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Supplemental information

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SUPPLEMENTAL INFORMATION

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Supplemental Note

The TOPMed mtDNA Working Group in the TOPMed Consortium

Gonçalo Abecasis[1], Avinash Abhyankar[2], Micheala A. Aldred[3], Dan E. Arking[4], Allison E. Ashley-Koch[5], Abraham Aviv[6], Kathleen Barnes[7], Emily Barron-Casella[8], David Beame[9], Stephanie Battle[4], Thomas W. Blackwell[1], Michael Bowers[9], Christina A. Castellani[4,10], Suzy Comhair[11], Adolfo Correa[12], Mariza de Andrade[13], Dawn L. DeMeo[14], Jun Ding[15], Serpil C. Erzurum[16], Samar Farha[17], Jessica L. Fetterman[18], Mao Fu[19], Einat Granot-Hershkovitz[14], Charles C. Gu[20], Ryan Hernandez[21], Yi-Hsiang Hsu[22], Anne E. Justice[23], Addison Keely[24], Leslie Lange[7], Daniel Levy[25,26], Honghuang Lin[25,27], Chunyu Liu[25,28], Ryan J. Longchamps[4], Jiantao Ma[29], JoAnn E. Manson[14], Merry-Lynn McDonald[30], Stephen T McGarvey[31], Julie L. Mikulla[32], Courtney Montgomery[33], Rajeeva L. Musunuri[34] , Jeffrey R. O'Connell[35], Nathan Pankratz[36], Jennifer A. Purnell[9], Yong Qian[15], Jerome I. Rotter[37], Jessica R. Shaw[38], Albert V. Smith[1], Tamar Sofer[14,39], Elizabeth A. Streeten[40], Weihong Tang[41], Kent D. Taylor[37], Marilyn Telen[42], Hemant Tiwari[43], Emily S. Wan[44], Heming Wang[39], Penglong Wang[26], Kate Wehr[9], Bruce Weir[9], Keoki L. Williams[45], James G. Wilson[46], Shujie Xiao[45], Weiling Xu[16], Yu-Chung Yang[47], Wei Zhao[48]

[1]TOPMed Informatics Research Center, University of Michigan, Ann Arbor, MI 48109, USA; [2]New York Genome Center, New York, NY 10013, USA; [3]School of Medicine, Indiana University, Indianapolis, IN 46202, USA; [4]McKusick-Nathans Institute, Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, MD 21205, USA; [5]Department of Medicine, Duke University, Durham, NC 27708, USA; [6]Department of Pediatrics, Rutgers University, Newark, NJ 07101, USA; [7]School of Medicine, University of Colorado, Aurora, CO 80045, USA; [8]Department of Pediatrics, School of Medicine, Johns Hopkins University, Baltimore, MD 21218, USA; [9]Genetic Analysis Center, Department of Biostatistics, University of Washington, Seattle, WA 98195, USA; [10]Department of Pathology and Laboratory Medicine, Western University, London, ON, Canada; [11]Cleveland Clinic, Immunity and Immunology, Cleveland, Ohio 44195, USA; [12]Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA; [13]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN 55902, USA; [14]Department of Medicine, Brigham & Women's Hospital, Boston, MA 02115, USA; [15]Longitudinal Studies Section, Translational Gerontology Branch, NIA/NIH, Baltimore, MD 21224, USA; [16]Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA; [17]Department of Pulmonary Medicine, Cleveland Clinic, Cleveland, OH 44195, USA; [18]Evans Department of Medicine and Whitaker Cardiovascular Institute, School of Medicine, Boston University, Boston, MA 20118, USA; [19]School of Medicine, University of Maryland, Baltimore, MD 21201, USA; [20]Division of Biostatistics, School of Medicine, Washington University, St Louis, MO 63130, USA; [21]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA 94143, USA; [22]HSL Institute for Aging Research, Harvard Medical School, Harvard University, Boston, MA 02115, USA; [23]Department of Population Health Sciences, Geisinger Health System, Danville, PA, 17822, USA; [24]Deapartment of Biostatistics, University of Washington, Seattle, WA 91895, USA; [25]Framingham Heart Study, NHLBI/NIH, Framingham, MA 01702, USA; [26]Population Sciences Branch, NHLBI/NIH, Bethesda, MD 20892, USA; [27]Department of Computational Biomedicine, School of Medicine, Boston University, Boston, MA 02115, USA; [28]Department of Biostatistics, School of Public Health, Boston University, Boston, MA 02118, USA; [29]Nutrition Epidemiology and Data Science, Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA 02111, USA; [30]Department of Pulmonary, Allergy, and Critical Care, University of Alabama, Birmingham, AL 35487, USA; [31]Department of Epidemiology, Brown University, Providence, RI 02912, USA; [32]Office of Clinical Research, NHLBI/NIH, Bethesda, MD 20892, USA; [33] Genes and Human Disease, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA; [34]New York Genome Center, New York, NY 10013, USA; [35]Department of Medicine, University of Maryland, Baltimore, MD 21201, USA; [36]Department of Computational Pathology, University of Minnesota, Minneapolis, MN 55455, USA; [37]The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA 90502, USA; [38]Linda Crnic Institute, School of Medicine, University of Colorado, Denver, CO 80204, USA; [39]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA 02115, USA; [40]Division of Endocrinology, Diabetes and Nutrition, School of Medicine, University of Maryland, Baltimore, MD 21201, USA; [41]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55455, USA; [42]Department of Medicine, School of Medicine, Duke University,

Durham, NC 27708, USA; [43]Department of Biostatistics, School of Public Health, University of Alabama, Birmingham, AL, 35401, USA; [44]Pulmonary Division, Brigham and Women's Hospital, Boston, MA 02115, USA; [45]Henry Ford Health System, Detroit, MI 48109, USA; [46]Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS 39216, USA; [47]Division of Blood Diseases and Resources, NHLBI/NIH, Bethesda, MD 20892, USA; [48]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA

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Table S1. Participant characteristics, Related to Figure 1 and Table 1.

Variable Mean (sd) or N (%)	ARIC (n=2763)	CARDIA (n=1840)	CHS (n=2788)	FHS (n=4124)	MESA (n=1863)	UKB (n=381,470)
Ancestry	EA	EA	EA	EA	EA	EA
mtDNA CN (men)	271 (77)	197 (71)	249 (119)	145 (50)	238 (70)	-0.19 (0.98)
mtDNA CN (women)	313 (75)	221 (94)	281 (136)	151 (49)	255 (74)	0.14 (0.98)
Age	59 (6)	45 (7)	74 (6)	60 (16)	62 (10)	57 (8)
Women	(1425) 51%	989 (54%)	1589 (57%)	2227 (54%)	911 (49%)	206031 (54%)
Obesity	750 (27%)	500 (27%)	502 (18%)	1116 (28%)	519 (28%)	91415 (24%)
HTN	1013 (37%)	275 (15%)	1868 (67%)	1909 (48%)	781 (42%)	191963 (50%)
DIAB	362 (13%)	88 (5%)	390 (14%)	441 (11%)	96 (5%)	18277 (5%)
Hyperlipidemia	1911 (69%)	943 (51%)	1979 (71%)	2616 (66%)	1240 (67%)	308822 (81%)

Variable Mean (sd) or (%)	ARIC (n=201)	CARDIA (n=1612)	CHS (n=705)	GENOA (n=1234)	JHS (n=3160)	MESA (n=1108)
Ancestry	AA	AA	AA	AA	AA	AA
mtDNA CN (men)	304.2 (86)	220 (83)	278 (118)	238 (77)	122 (42)	243 (71)
mtDNA CN (women)	292 (77)	247 (112)	283 (121)	255 (76)	134 (48)	268 (84)
Age	59 (6)	44 (7)	74 (6)	62 (10)	55 (13)	63 (10)
Women	118 (59%)	948 (59%)	444 (63%)	877 (70%)	1960 (62%)	499 (45%)
Obesity	80 (40%)	822 (51%)	247 (35%)	677 (54%)	1699 (54%)	510 (46%)
HTN	128 (64%)	557 (35%)	557 (79%)	977 (78%)	1886 (60%)	676 (61%)
DIAB	66 (33%)	169 (10%)	169 (24%)	363 (29%)	725 (23%)	199 (18%)
Hyperlipidemia	138 (69%)	707 (44%)	444 (63%)	852 (68%)	1706 (59%)	499 (45%)

Variable Mean (sd) or (%)	MESA (n=601)	MESA (n=1024)	HCHS/SOL (n=3868)
Ancestry	EAS	HA	HA
mtDNA CN (men)	227 (64)	232 (64)	202 (36)
mtDNA CN (women)	245 (70)	254 (69)	218 (40)
Age	62 (10)	62 (11)	47 (14)
Women	299 (50%)	526 (51%)	2294 (60%)
Obesity	33 (4%)	455 (39%)	1760 (46%)
HTN	301 (39%)	508 (43%)	839 (22%)
DIAB	401 (13%)	219 (19%)	827 (21%)
Hyperlipidemia	419 (54%)	762 (65%)	634 (16%)

AA, African ancestry; EA, Participants of European ancestry; EAS, East Asian (Chinese) ancestry. HA, Hispanic and Latino Americans. ARIC, Atherosclerosis Risk in Communities study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; GENOA, Genetic Epidemiology Network of Arteriopathy Study; Hispanic Community Health Study/Study of Latinos (HCHS/SOL); JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; UKB, the UK Biobank.

Table S2. Meta-analysis combining results among TOPMed participants of African ancestry, Related to Table 1, Figure 1

Traits	TOPMed participants of African ancestry (n=8,020)		
	Beta	SE	P-value
Obese	0.017	0.027	0.52
HTN	0.052	0.030	0.085
Diabetes	0.14	0.036	2.0×10^{-4}
Hyperlipid	-0.0061	0.028	0.83
BMI	0.061	0.077	0.43
DBP	0.071	0.028	0.013
SBP	0.75	0.24	2.0×10^{-3}
FBG	0.14	0.11	0.23
HDL	-0.00010	0.0032	0.97
LDL	0.0010	0.0046	0.83
TRIG	0.0077	0.0027	0.0039

Association analysis of mtDNA CN with CMD traits was performed in each cohort of TOPMed participants of African ancestry (ARIC, CARDIA, CHS, GENOA, JHS, and MESA). Meta-analysis using fixed effects inverse variance method was applied to summarize the results. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN. DBP, diastolic blood pressure; SBP, systolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; TRIG, triglyceride; Obese, obesity; HTN, hypertension; Diabetes, Diabetes; Hyperlipid, hyperlipidemia.

Table S3. Association analysis between mtDNA CN and metabolic phenotypes in participants of Hispanic and Latino Americans and Chinese ancestry, Related to Table 1, Figure 1

	Hispanic/Latino Americans (n=4,892)		Chinese ancestry (n=601)	
Traits	Beta/SE	P	Beta/SE	P
Obese	0.017/0.025	0.49	-0.069/0.22	0.75
HTN	0.046/0.042	0.28	-0.036/0.099	0.71
DIAB	0.13/0.043	0.002	0.20/0.14	0.16
Hyperlipid	-0.011/0.047	0.81	0.36/0.094	0.00014
BMI	0.27/0.12	0.026	-0.16/0.14	0.24
DBP	0.11/0.21	0.61	-0.10/0.49	0.83
SBP	0.21/0.33	0.53	-0.87/0.94	0.36
FBG	-0.021/0.19	0.91	-0.068/0.46	0.88
HDL	-0.015/0.0079	0.06	0.0001/0.0093	0.99
LDL	-0.016/0.0056	4.30×10^{-3}	0.020/0.011	0.068
TRIG	0.020/0.0093	0.037	0.027/0.020	0.18

Association analysis of mtDNA CN with CMD traits was performed in Hispanic and Latino American participants in MESA and SOL study, and participants of Chinese ancestry in MESA study. Meta-analysis using fixed effects inverse variance method was used to summarize the Hispanic and Latino Americans results. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN.

Table S4. Meta-analysis combining results in participants of all ancestries from TOPMed and UK Biobank, Related to Table 1, Figure 1

	All ancestries (n=408,361)		
Traits	Beta	SE	P-value
Obese	0.13	0.0039	8.90×10^{-227}
HTN	0.057	0.0038	1.08×10^{-49}
Diabetes	0.041	0.0079	2.01×10^{-7}
Hyperlipid	0.073	0.0047	1.40×10^{-54}
BMI	0.29	0.0075	9.9×10^{-336}
DBP	0.18	0.015	3.60×10^{-32}
SBP	0.62	0.032	8.80×10^{-86}
FBG	0.22	0.018	1.06×10^{-31}
lnHDL	0.0030	4.00×10^{-4}	1.96×10^{-14}
lnLDL	0.0062	5.00×10^{-4}	1.01×10^{-40}
lnTRIG	0.020	8.00×10^{-4}	5.77×10^{-152}

Association analyses of mtDNA CN with CMD traits was performed in cohorts of European ancestry (n=13,378), African ancestry (n=8,020), Hispanic and Latino Americans (N=4,892), and Chinese ancestry (n=601) in TOPMed and in UK Biobank participants of European ancestry (n=381,470). Meta-analysis using fixed ($P_Q \geq 0.01$) effects inverse variance method was used to summarize the results. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN.

