96)	0.276
Weighted median	•	4	2.022(0.090-0.00) 1.084(0.632-1.858)	0.370
Inverse variance weighted		4	1.00+(0.032-1.030) 1.057(0.641-1.742)	0.770
Simple mode	•	4	0.817(0.357-1.873)	0.666
Simple mode	· · · · · · · · · · · · · · · · · · ·	4	1.231(0.676-2.24)	0.545
DNA methylation Phone Age acceleration	•	-		
MR Egger			4 000(0 000 0 074)	0.400
MR Eggel		4	1.626(0.989-2.674)	0.196
weighted median		4	1.220(0.931-1.013)	0.140
Inverse variance weighted	•	4	1.100(0.939-1.503)	0.152
Simple mode	•	4	1 256(0 915-1 723)	0.307
weighted mode	•	-	1.200(0.010-1.720)	0.200
MR Egger	-	4	1.008(0.96-1.06)	0.773
Weighted median	•	4	0.993(0.979-1.007)	0.308
Inverse variance weighted	•	4	0.991(0.969-1014)	0.458
Simple mode	•	4	1.000(0.978-1.023)	0.987
Weighted mode	• · · · · · · · · ·	4	0.993(0.977-1.006)	0.410
0.5 0.7	5 1 1.25 1.5 1.75 2 2.25 2.5			

Supplementary Figure 1. Examination of the association between an increase in Cardioembolic stroke exposure and the risk of DNA histone modifications-estimated phenotypes and Telomere length, utilising Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods				Duralius
DNA methylation-estimated granulocy	te proportions	nSNP	OR(95% CI)	P value
MR Egger	•	4	1.009(0.992-1027)	0.405
Weighted median	•	4	0.996(0.990-1.002)	0.179
Inverse variance weighted	•	4	0.999(0.993-1.005)	0.744
Simple mode	•	4	0.996(0.987-1.005)	0.399
Weighted mode	•	4	0.995(0.988-1.002)	0.277
DNA methylation GrimAge acceleratio	n			
MR Egger	•	4	1 207(0 631-2 309)	0 627
Weighted median	·•	4	0.901(0.698-1.161)	0.42
Inverse variance weighted	_	4	0.905(0.734-1.116)	0.351
Simple mode	•	4	0.894(0.644-1241)	0.55
Weighted mode	•	4	0.873(0.628-1.213)	0.477
DNA methylation Hannum age acceler	ration			
MR Egger	•	4	0 060/0 400 1 018)	0.027
Weighted median		4	0.909(0.490-1.910) 0.888(0.602-1.14)	0.937
Inverse variance weighted		4	0.000(0.032-1.14) 0.904(0.733-1.114)	0.343
Simple mode		4	0.878(0.607-1.269)	0.538
Weighted mede		4	0.862(0.626-1.188)	0.431
Intrincia opigonatio ago accoloration	• • • • • • • • • • • • • • • • • • •			
			0 500/0 000 4 404	0.050
	•	4	0.583(0.300-1.131)	0.252
weighted median	•	4	1.147(0.890-1.479)	0.289
Inverse variance weighted	•	4	1.001(0.034-1.349)	0.03
Simple mode	•	4	1.159(0.04-1.596)	0.435
Weighted mode	• • •	-	1.139(0.070-1.333)	0.570
DNA methylation-estimated plasminog	gen activator inhibitor-1 levels			
MR Egger		4	0.002(0-0.332)	0.14
Weighted median	•	- 4	1.501(0.701-3.213)	0.296
Inverse variance weighted	•	- 4	1.152(0.495-2.684)	0.743
Simple mode	•	- 4	1.678(0752-3.746)	0.296
Weighted mode	•	4	1.392(0.654-2.963)	0.454
DNA methylation PhenoAge accelerat	ion			
MR Egger		4	0.499(0.195-1.277)	0.284
Weighted median	·	4	0.947(0.684-1.311)	0.744
Inverse variance weighted	••	4	0.902(0.688-1.183)	0.457
Simple mode	•	4	1.035(0.632-1.696)	0.899
Weighted mode		4	0.999(0.646-1.546)	0.996
telomere length				
MR Egger		4	1.01(0.973-1.048)	0.664
Weighted median	•	4	0.994(0.978-1.009)	0.425
Inverse variance weighted	•	4	0.993(0.980-1.007)	0.314
Simple mode	•	4	1.001(0.977-1.026)	0.931
Weighted mode	•	4	0.990(0.969-1.011)	0.408
	0.5 0.75 1 1.25 1.5 1.75 2 2.25 2	5		

