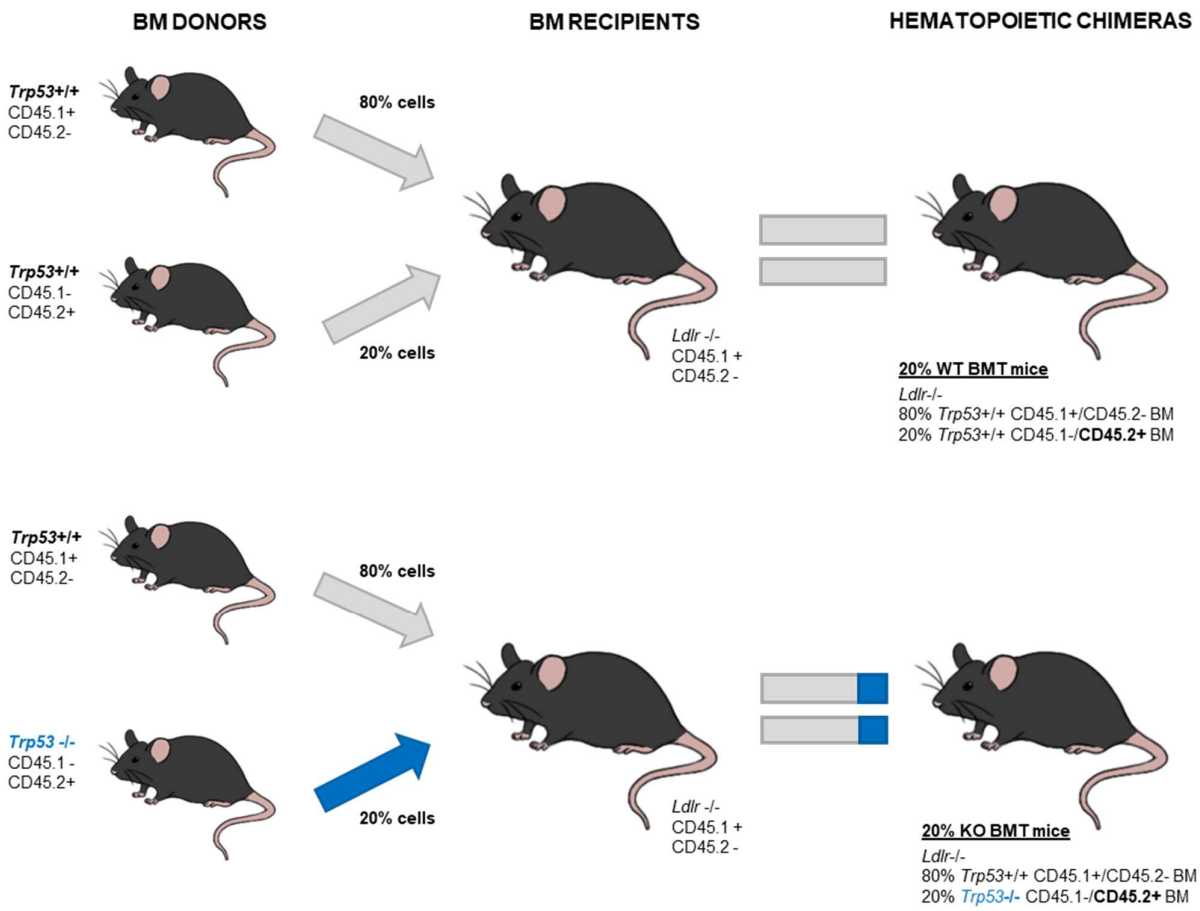
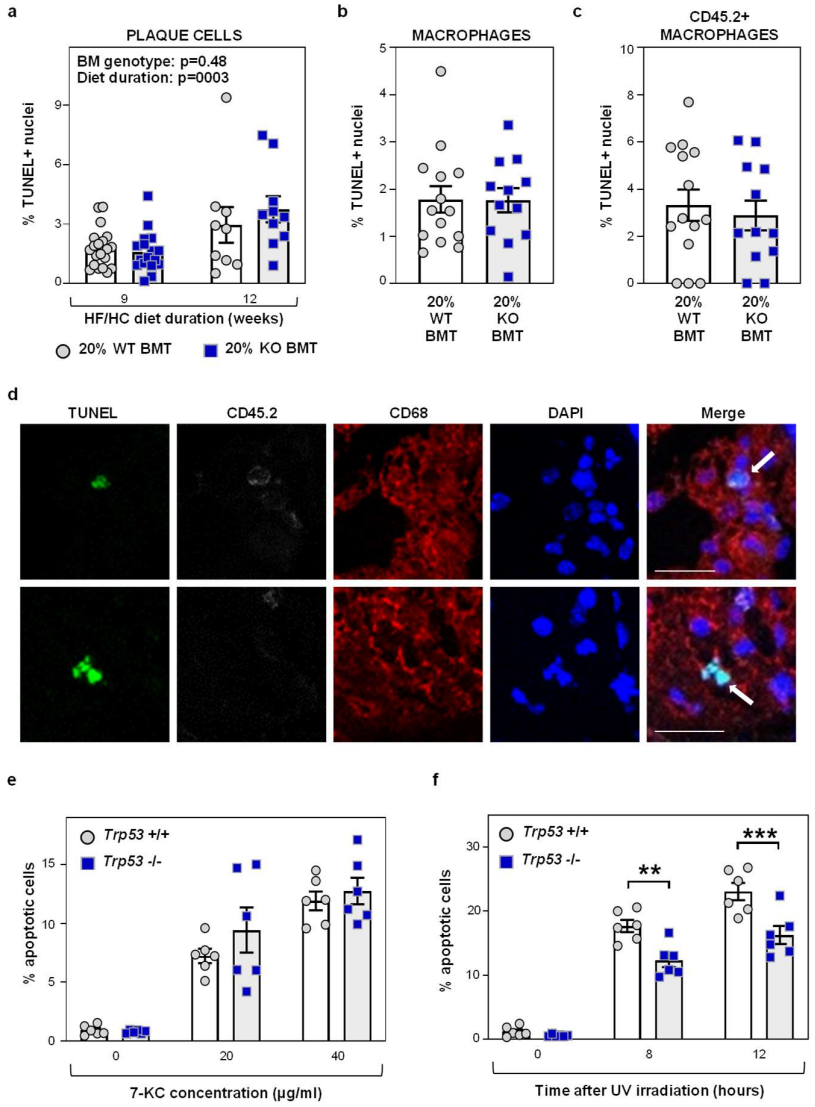
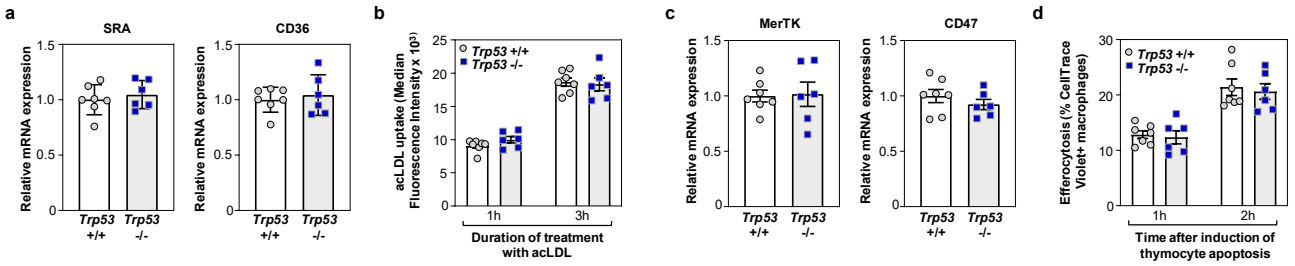


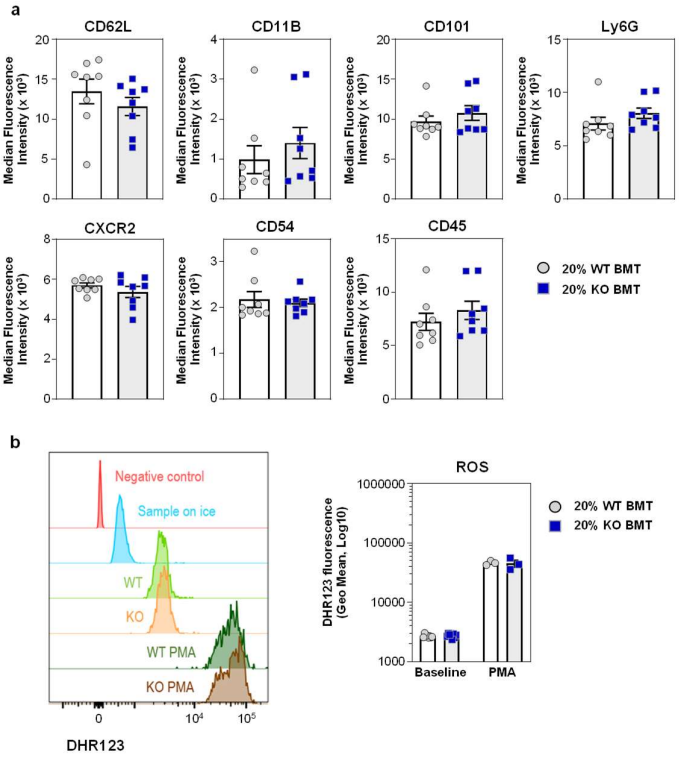