Table S5. Association analyses of mtDNA CN with white blood cell count and platelets, Related to STAR Methods

5A. Methods to obtain white blood cell count and platelets

Cohort	Directly measured	Imputed based on gene expression or DNA methylation data
ARIC	Yes	
FHS*		Yes. Imputed based on using gene expression data with partial least squares.
GENOA		Yes. Imputed based on using DNA methylation data with the Houseman method.
JHS	Yes	
SOL	Yes	
UKB	Yes	

5B. Association analysis of mtDNA CN with white blood cell count and platelets

Independent variable (count)	FHS (n=2,643)		GENOA (n=878)		JHS (n=2,840)		UKB (n=381,470)		SOL (n=3,613)	
	Coef	P-value	Coef	P-value	Coef	P-value	Coef	P-value	Coef	P-value
White blood cell	-0.11	5.1×10^{-13}	na	na	-0.055	7.0×10^{-8}	na	na	-0.60	6.7×10^{-44}
Neutrophil	-0.020	0.094	na	na	na	na	-0.072	<2e-16	-0.55	5.7×10^{-47}
Lymphocyte	0.0062	0.49	na	na	0.024	8.5×10^{-42}	0.026	<2e-16	0.021	0.11
Eosinophil	-0.0011	0.94	na	na	1.8×10^{-4}	0.98	-0.024	0.040	0.1	0.38
Basophil	0.11	0.18	na	na	0.048	0.27	-0.11	0.0022	-0.0017	0.043
Monocyte	na	na	10.45	0.14	-.014	0.067	-0.055	4.4×10^{-8}	-0.035	1.8×10^{-4}
Platelet	0.0036	3.2×10^{-14}	na	na	0.0011	1.7×10^{-5}	0.00074	<2e-16	0.4756	3.5×10^{-28}
Red blood cell	0.062	0.21	na	na	-0.018	0.55	0.22	0.0077	-0.0074	1.4×10^{-13}
CD8T	na	na	-12.80	0.063	na	na	na	na	na	na
CD4T	na	na	-11.89	0.087	na	na	na	na	na	na
Natural killer cell	na	na	-11.71	0.066	na	na	na	na	na	na
B lymphocytes cell	na	na	-11.72	0.088	na	na	na	na	na	na
Granulocytes cell	na	na	-14.79	0.032	na	na	na	na	na	na
Adjusted R2	10.4%		10.6%		11.6%		14.3%			

mtDNA CN residuals were obtained by regressing mtDNA CN on batch effect (i.e., year at blood collection), age (at blood collection), age-squared, and sex. We performed a regression model with mtDNA CN residuals as a dependent variable and all blood compositions as independent variables. The effect size estimates are changes in s.d. of mtDNA CN level in response to one unit increase in WBCs. R^2 represents the variance in mtDNA CN that is jointly explained by blood cell compositions in the table.

5C. Association of continuous CMD traits with white blood cell count/platelets

Trait	FHS (n=2643)						
	White blood cell count		Neutrophils		Platelets		R^2 (%)
	Beta	P	Beta	P	Beta	P	
DBP	0.59	9.7×10^{-4}	0.0099	0.75	-0.010	0.078	0.51
SBP	1.69	8.7×10^{-7}	0.12	0.044	-0.0068	0.54	1.7
BMI	0.65	6.8×10^{-15}	0.0085	0.55	0.0020	0.45	3.4
FBG	0.67	0.00017	0.061	0.047	-0.0095	0.099	1.3
lnHDL	-0.042	0.2×10^{-17}	1.0×10^{-4}	0.87	0.0016	2.2×10^{-24}	5.7
lnLDL	0.015	0.0016	-0.0015	0.068	0.0005	0.0019	0.92
lnTrig	0.0095	2.4×10^{-32}	-0.0048	0.00038	-0.0018	8.2×10^{-13}	5.8

Trait	JHS (n=2740)						
	White blood cell count		Lymphocytes		Platelets		R^2 (%)
	Beta	P	Beta	P	Beta	P	
DBP	0.039	0.75	0.0083	0.70	-0.0034	0.28	7
SBP	0.54	0.026	-0.11	0.013	-0.024	0.00013	0.9
BMI	0.56	1.5×10^{-11}	0.085	8.0×10^{-9}	0.015	4.2×10^{-12}	4.9
FBG	-0.11	0.41	-0.047	0.035	-0.0066	0.039	0.34
lnHDL	-0.012	0.00050	-0.0011	0.084	0.0002	0.025	0.43
lnLDL	-0.014	0.00019	0.0005	0.45	0.0003	0.0058	0.76
lnTrig	0.044	2.3×10^{-12}	0.004	0.00036	-0.0001	0.45	1.9

Trait	UKB (n=381,470)						
	White blood cell count		Neutrophils		Platelets		R^2 (%)
	Beta	P	Beta	P	Beta	P	
DBP	0.16	3.0×10^{-34}	0.39	6.6×10^{-87}	0.0001	0.63	0.57
SBP	0.23	3.4×10^{-21}	1.07	2.2×10^{-192}	-0.01	7.3×10^{-87}	0.83
BMI	0.28	7.5×10^{-607}	0.14	5.5×10^{-74}	-0.0007	1.2×10^{-8}	2.5
FBG	-0.16	1.2×10^{-38}	0.45	2.4×10^{-119}	-0.0036	1.1×10^{-37}	0.17
lnHDL	-0.014	2.6×10^{-474}	-0.012	7.2×10^{-143}	0.00047	1.1×10^{-1326}	3.3
lnLDL	0.0035	1.4×10^{-45}	-0.020	9.3×10^{-455}	0.00054	1.3×10^{-1558}	1.9
lnTrig	0.033	6.3×10^{-754}	0.012	6.1×10^{-51}	-1.1×10^{-5}	0.38	3.1

We performed a regression analysis with a continuous CMD trait as a dependent variable, and white blood cell count, neutrophil, and platelet count jointly as independent variables. The effect size estimates are in units of CMD traits corresponding to one unit increase in a cell composition. R^2 represents the variance in a CMD trait that is jointly explained by the three blood cell compositions in the table.

Table S6. Comparison of results adjusting for white blood cell count and platelet in participants of European ancestry in TOPMed and UK Biobank. Related to Figure 2C.

Traits	TOPMed WGS EA and UK Biobank WES EA (n=386,526)			
	w/o adjusting for cell counts		Adjusting for cell counts	
	Beta/SE	P-value	Beta/SE	P-value
Obesity	0.13/0.0041	6.4×10^{-238}	0.043/0.004	4.7×10^{-27}
HTN	0.059/0.0039	1.2×10^{-50}	0.0065/0.0039	0.098
Diabetes	0.028/0.0055	3.5×10^{-7}	0.048/0.0057	1.3×10^{-17}
Hyperlipid	0.078/0.0049	1.1×10^{-56}	0.12/0.0049	6.2×10^{-125}
BMI	0.30/0.0077	1.7×10^{-336}	0.11/0.0076	3.0×10^{-48}
DBP	0.24/0.018	4.1×10^{-39}	0.11/0.018	2.6×10^{-9}
SBP	0.65/0.033	1.6×10^{-87}	0.24/0.032	6.3×10^{-14}
FBG	0.23/0.019	5.0×10^{-33}	0.15/0.019	7.5×10^{-15}
lnHDL	0.0031/0.0004	3.4×10^{-15}	0.010/0.0004	3.5×10^{-146}
lnLDL	0.0064/0.0005	6.1×10^{-42}	0.019/0.0005	9.1×10^{-344}
lnTrig	0.022/0.0008	1.0×10^{-153}	0.012/0.0008	5.1×10^{-51}

WGS, whole genome sequencing; WES, whole exome sequencing. Association analysis of mtDNA CN with CMD traits was performed in the participants with imputed cell counts in participants of European ancestry in TOPMed and UK Biobank. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN.

Table S7. The investigation of effect modification by sex or age on associations of mtDNA CN with CMD traits, Related to Table 1, Figure 1.

	CARDIA EA		CHS EA		FHS EA		MESA EA		UKB European ancestry		META results	
Traits	age	sex	age	sex	age	sex	age	sex	age	sex	age	sex
BMI	0.94	0.86	0.08	0.44	0.46	0.48	0.90	0.83	0.0016	0.00013	0.00057	0.000088
DBP	0.50	0.31	0.80	0.71	0.51	0.29	0.41	0.45	0.49	0.071	0.41	0.053
SBP	0.95	0.16	0.77	0.27	0.29	0.62	0.84	0.57	0.0093	0.077	0.022	0.051
FBG	0.27	0.79	0.01	0.14	0.98	0.07	0.53	0.10	0.00042	0.85	0.00031	0.91
HDL	0.06	0.93	0.62	0.93	0.13	0.47	0.56	0.90	7.0×10^{-4}	0.79	0.00084	0.85
LDL	0.72	0.45	0.74	0.22	0.19	0.58	0.85	0.21	6.0×10^{-4}	0.81	0.00035	0.96
TRIG	0.03	0.46	0.57	0.43	0.12	0.61	0.66	0.10	8.6×10^{-5}	0.07	0.00029	0.076
Obesity	0.75	0.80	0.11	0.26	0.60	0.84	0.39	0.48	0.0045	0.12	0.0038	0.11
HTN	0.32	0.73	0.78	0.95	0.40	0.31	0.52	0.61	0.42	0.0041	0.57	0.0027
DIAB	0.22	0.06	0.25	0.21	0.01	0.94	0.58	0.54	0.19	0.64	0.66	0.55
Hyperlipid	0.25	0.44	0.34	0.58	0.96	0.59	0.83	0.19	0.78	0.50	0.78	0.64

	CARDIA AA		CHS AA		GENOA AA		JHS AA		MESA AA		META results	
Traits	age	sex	age	sex	age	sex	age	sex	age	sex	age	sex
BMI	0.73	0.26	0.77	0.12	0.51	0.34	0.74	0.21	0.90	0.91	0.47	0.52
DBP	0.74	0.25	0.92	0.17	0.27	0.53	0.13	0.51	0.41	0.16	0.47	0.69
SBP	0.48	0.46	0.69	0.38	0.51	0.73	0.56	0.14	0.84	0.91	0.57	0.81
FBG	0.48	0.67	0.31	0.15	0.94	0.89	0.01	0.82	0.53	0.27	0.49	0.86
HDL	0.02	0.60	0.63	0.28	0.39	0.66	0.60	0.94	0.56	0.91	0.66	0.85
LDL	0.05	0.47	0.02	0.66	0.92	0.37	0.56	0.10	0.85	0.08	0.46	0.10
TRIG	0.28	0.40	0.04	0.71	0.38	0.57	0.14	0.76	0.66	0.94	0.17	0.75
Obesity	0.15	0.69	0.79	0.23	0.63	0.69	0.52	0.11	0.38	0.23	0.85	0.43
HTN	0.61	0.61	0.62	0.85	0.24	0.24	0.65	0.05	0.52	0.98	0.28	0.60
DIAB	0.89	0.51	0.86	0.11	0.70	0.60	0.07	0.79	0.58	0.99	0.06	0.81
Hyperlipid	0.56	0.35	0.01	0.86	0.32	0.86	0.10	0.17	0.83	0.09	0.02	0.073

Association analysis of mtDNA CN with CMD traits was performed to test interaction with age or sex in each cohort of European ancestry participants (N=13,378) and African ancestry (N=8,020) in TOPMed and also in UK Biobank participants of European ancestry (N=381,470). Fixed-effect inverse variance meta-analysis was used to summarize the results in European ancestry or African ancestry in TOPMed. An interaction term of mitoage (residual mtDNA CN*age) or mitosex (residual mtDNA CN*sex) was included in the model to investigate whether age or sex was effect modifier of the association between mtDNA CN and CMD traits. Residual mtDNA CN was obtained by regressing mtDNA CN on batch effect, obtained the residuals then multiply age or sex. The “age” and “sex” columns indicate p-values of the interaction terms in the model. EA, European ancestry; AA, African ancestry; UKB, UK Biobank.