Supplementary Figure 2. Examination of the association between an increase in Large-artery atherosclerosis stroke exposure and the risk of DNA histone modifications-estimated phenotypes and Telomere length, utilising Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods				Dualua
DNA methylation-estimated granulocyte pr	roportions	NSNP	UK(95% CI)	P value
MR Egger	•	31	1.001(0.996-1.006)	0.699
Weighted median	•	31	1.003(1.000-1.006)	0.067
Inverse variance weighted	•	31	1.002(1.000-1.004)	0.078
Simple mode	•	31	1.004(0.998-1.011)	0.215
Weighted mode	•	31	1.004(0.998-1.010)	0.188
DNA methylation GrimAge acceleration				
MR Egger		31	0.798(0.630-1.012)	0.072
Weighted median	+	31	0.934(0.810-1.075)	0.341
Inverse variance weighted		31	0.941(0.846-1.047)	0.267
Simple mode		31	0.937(0.710-1.237)	0.650
Weighted mode	••	31	0.946(0.727-1.230)	0.681
DNA methylation Hannum age acceleratio	n			
MR Egger	·	31	1,296(1,026-1,637)	0.038
Weighted median	·•	31	1.017(0.893-1.158)	0.798
Inverse variance weighted		31	0.988(0.882-1.107)	0.841
Simple mode	·	31	1.029(0.817-1.296)	0.810
Weighted mode	•	31	1.058(0.829-1.351)	0.651
Intrinsic epigenetic age acceleration				
MR Egger	· · · · · · · · · · · · · · · · · · ·	31	1 207(0 968-1 505)	0 106
Weighted median		31	0.986(0.857-1.134)	0.841
Inverse variance weighted	_ _	31	0.968(0.877-1.068)	0.514
Simple mode	•	31	1.008(0.776-1.309)	0.954
Weighted mode	······	31	1.000(0.760-1.315)	0.999
DNA methylation-estimated plasminogen a	activator inhibitor-1 levels			
MR Egger	•	31	0 896(0 267-3 007)	0 860
Weighted median		31	1.299(0.870-1.940)	0.201
Inverse variance weighted		31	1.319(0.967-1.798)	0.081
Simple mode	•	31	0.909(0.248-3.334)	0.886
Weighted mode	•	31	0.909(0.243-3.401)	0.888
DNA methylation PhenoAge acceleration				
MR Egger	·	31	0.986(0.721-1.348)	0.932
Weighted median	-	31	0.947(0.791-1.133)	0.549
Inverse variance weighted	- _	31	0.967(0.845-1.105)	0.620
Simple mode		31	0.988(0.700-1.395)	0.945
Weighted mode	· · · · · · · · · · · · · · · · · · ·	31	1.058(0760-1.474)	0.741
telomere length				
MR Egger	•	31	1.003(0.989-1018)	0.648
Weighted median	•	31	1.003(0.994-1.011)	0.531
Inverse variance weighted	+	31	1.006(0.999-1.014)	0.079
Simple mode	+	31	1.003(0.984-1.021)	0.785
Weighted mode	+	31	1.001(0.982-1.020)	0.924
0.5	0.75 1 1.25 1.5 1.75 2 2.25 2.5	5		