Table S8. Age-specific meta-analysis in participants of European ancestry in TOPMed and UK Biobank. Related to Figure 2D.

Traits	Participants of European ancestry in TOPMed and UK Biobank			
	<65 years (n=315,708)		≥65 years (n=79,782)	
	Beta/SE	P-value	Beta/SE	P-value
Obesity	0.14/0.0045	1.3×10^{-218}	0.098/0.0090	1.7×10^{-27}
HTN	0.058/0.0043	5.0×10^{-41}	0.057/0.0091	4.7×10^{-10}
Diabetes	0.031/0.010	0.0022	0.065/0.015	1.1×10^{-5}
Hyperlipid	0.077/0.0052	4.1×10^{-50}	0.080/0.013	1.0×10^{-9}
BMI	0.32/0.0086	2.1×10^{-300}	0.22/0.016	4.7×10^{-42}
DBP	0.24/0.02	2.9×10^{-32}	0.22/0.042	3.1×10^{-7}
SBP	0.63/0.035	1.7×10^{-71}	0.70/0.080	2.0×10^{-18}
FBG	0.20/0.021	9.6×10^{-22}	0.31/0.044	1.3×10^{-12}
lnHDL	0.0030/0.00040	9.6×10^{-12}	0.0033/0.0009	3.0×10^{-4}
lnLDL	0.0065/0.00050	4.9×10^{-36}	0.0057/0.001	4.7×10^{-8}
lnTrig	0.023/0.0009	1.3×10^{-136}	0.019/0.0017	2.3×10^{-28}

Association and inverse variance weighting meta-analyses of mtDNA CN with CMD traits was performed in participants of European ancestry in TOPMed and UK Biobank. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN.

Table S9. Comparison of results of mtDNA CN with CMD disease phenotypes in WGS, Affymetrix, and low-pass in non-overlap participants in ARIC, Related to STAR Methods.

	Traits	TOPMed WGS (n=2,768)			Affymetrix (n=5,194)			Low-pass sequencing (n=1,441)		
		Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
Binary	Obese	0.12	0.044	0.0086	0.078	0.033	0.017	0.16	0.063	0.011
	HTN	0.16	0.044	3.7×10^{-4}	0.092	0.032	4.4×10^{-3}	0.081	0.061	0.18
	Diabetes	0.40	0.063	2.4×10^{-10}	0.25	0.045	2.9×10^{-8}	0.34	0.1	0.00091
	Hyperlipid	0.097	0.043	0.025	-0.015	0.03	0.61	0.012	0.059	0.84
Continuous outcomes	BMI	0.31	0.098	0.0018	0.18	0.07	0.012	0.41	0.14	0.0034
	DBP	0.43	0.22	0.046	0.37	0.15	0.015	0.23	0.29	0.42
	SBP	1.13	0.38	0.0029	1.00	0.26	1.6×10^{-4}	0.74	0.51	0.15
	FBG	0.10	0.20	0.60	0.12	0.13	0.37	0.024	0.28	0.93
	HDL	-0.030	0.005	4.3×10^{-8}	-0.022	0.0041	5.5×10^{-8}	-0.0085	0.0077	0.27
	LDL	0.51	0.82	0.54	-0.079	0.56	0.89	-1.44	1.09	0.19
	TRIG	0.053	0.0091	6.9×10^{-9}	0.024	0.0069	6.4×10^{-4}	0.0097	0.013	0.47

The beta estimates are in units of CMD traits corresponding to one s.d. lower mtDNA CN. Association analysis of mtDNA CN with CMD traits was performed in ARIC with WGS, Affymetrix Genome-Wide Human SNP Array 6.0 and low-pass whole genome sequencing. mtDNA CN can be measured by qPCR or estimated by genotyping or sequencing, and the performance of several technologies (e.g., qPCR, different genotyping array, WGC) in estimating mtDNA CN was evaluated previously.[1] In a previous study, mtDNA CN was determined using the Genvisis15 software package for the Affymetrix Genome-Wide Human SNP Array 6.0. A list of high-quality mitochondrial SNPs were hand-curated by employing BLAST to remove SNPs without a perfect match to the annotated mitochondrial location and SNPs with off-target matches longer than 20bp. The probe intensities of the remaining mitochondrial SNPs (25 Affymetrix, 58 Illumina Exome Chip) were determined using quantile sketch normalization (apt-probeset-summarize) as implemented in the Affymetrix Power Tools software. The median of the normalized intensity, log R ratio (LRR) for all homozygous calls was GC corrected and used as initial estimates of mtDNA CN for each sample. Technical covariates such as DNA quality, DNA quantity, and hybridization efficiency were captured via surrogate variable analysis described2. Surrogate variables were applied to the BLAST filtered, GC corrected LRR of the remaining autosomal SNPs (43,316 Affymetrix, 47,512 Exome Chip). These autosomal SNPs were selected based on the following quality filters: call rate > 98%, HWE p value > 0.00001, PLINK mishap for non-random missingness p value > 0.0001, association with sex p value > 0.00001, linkage disequilibrium pruning ($r2 < 0.30$), with maximal spacing between autosomal SNPs of 41.7 kb. Low-pass whole genome sequencing data for ARIC was generated at the Baylor College of Medicine Human Genome Sequencing Center using Nano or PCR-free DNA libraries on the Illumina HiSeq 2000. Sequence reads were mapped to the hg19 reference genome using BWA.[2] Quality control was performed as previously described.[3] A count for the total number of reads in a sample was scraped from the NCBI sequence read archive using the R package RCurl[4] while reads aligned to the mitochondrial genome were downloaded directly through Samtools (version 1.3.1). A raw measure of mtDNA CN was calculated as the ratio of mitochondrial reads to the number of total aligned reads. The final mtDNA CN phenotype for all measurement techniques is represented as the standardized residuals from a linear model adjusting the raw measure of mtDNA CN for age, sex, DNA collection center, any technical covariates. As mtDNA CN was standardized, the effect size estimates are in units of standard deviations, with positive betas corresponding to an increase in mtDNA CN.

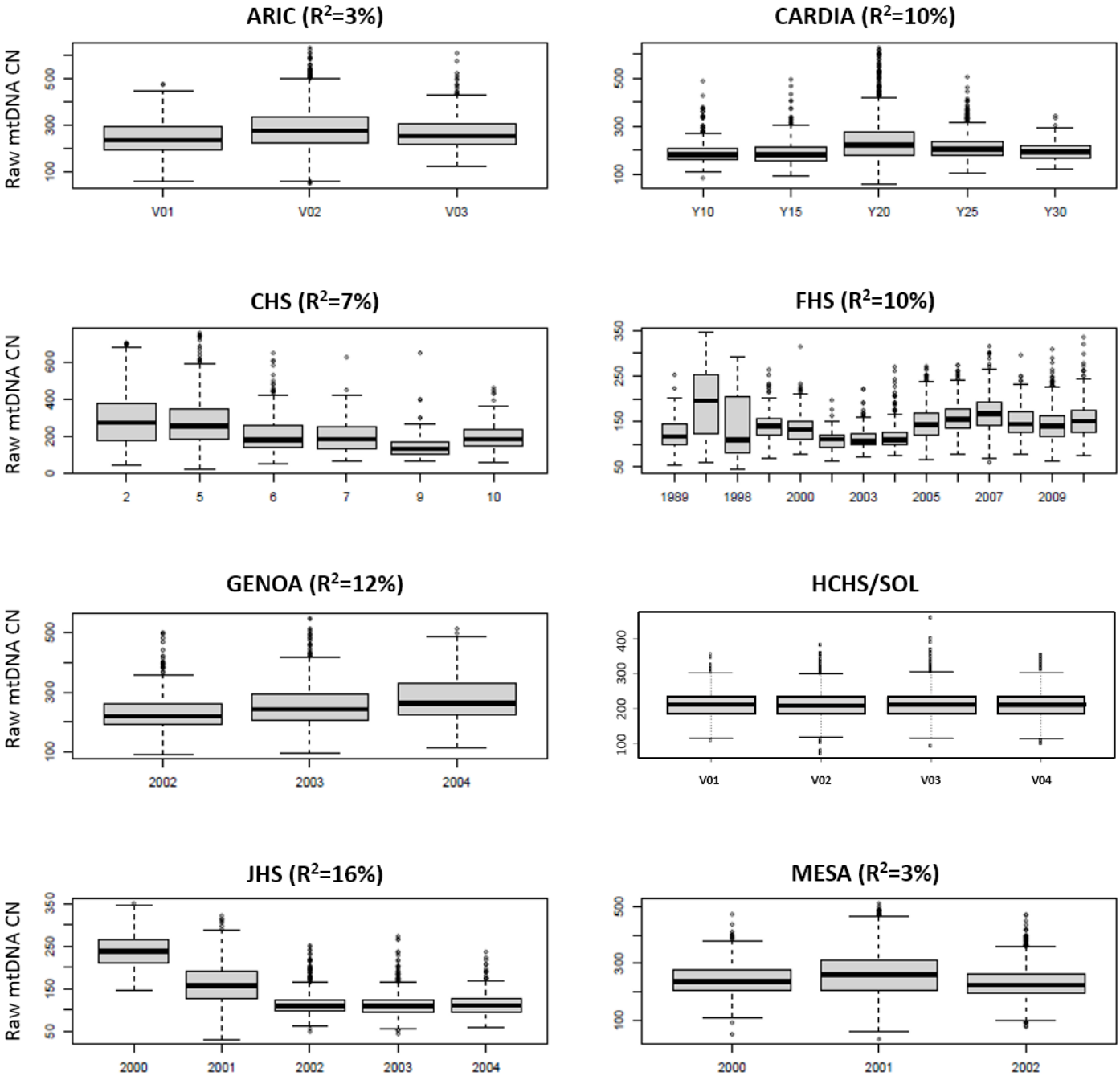


Figure S1. The effect of the year at blood collection on mtDNA CN estimated from whole genome sequencing in TOPMed, Related to STAR Methods. The year of blood collection was provided as calendar year (treated as a batch variable) in each TOPMed cohort. A number in the parenthesis in the title of each plot indicates the variance in mtDNA CN that can be explained by "blood collection year" in a cohort. Due to a study design, R^2 was unavailable in HCHS/SOL.

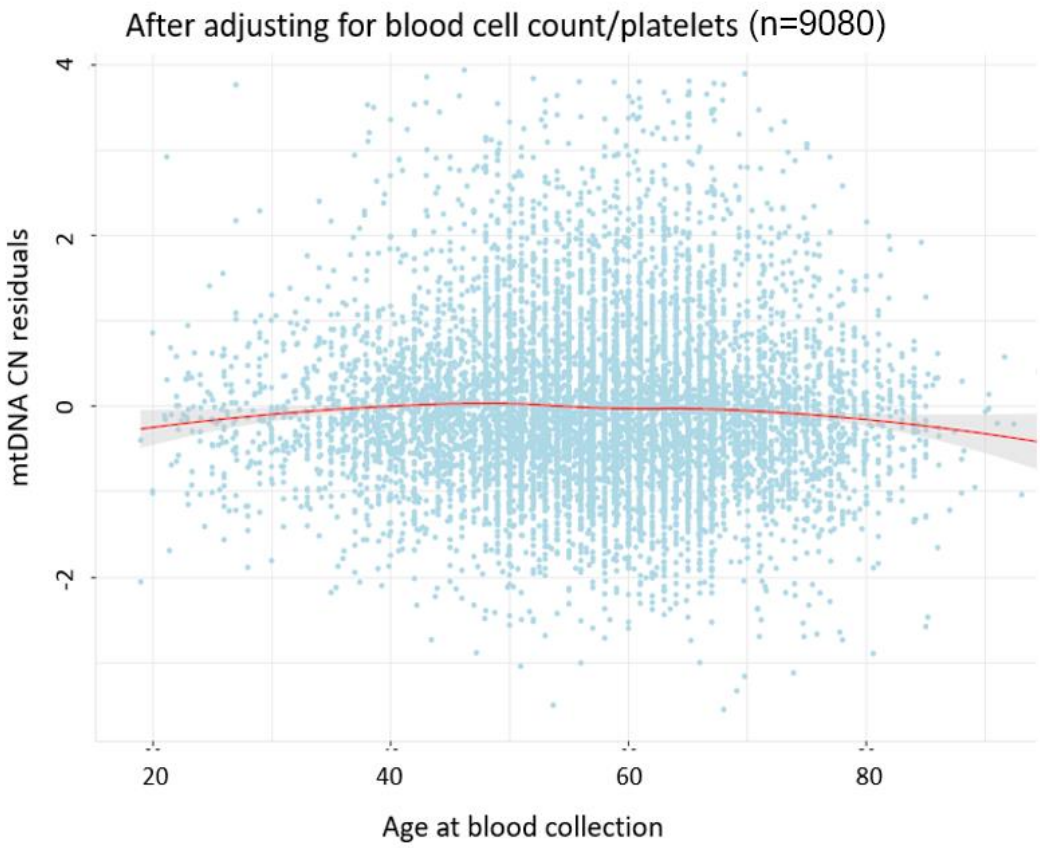


Figure S2. The relationship of mtDNA CN with age after adjusting for white blood cell count and platelets. Related to Figure S1, STAR Methods. mtDNA CN residuals were obtained by regressing mtDNA CN on batch effect and cell count/platelets.

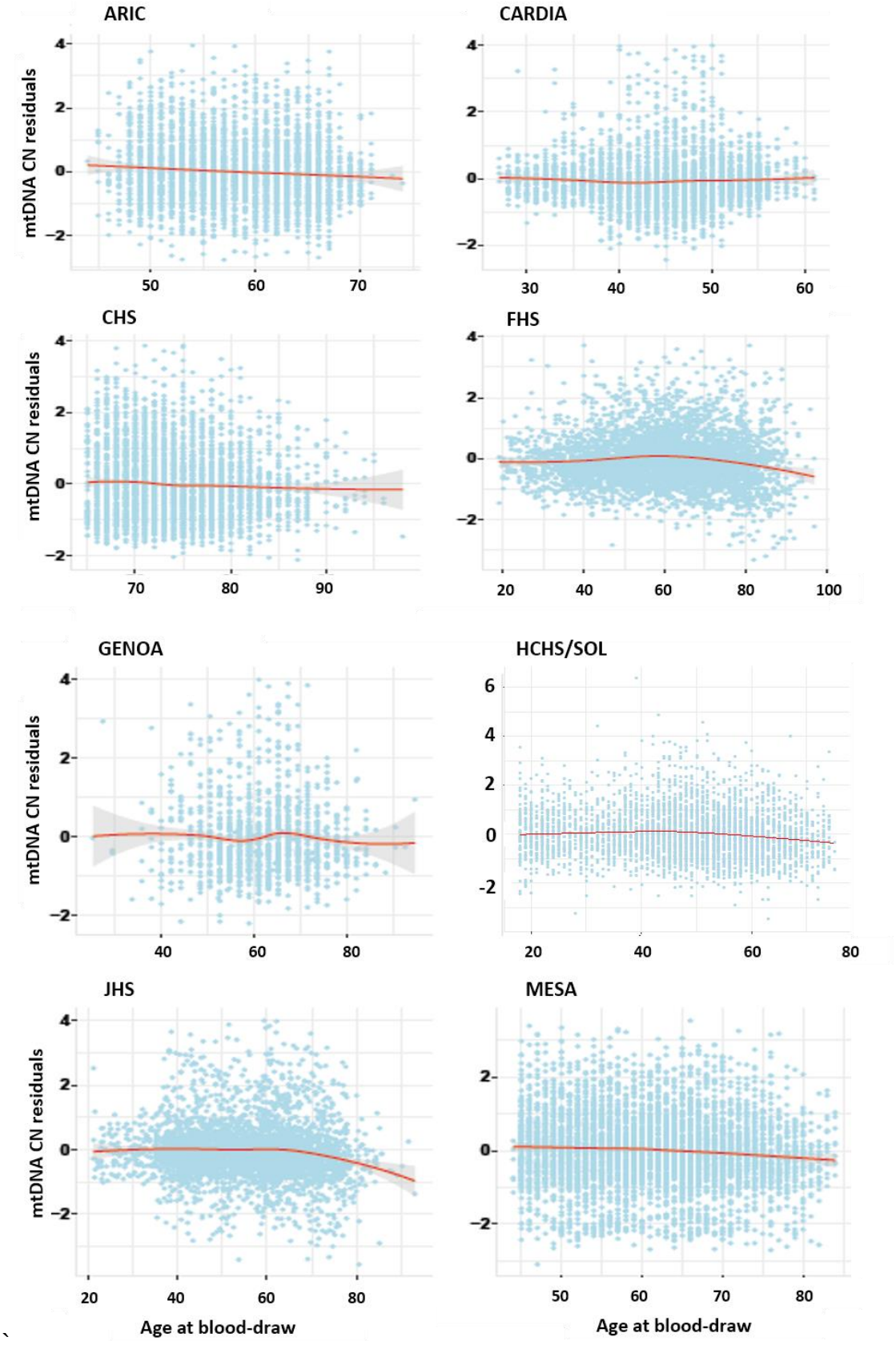
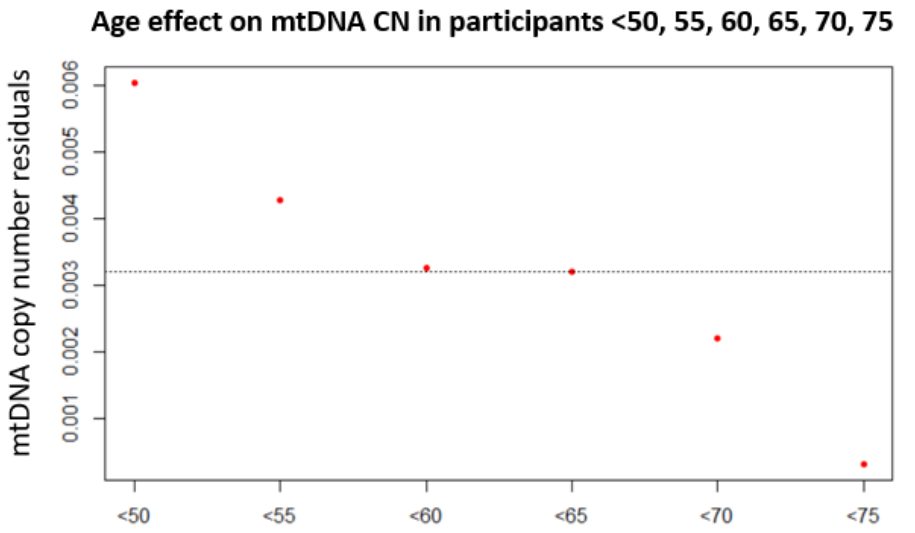
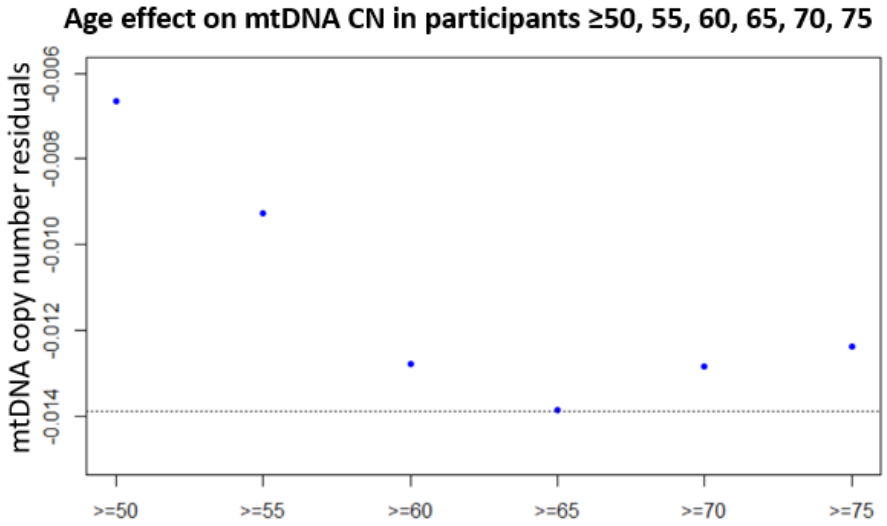


Figure S3. The relationship of mtDNA CN residuals with age in each of the TOPMed cohorts, Related to STAR Methods.



Age group	<50	<55	<60	<65	<70	<75
Sample size	5456	7979	9994	11817	14546	17197



Age group	≥50	≥55	≥60	≥65	≥70	≥75
Sample size	14799	12276	10261	8438	5709	3058

Figure S4. Identification of threshold effect of age on mtDNA copy number, Related to Figure 2B, STAR Methods. We analyzed the relationship of mtDNA CN with age in participants who were younger than 50 years, and again who were younger than 55 years, and similarly for 60, 65, 70, and 75 years of age; and in contrast, we analyzed the relationship in those who were at least 50 years, and again who were at least 55 years, and similarly for 60, 65, 70, and 75 years of age. We found that age displayed a positive effect on mtDNA CN (top figure) in participants who were younger than 50, 55, 60, 65, 70, and 75 years old with similar effects at <60 and <65 years old. In contrast, age displayed negative effects on mtDNA CN (bottom figure) in participants who were at least 50, 55, 60, 65 (with the lowest effect size), 70, 75 and 80 years of age. In addition, most medical studies consider participants aged 65+ as older individuals in studying age-related diseases (e.g., cardiovascular disease or Alzheimer's disease). Therefore, we chose to use 65 years as a cutoff to evaluate the age threshold effect in association analyses based on these findings and common social norms.

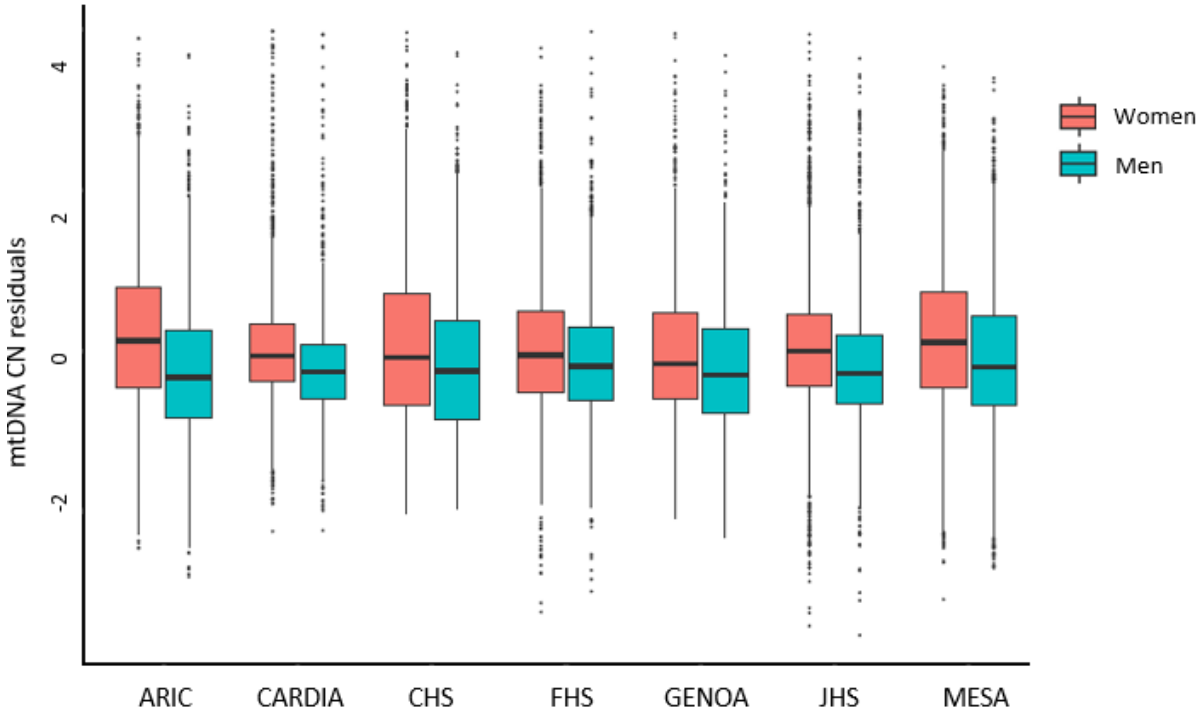


Figure S5. The relationship of mtDNA CN with sex, Related to STAR methods. mtDNA CN residuals was obtained by regressing mtDNA CN on batch effect and age in each cohort.