Supplementary Figure 3. Examination of the association between an increase in Small-vessel stroke exposure and the risk of DNA histone modifications-estimated phenotypes and Telomere length, utilising Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods	to proportions	nSNP	OR(95% CI)	P value
Inverse variance weighted		2	0 201/0 50080 867)	0.945
DNA methylation GrimAge acceleration		2	0.301(0-30069.667)	0.045
MR Egger		4	2 222 0 242 20 272)	0 550
Weighted median	•	4	2.227(0.243-20.377) 0.050(0.832.1.106	0.552
Inverse variance weighted		4	0.935(0.832-1.100	0.304
Simple mode		4	0.902(0.72 - 1.132)	0.439
Simple mode		4	1003(0.829-1213)	0.977
NA mothylation Hannum and accolo	ration			
MD Error	allon	0	0 760/0 604 0 070)	0.077
MR Egger		O Q	0.769(0.604-0.979) 0.047(0.860.1.032)	0.077
		8	0.947(0.809-1.032) 0.947(0.886-1011)	0.217
Inverse variance weighted	•	8	0.947(0.000-1011)	0.348
Simple mode	•	8	0.925(0.823-1.039)	0.232
Weighted mode	•	Ū	0.010(0.010 1.000)	0.202
Intrinsic epigenetic age acceleration				
MR Egger	•	24	0.996(0.889-1.116)	0.943
Weighted median	•	24	101(0.959-1.064)	0.715
Inverse variance weighted		24	1028(0.987-1.071)	0.188
Simple mode	•	24	1.055(0.935-1.19)	0.395
Weighted mode		24	0.993(0.91-1084)	0.883
DNA methylation-estimated plasminog	gen activator inhibitor-1 levels			
MR Egger	•	5	1(1-1)	0.705
Weighted median	•	5	1(1-1)	0.321
Inverse variance weighted	•	5	1(1-1)	0.858
Simple mode	•	5	1(1-1)	0.371
Weighted mode	•	5	1(1-1)	0.409
DNA methylation PhenoAge accelerat	tion			
MR Egger	•	11	0.957(0.869-1.054)	0.393
Weighted median		11	0.977(0.926-1.031)	0.403
Inverse variance weighted		11	0.996(0.956-1037)	0.839
Simple mode	•	11	0.943(0.849-1047)	0.300
Weighted mode	·•	11	0.952(0.879-1032)	0.259
telomere length				
MR Egger	·	133	1.01(0.73-1.398)	0.954
Weighted median	·	133	1.011(0.773-1322)	0.938
Inverse variance weighted	•	133	1.015(0.849-1.214)	0.867
Simple mode	· · · · · · · · · · · · · · · · · · ·	133	0.829(0.44-1.561)	0.562
Weighted mode		133	0.977(0.655-1.457)	0.909
-	0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5			

Supplementary Figure 4. Analysis of the association between DNA methylation-estimated phenotypes and Telomere length exposure and the risk of Cardioembolic stroke using Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods		nSNP	OR(95% CI)	P value
DNA methylation-estimated granulocyt	e proportions			
Inverse variance weighted	·	2	0.091(0-71.62)	0.481
DNA methylation GrimAge acceleration	า			
MR Egger		4	0.184(0.012-2.922)	0.353
Weighted median	• • • • • • • • • • • • • • • • • • •	4	0.909(0.753-1.097	0.319
Inverse variance weighted		4	0.839(0702-1.001)	0.052
Simple mode	· · · · · · · · · · · · · · · · · · ·	4	0.928(0.701-1.228)	0.637
Weighted mode	• • • • • • • • • • • • • • • • • • •	4	0.9210.699-1.214)	0.600
DNA methylation Hannum age acceler	ation			
MR Egger	•	8	0.752(0.496-1.139)	0.227
Weighted median	•	8	1.032(0.925-1.151)	0.576
Inverse variance weighted	•	8	1.043(0.922-1.181)	0.503
Simple mode	······	8	1.032(0.89-1.198)	0.687
Weighted mode	······	8	1.025(0.91-1.155)	0.692
Intrinsic epigenetic age acceleration				
MR Egger	· · · · · · · · · · · · · · · · · · ·	24	1 1(0 971-1 246)	0 1/18
Weighted median	·•	24	1013(0 948-1 082)	0.140
Inverse variance weighted	· •	24	1 012(0 966-1 06)	0.628
Simple mode		24	0.937(0.828-1.062)	0.319
Weighted mode	·····•	24	0.935(0.838-1.045)	0.252
DNA methylation-estimated plasminor	en activator inhibitor-1 levels			
MR Egger		5	1(1-1)	0 718
Weighted median	•	5	1(1-1)	0.792
Inverse variance weighted	•	5	1(1-1)	0.669
Simple mode	•	5	1(1-1)	0.529
Weighted mode		5	1(1-1)	0.917
DNA methylation PhonoAge accelerati	on			
MR Eggor				0.040
Woighted median		11	0.953(0.793-1.144)	0.616
Inverse verience weighted		11	0.936(0.87 - 1.006)	0.073
		11	0.901(0.095-1.052) 0.004(0.8-1.02)	0.277
Simple mode		11	0.904(0.816-1.02)	0.133
vveigntea mode	•		0.300(0.010-1.01)	0.107
MR Egger	•	133	0.915(0.6-1398)	0.683
weighted median	•	133	0.849(0.615-1.173)	0.321
inverse variance weighted	•	133	0.912(0/23-1151)	0.437
Simple mode	· · · · · · · · · · · · · · · · · · ·	133	1.004(0.522-1.931)	0.991
Weighted mode		133	1.004(0.080-1.408)	0.980
	0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5			