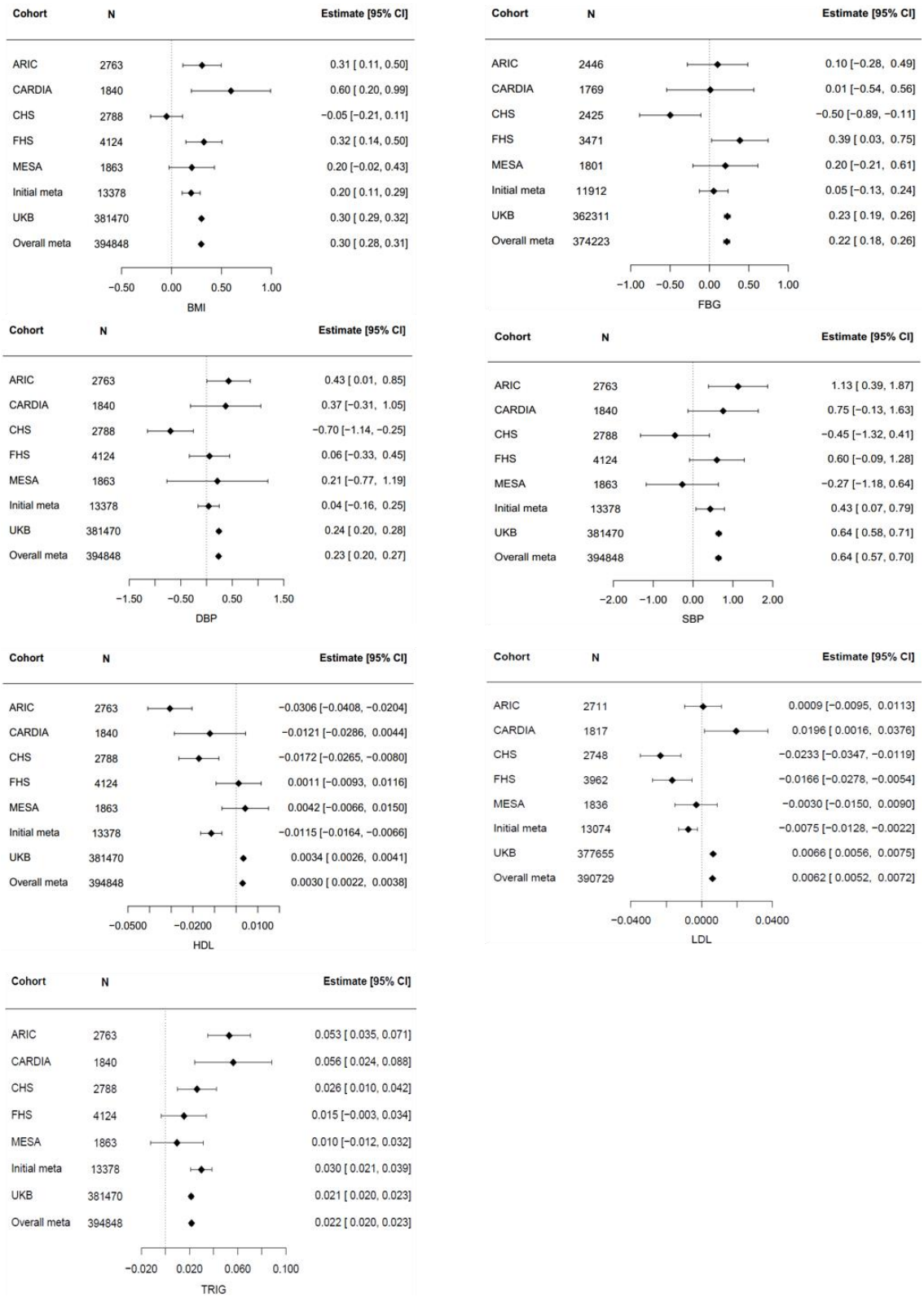
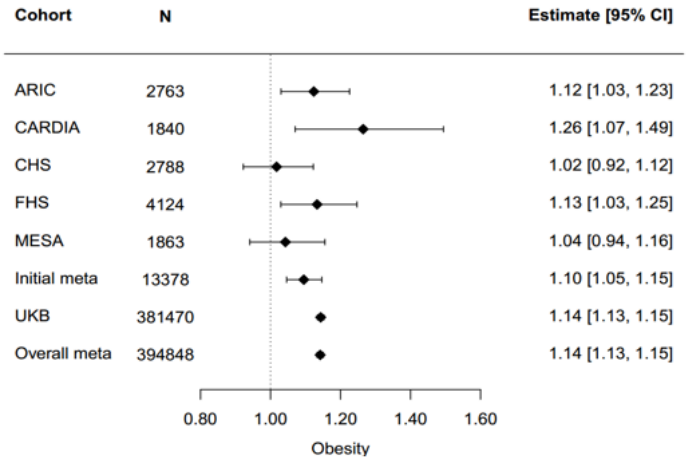
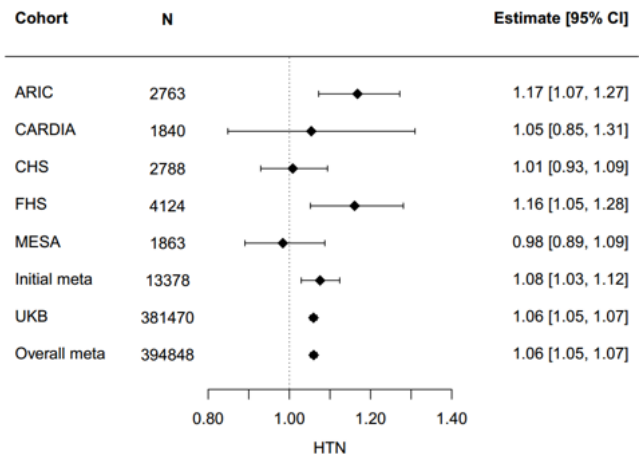
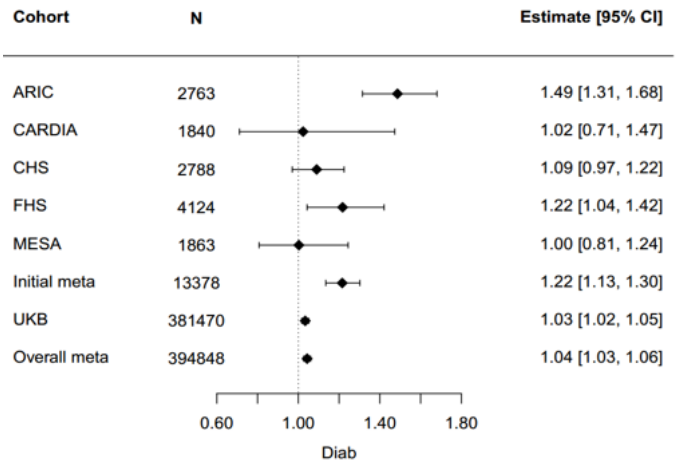


Figure S6. Forest plot of beta estimates in association analyses of mtDNA with CMD continuous traits in participants of European ancestry in TOPMed and UK Biobank, Related to Table 1, Figure 2B. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN. In meta-analyses of TOPMed cohorts, the observed heterogeneity measure (I^2) was 75.2% for BMI, 65.5% for FBG, 73.8% for DBP, 61.8% for SBP, 86.1% for HDL, 81.5% for LDL, 72.8% for TRIG, 40.5% for obesity, 64.7% for HTN, 77.3% for diabetes, and 48.3% for hyperlipidemia. In combining TOPMed and the UK Biobank data, the heterogeneity measure I^2 was 79.8% for BMI, 70.2% for FBG, 71.4% for DBP, 24.0% for SBP, 97.1% for HDL, 96.2% for LDL and 71.0% for TRIG.







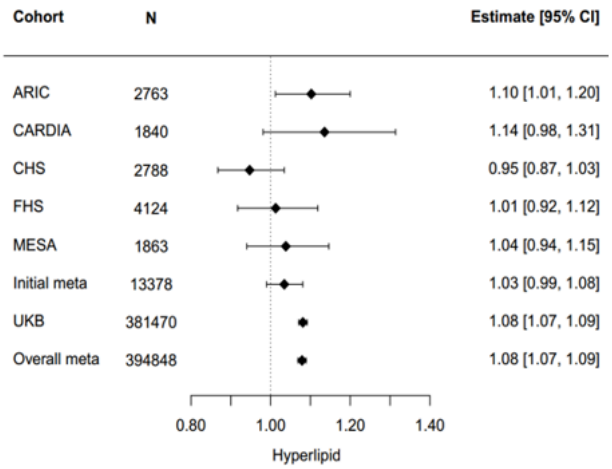


Figure S7. Forest plot of beta estimates in association analyses of mtDNA with CMD binary traits in participants of European ancestry in TOPMed and UK Biobank, Related to Table 1, Figure 2B. The effect size estimates are in units of CMD traits corresponding to one s.d. decrease in mtDNA CN. In meta-analyses of TOPMed cohorts, the observed heterogeneity measure (I^2) was 69.8% for obesity, 0% for HTN, 95.0% for diabetes, and 73.1% for hyperlipidemia.

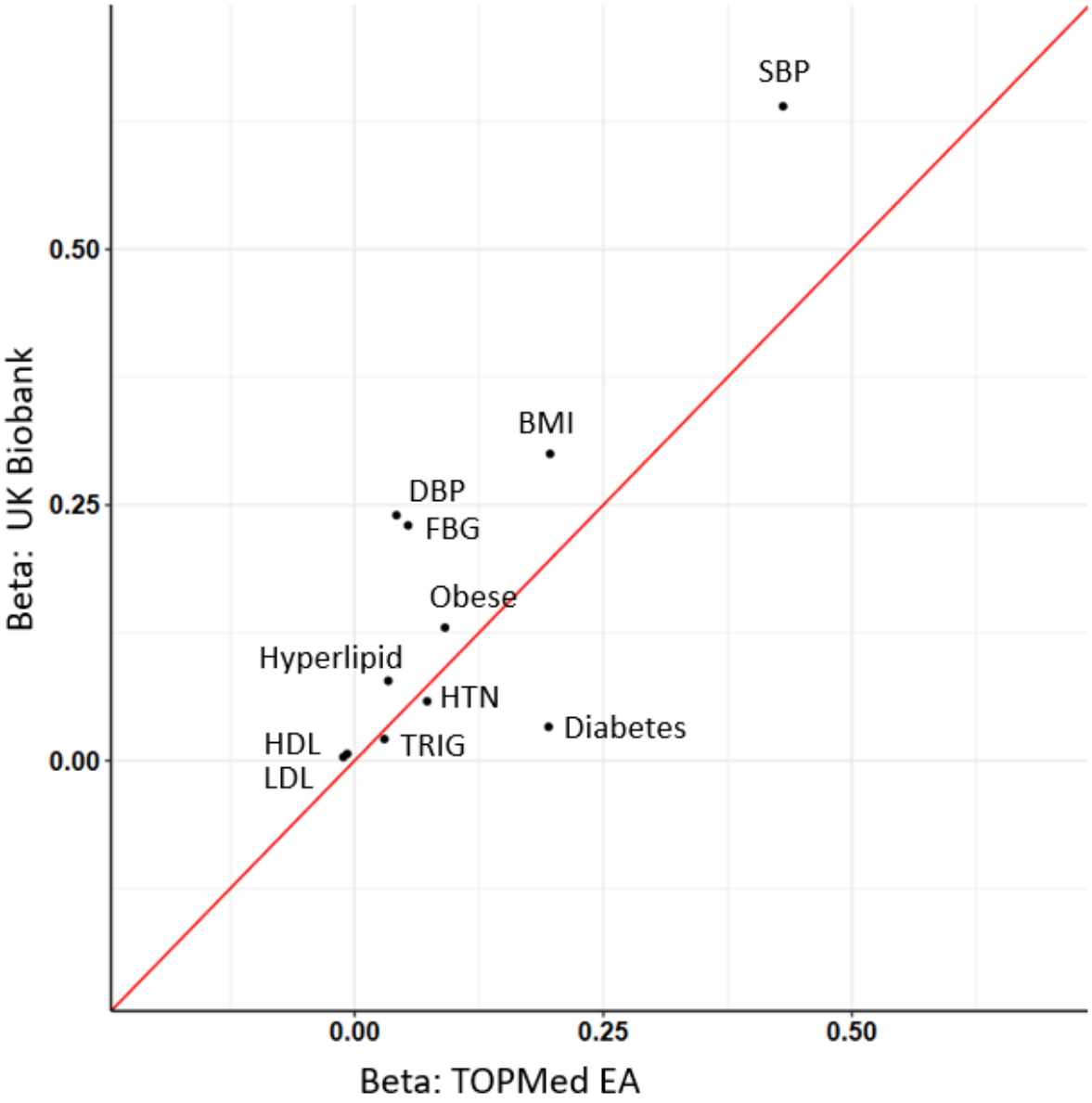


Figure S8. Comparison of regression coefficients of mtDNA CN with CMD traits in participants of European ancestry in TOPMed (n=13,378) vs UK Biobank (n=318,470), Related to Table 1, Figure 2B. Comparison of beta of CMD traits in the participants of European ancestry between TOPMed and UK Biobank.