Supplementary Figure 5. Analysis of the association between DNA methylation-estimated phenotypes and Telomere length exposure and the risk of Large-artery atherosclerosis stroke using Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods	to proportions		nSNP	OR(95% CI)	P value
DNA methylation-estimated granulocy	te proportions		2 1	2 544/0 029 6490 406	0 400
DNA mothylation GrimAge acceleration	n		2 1	3.341(0.020-0400.490) 0.400
MR Egger			4	0.044/0.000.4.704)	0.004
Weighted median			4	0.211(0.020-1.724) 0.069(0.927.1.122)	0.284
Inverse variance weighted			4	0.900(0.027-1.133) 0.964(0.845-1.1)	0.003
Simple mode	•	•	4	1047(0 82-1 337)	0.300
Simple mode			4	1.053(0.816-1.358)	0.719
NA mothylation Hannum and accel	rotion	·			•••••
DNA methylation Hannum age accele	ration		0	0 940/0 620 4 445)	0.225
MR Egger			ð Q	0.849(0.629-1.145)	0.325
weighted median	•		0 8	0.90(0.004-1.000) 0.90(0.911-1.077)	0.444
Inverse variance weighted	•		8	0.93(0.911-1.077) 0.939(0.791-1.114)	0.023
Simple mode			8	0.944(0.816-1.091)	0.458
vveignted mode	•		•		
Intrinsic epigenetic age acceleration					
MR Egger		•	24	1.162(1.021-1.322)	0.033
Weighted median		•	24	1.035(0.973-1.102)	0.274
Inverse variance weighted		◆	24	1.018(0.968-1.07)	0.495
Simple mode	,	•	24	1.037(0.919-1.17) 1.061(0.068 1.164)	0.557
Weighted mode		•	24	1.001(0.900-1.104)	0.219
DNA methylation-estimated plasminog	gen activator inhib	oitor-1 levels	_		
MR Egger	•	•	5	1(1-1)	0.490
Weighted median	•	•	5	1(1-1)	0.859
Inverse variance weighted	•	,	5	1(1-1)	0.800
Simple mode	•	,	5	1(1-1)	0.043
Weighted mode	•	,	5	(())	0.012
DNA methylation PhenoAge accelerat	ion				
MR Egger		•	11	1.086(0.922-1.279)	0.350
Weighted median		•	11	1072(0.996-1.154)	0.064
Inverse variance weighted		♦	11	1.021(0.955-1.091)	0.542
Simple mode	•		11	0.956(0.814-1.123)	0.596
Weighted mode		•	11	1.087(0.973-1.213)	0.170
telomere length					
MR Egger		•,	133	1048(0.719-1.528)	0.806
Weighted median	•		133	0.923(0.669-1.273)	0.624
Inverse variance weighted			133	0.998(0.811-1.228)	0.981
Simple mode	•		133	0.763(0.398-1.465)	0.418
Weighted mode	•		133	0.838(0.59-1.191)	0.327
	0.6 0.7 0.8 0.9	1 1.1 1.2 1.3 1.4 1.5			

Supplementary Figure 6. Analysis of the association between DNA methylation-estimated phenotypes and Telomere length exposure and the risk of Small-vessel stroke using Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods		nSNP	OR(95% CI)	P value
DNA methylation-estimated granulocyte pr	oportions			
Inverse variance weighted		2	2.7(0.029-248.09)	0.667
DNA methylation GrimAge acceleration				
MR Egger +		4	0.61(0.25-1.492)	0.392
Weighted median	·•	4	0.97(0.906-1.04)	0.394
Inverse variance weighted		4	0.965(0.913-1.021)	0.215
Simple mode	·····•	4	0.972(0.885-1.068)	0.596
Weighted mode		4	0.978(0.889-1.076)	0.677
DNA methylation Hannum age acceleration	n			
MR Egger	·····•	8	0.822(0.734-0.92)	0.014
Weighted median	_ -	8	1.008(0.964-1.054)	0.723
Inverse variance weighted		8	1004(0.955-1.055)	0.886
Simple mode		8	1046(0.975-1123)	0.248
Weighted mode	·•	8	1.01(0.955-1.068)	0.745
Intrinsic epigenetic age acceleration				
MR Eager		24	1 036(0 077-1 1)	0 248
Weighted median		24	1.030(0.377-1.1)	0.240
Inverse variance weighted	- • -	24	1.01(0.988-1.032)	0.393
Simple mode	_ _	24	0.986(0.946-1.028)	0.514
Weighted mode	-	24	1.02(0.986-1.055)	0.261
DNA methylation-estimated plasminogen a	activator inhibitor-1 levels		· · · ·	
MR Egger		5	1(1-1)	0.362
Weighted median	•	5	1(1-1)	0.853
Inverse variance weighted	•	5	1(1-1)	0.767
Simple mode	•	5	1(1-1)	0.941
Weighted mode	•	5	1(1-1)	0.753
DNA methylation PhenoAge acceleration				
MR Egger		11	1 025(0 007 1 005)	0 100
Weighted median	a - • • • • •	11	1.035(0.967-1.065)	0.100
Inverse variance weighted		11	1 003(0 983-1 025)	0.409
Simple mode		11	0.984(0.932-1.038)	0.559
Weighted mode	•	11	1024(0.985-1.065)	0.254
telomere length				
MR Egger		400	0 070/0 044 4 477)	0.047
Weighted median		133	0.978(0.814-1.177)	0.817
Inverse variance weighted	•	133	0.977(0.805-1.103)	0.704
Simple mode		133	0.802(0.60-1.055)	0.349
Weighted mode		133	0.995(0.857-1.156)	0.949
	07 08 00 1 11 12 12 14 15	100	0.000(0.007 1.100)	0.010
0.0	0.7 0.0 0.9 1 1.1 1.2 1.3 1.4 1.3			

Supplementary Figure 7. Analysis of the association between DNA methylation-estimated phenotypes and Telomere length exposure and the risk of Stroke using Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.

Methods		nSNP	OR(95% CI)	P value
DNA methylation-estimated granulocyt	e proportions			
Inverse variance weighted	· · · · · · · · · · · · · · · · · · ·	2	4.684(0.066-332.838)	0.478
DNA methylation GrimAge acceleration	n			
MR Egger		4	0.587(0.233-1.475)	0.375
Weighted median		4	0.977(0.911-1.048)	0.518
Inverse variance weighted		4	0.983(0.928-1.042)	0.565
Simple mode	••	4	0.967(0.867-1.079)	0.593
Weighted mode	•	4	0.958(0 868-1.058)	0.458
DNA methylation Hannum age acceler	ation			
MR Egger		8	0.825(0.73-0.933)	0.022
Weighted median		8	1.002(0.957-1.048)	0.945
Inverse variance weighted		8	0.997(0.947-1.049)	0.913
Simple mode		8	1.037(0.973-1.105)	0.305
Weighted mode	·	8	1.001(0.949-1.056)	0.971
Intrinsic epigenetic age acceleration				
MR Egger	· •	24	1 041/0 075 1 112)	0 242
Weighted median		24	1.041(0.975-1.112) 1.017(0.99-1.045)	0.242
Inverse variance weighted		24	1.017(0.33-1.043) 1.005(0.981-1.03)	0.68
Simple mode	_ _	24	0.982(0.936-1.029)	0.449
Weighted mode		24	1.029(0.992-1.068)	0.137
DNA methylation-estimated plasminge	en activator inhibitor-1 levels			
MR Egger		5	1(1-1)	0 298
Weighted median	•	5	1(1-1)	0.764
Inverse variance weighted	•	5	1(1-1)	0.851
Simple mode	•	5	1(1-1)	0.746
Weighted mode	•	5	1(1-1)	0.375
DNA methylation PhenoAge accelerati	on			
MR Egger	•	11	1 020/0 020 1 001)	0.460
Weighted median		11	1.039(0.969-1.091)	0.102
Inverse variance weighted	- + -	11	1.008(0.978-1039)	0.022
Simple mode	•	11	1(0.95-1.054)	0.989
Weighted mode		11	1.027(0.983-1.074)	0.258
telomere length				
MR Egger		100	0.000/0.044.4.400)	0.005
Weighted median	•	133	0.983(0.811-1.193)	0.865
Inverse variance weighted		133	0.900(0.004-1.129)	0.007
Simple mode	•	133	0.961(0.729-1.268)	0.001
Weighted mode		133	0.997(0.859-1.157)	0.966
weighted mode				5.000
	0.0 0.7 0.0 0.9 1 1.1 1.2 1.3 1.4 1.5			

Supplementary Figure 8. Analysis of the association between DNA methylation-estimated phenotypes and Telomere length exposure and the risk of Ischemic stroke using Inverse variance weighed, MR Egger, Simple mode, Weighted mode and Weighted median estimates.