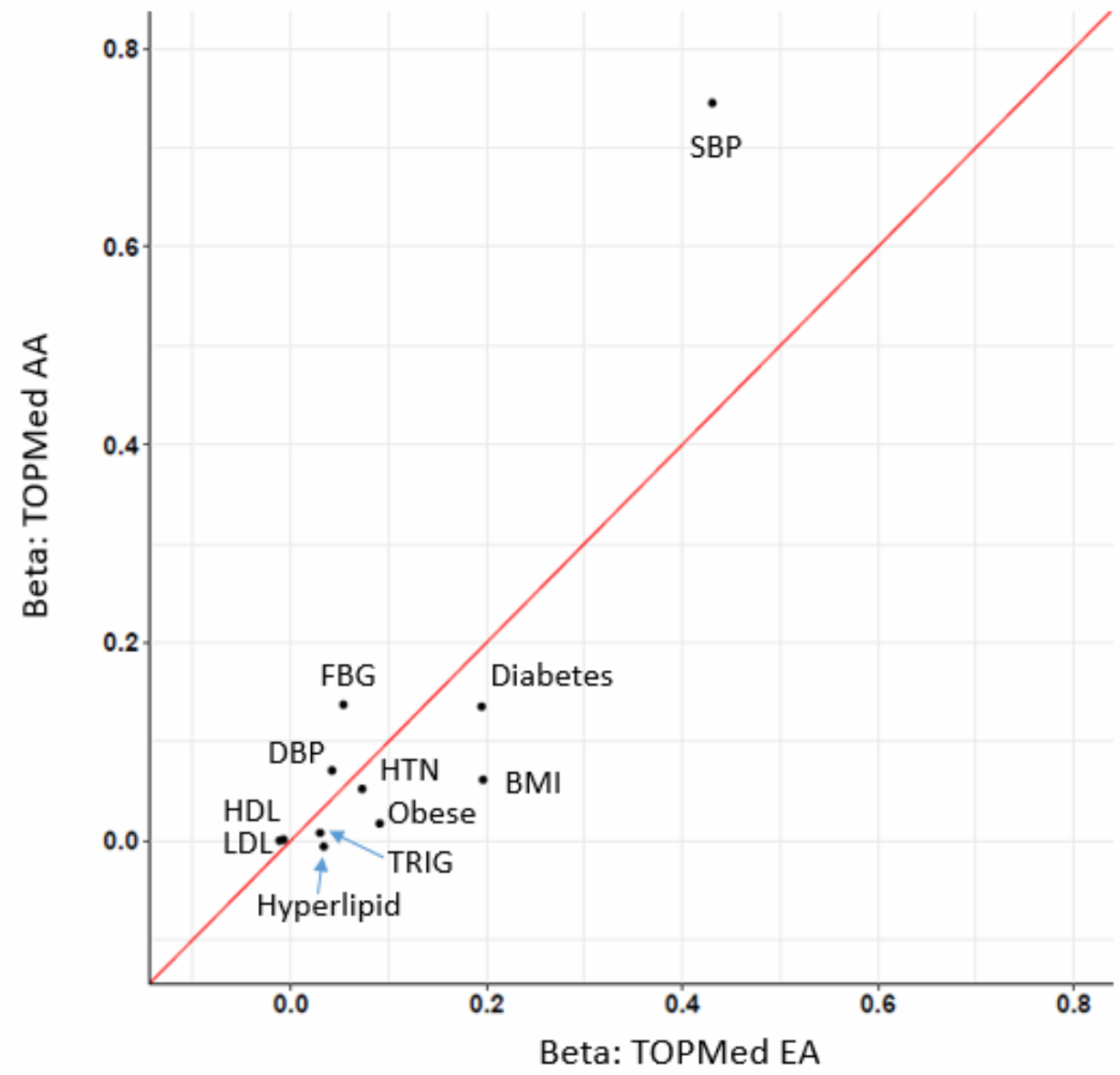


Figure S9. Comparison of beta of metabolic traits in participants of European Ancestry (n=13,378) and African Ancestry (n=8,020) in TOPMed, Related to Table 1, Figure 1. The beta estimates corresponds to one s.d. decrease in the mtDNA CN level.

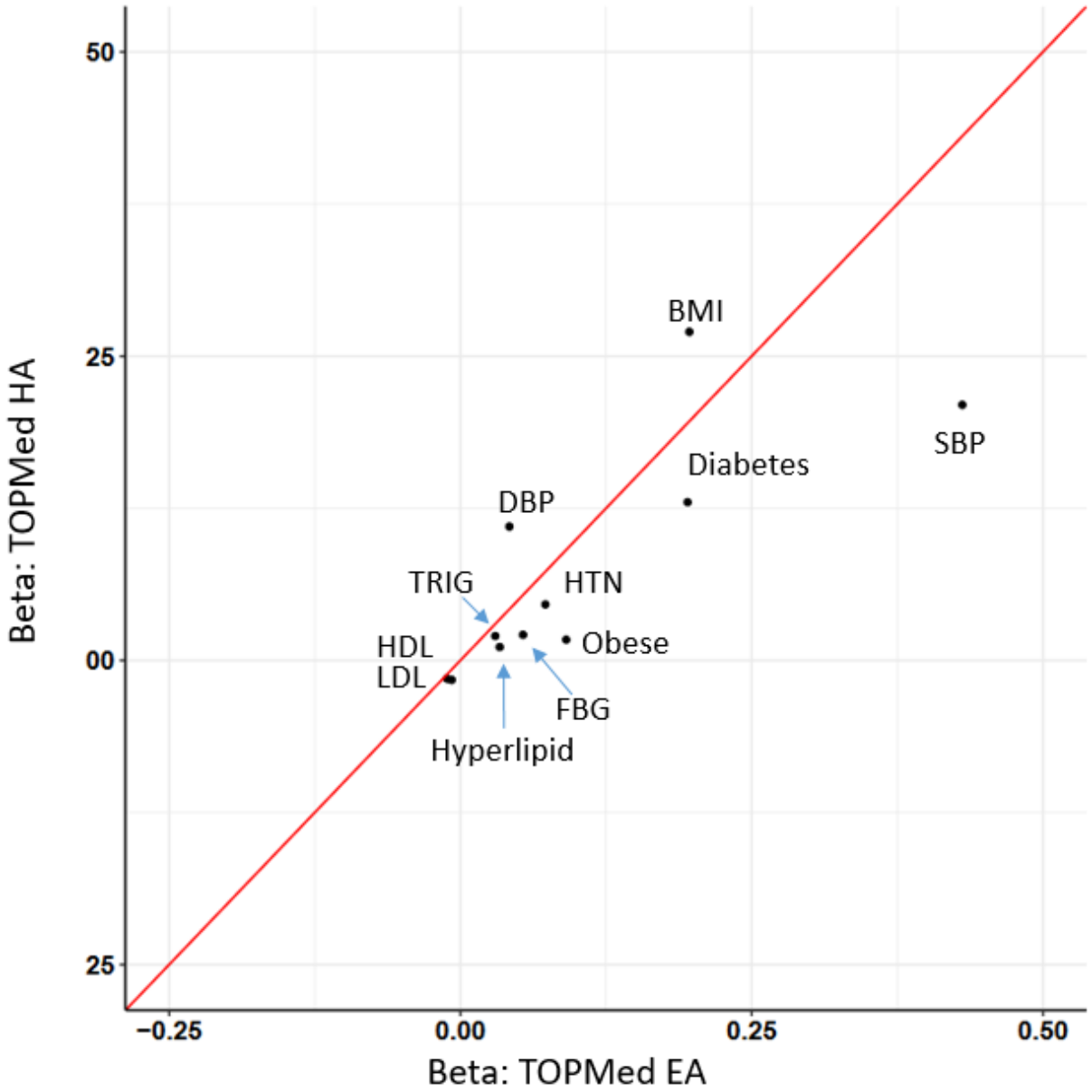


Figure S10. Comparison of regression coefficients of mtDNA CN with CMD traits in participants of European Ancestry (13,378) vs Hispanic/Latino (n=4,892) Americans in TOPMed, Related to Table 1, Figure 1. Comparison of beta of CMD traits in the participants of European ancestry and Hispanic Latino Americans in TOPMed.

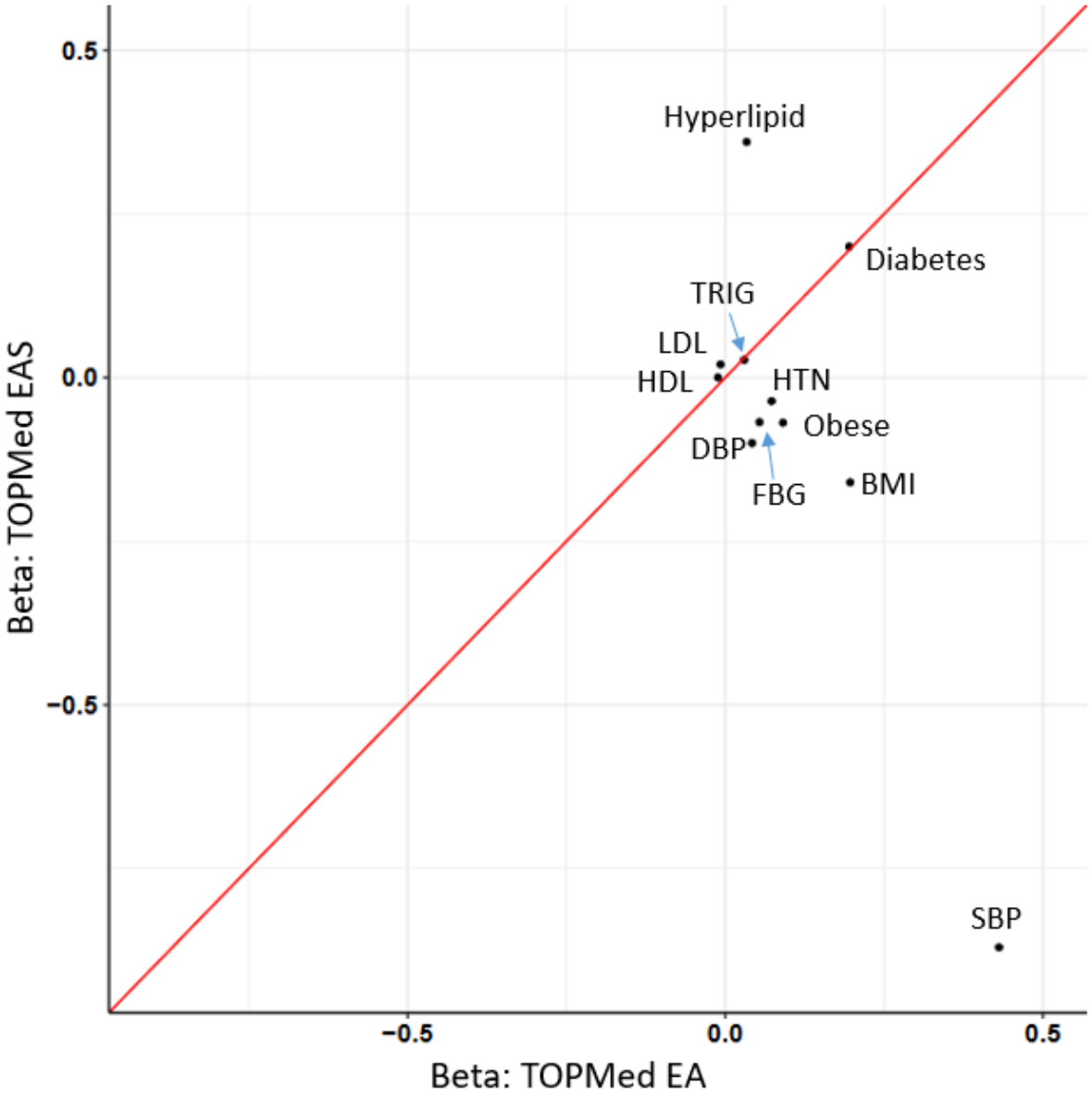


Figure S11 Comparison of regression coefficients of mtDNA CN with CMD traits in participants of European Ancestry (n=13,378) vs Chinese Ancestry (n=601) in TOPMed, Related to Table 1, Figure 1. Comparison of beta of CMD traits in the participants of European ancestry and Chinese ancestry in TOPMed.

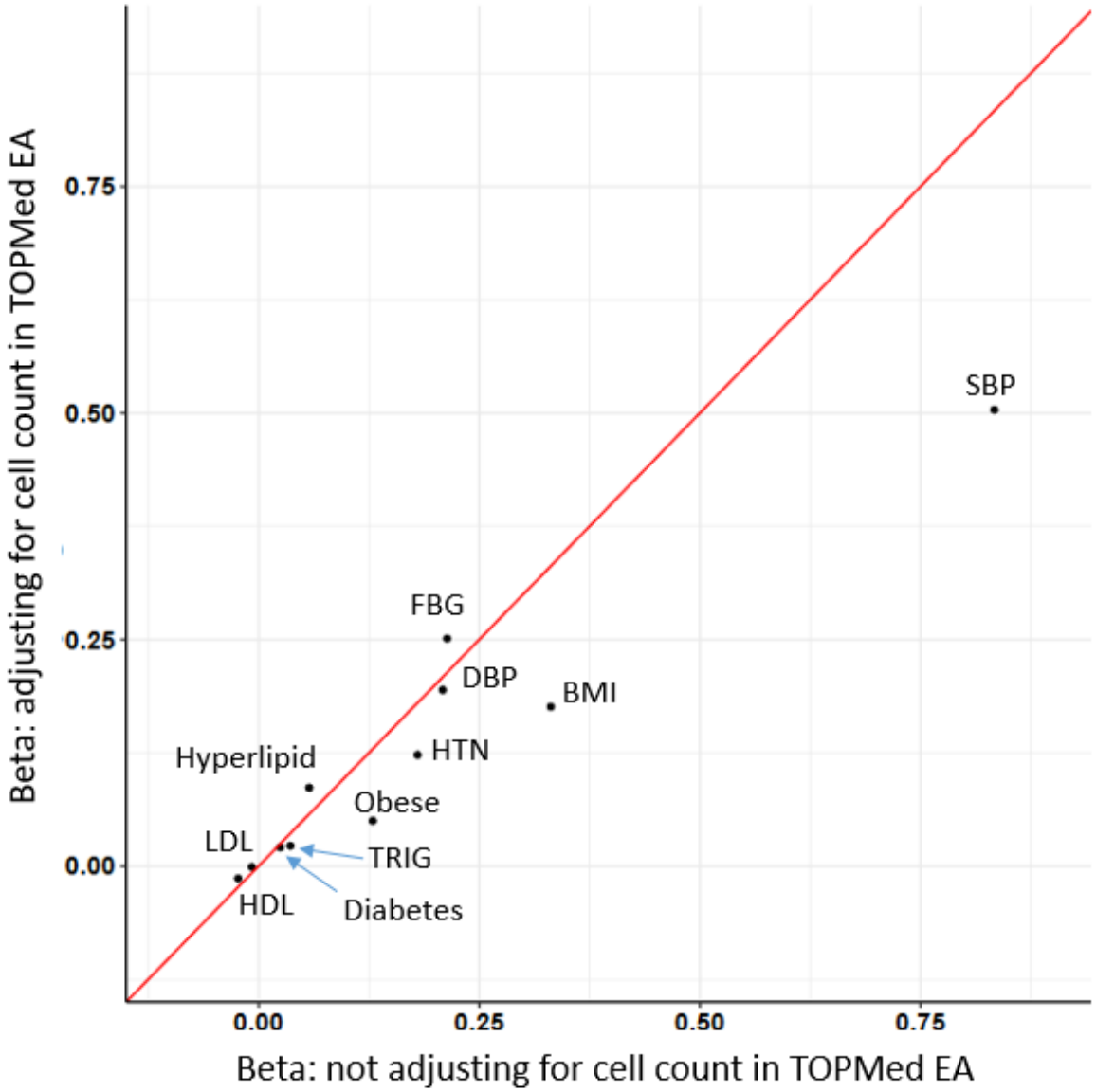


Figure S12. Comparison of regression coefficients of mtDNA CN with CMD traits in TOPMed participants of European Ancestry not adjusting for cell counts vs adjusting for cell counts, Related to Figure 2C. Comparison of beta of CMD traits of model not adjusting for cell counts vs adjusting for cell counts in the same participants of European ancestry in TOPMed (n=5,056).

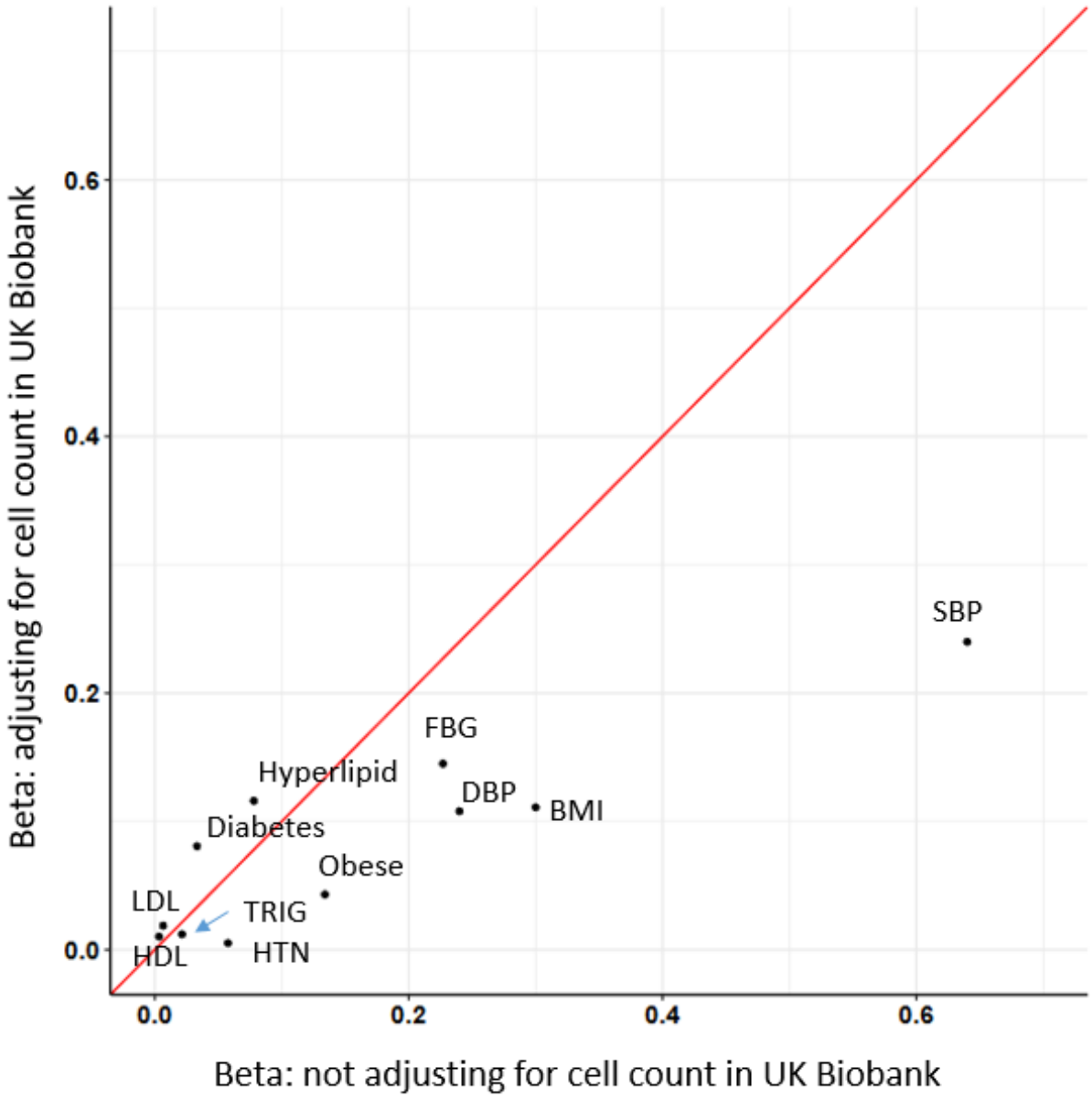


Figure S13. Comparison of regression coefficients of mtDNA CN with CMD traits in the UK Biobank participants of European ancestry not adjusting for cell counts vs adjusting for cell counts, Related to Figure 2C. Comparison of beta of CMD traits not adjusting for cell counts vs adjusting for cell counts in the participants of European ancestry in UK Biobank (UKB) (n=381,470).

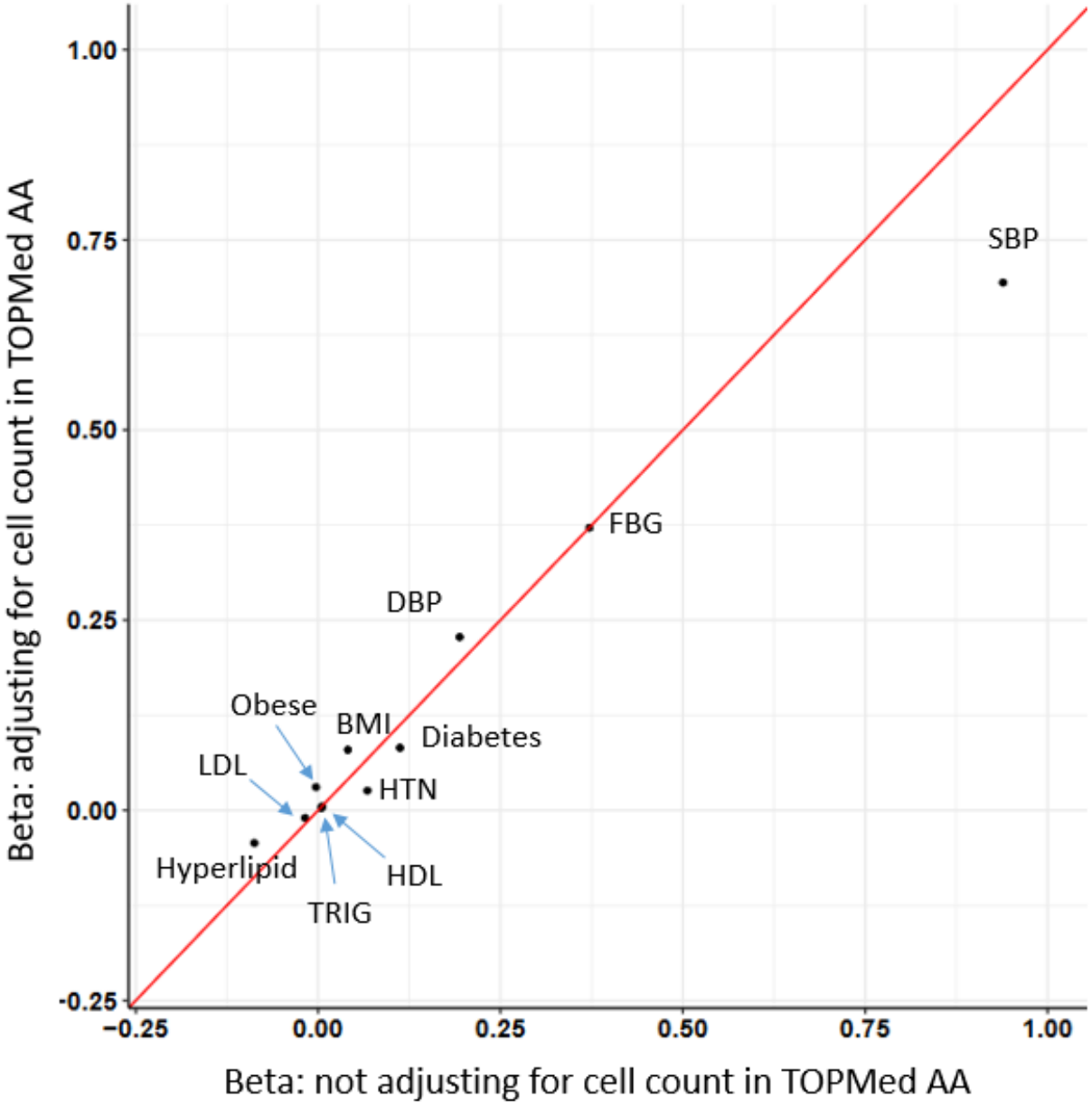


Figure S14. Comparison of regression coefficients of mtDNA CN with CMD traits in TOPMed participants of African Ancestry not adjusting for cell counts vs adjusting for cell counts, Related to Figure 2C. Comparison of beta of CMD traits of model not adjusting for cell counts vs adjusting for cell counts in the participants of African ancestry in TOPMed (n=3,733).

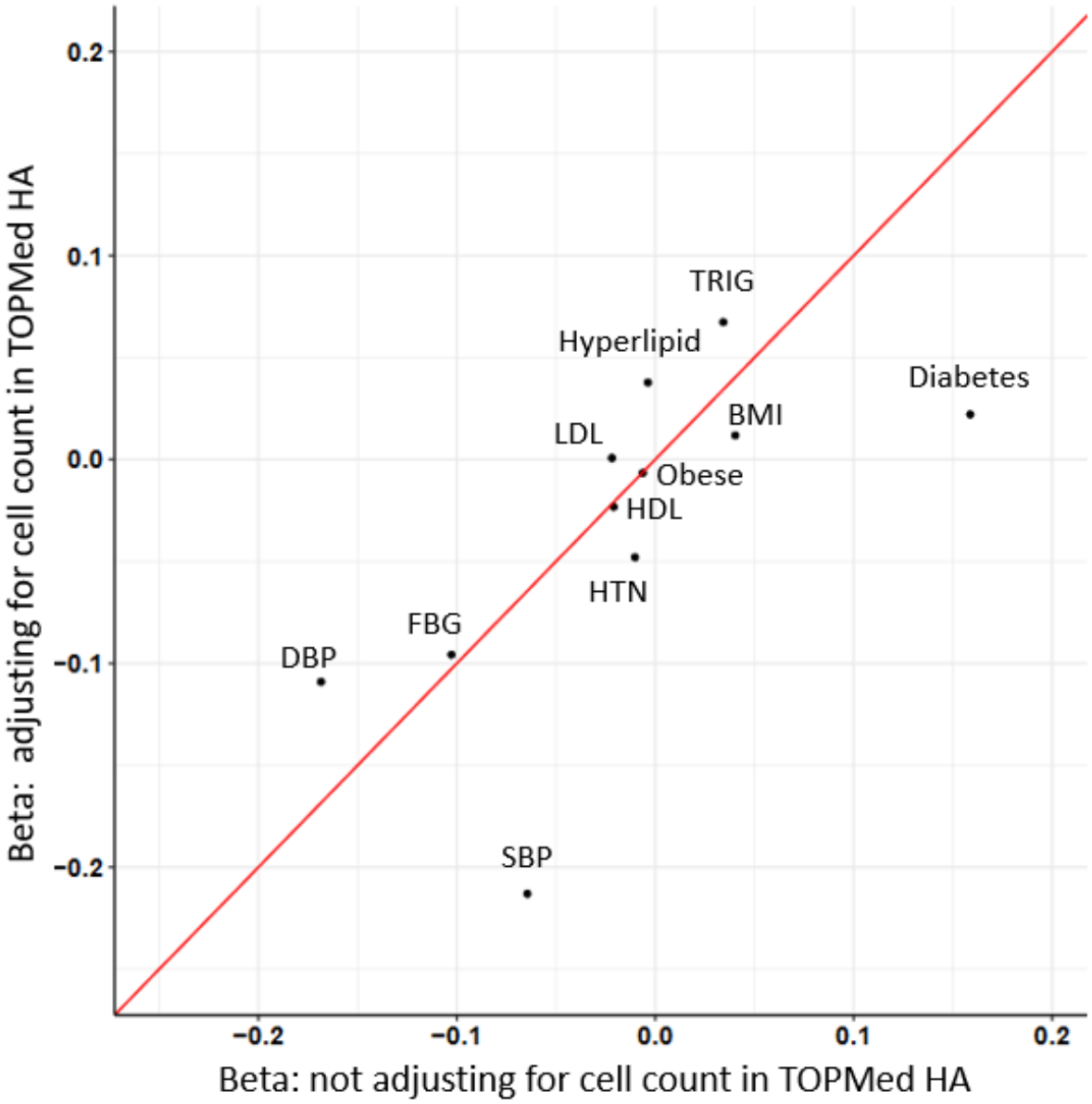


Figure S15. Comparison of regression coefficients of mtDNA CN with CMD traits in TOPMed Hispanic and Latino American participants not adjusting for cell counts vs adjusting for cell counts, Related to Figure 2C. Comparison of beta of CMD traits of model not adjusting for cell counts vs adjusting for cell counts in the participants of Hispanic and Latino Americans in TOPMed (n=3,613).

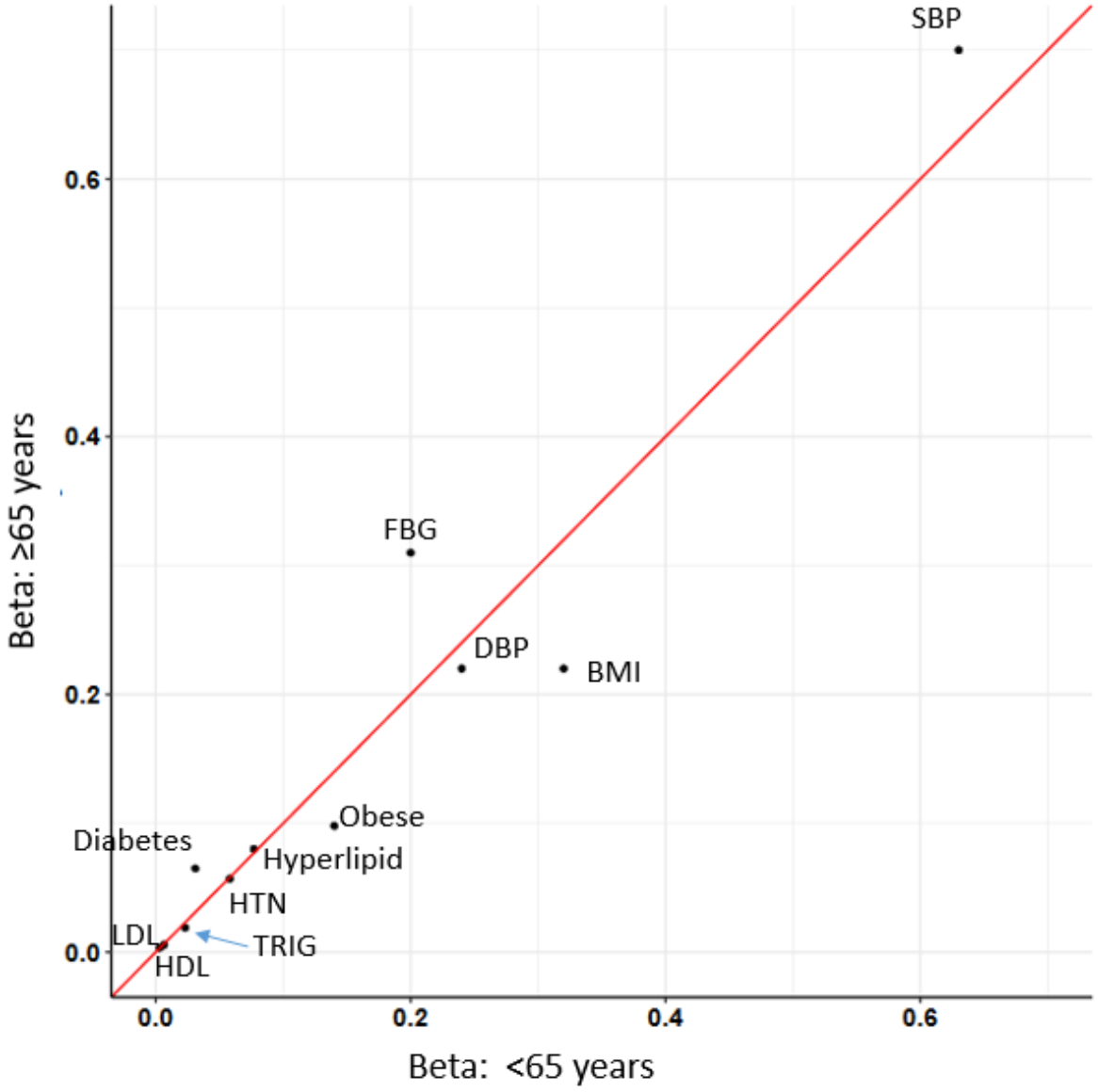


Figure S16. Comparison of regression coefficients of mtDNA CN with CMD traits in participants of European ancestry <65 years (n=315,708) vs >65 years (n=79,782) in TOPMed and UK BioBank after meta-analysis, Related to Figure 2D.

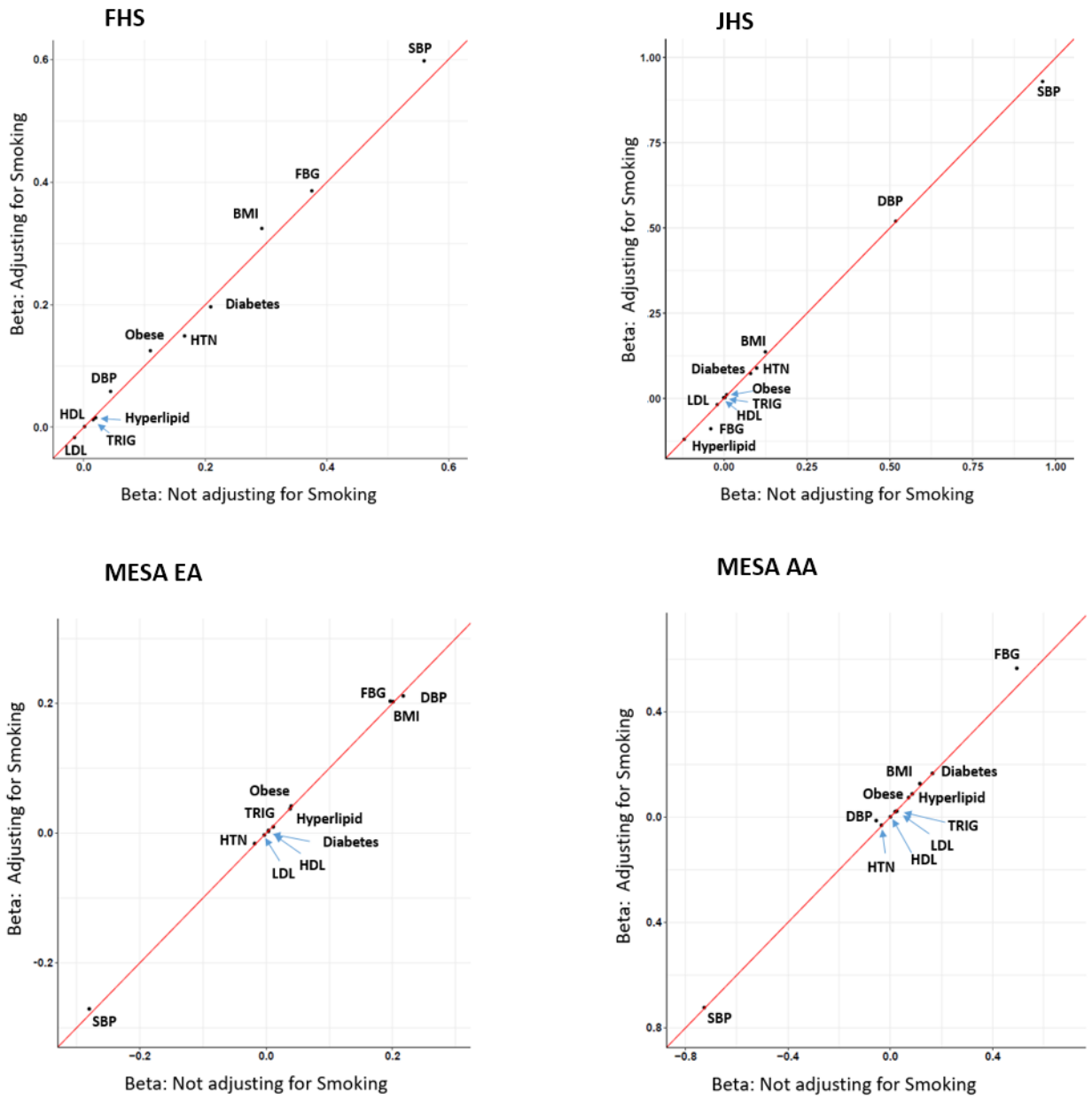


Figure S17. Sensitivity analysis of adjusting smoking as an additional covariate, Related to STAR Methods. We performed a sensitivity analysis with and without adjusting for smoking as an additional covariate to investigate whether smoking altered associations between mtDNA CN and CMD traits in FHS, JHS and MESA. Four of seven continuous traits displayed minor changes (<10%) in their beta estimates with mtDNA CN while three continuous traits and four binary traits appeared to have consistent beta estimates between models with and without smoking as a covariate The FHS consists of European ancestry (EA) and the JHS consists of African ancestry (AA). The MESA consists of both EA and AA.

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