Supplementary Figure 1. A competitive (80:20) bone marrow transplantation approach to generate a murine model of p53-deficient CHIP.



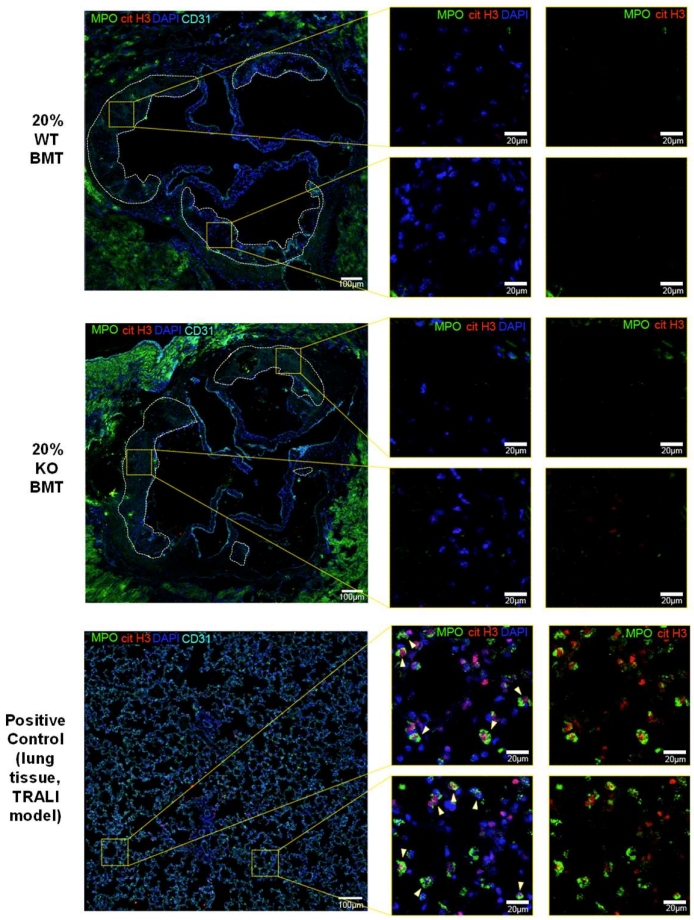
Supplementary Figure 2. No effect of p53-deficient CHIP on murine plaque macrophage apoptosis. a-d) 20% KO-BMT male mice and 20% WT-BMT controls were fed a high-fat/high cholesterol (HF/HC) diet for 9 or 12 weeks, starting 4 weeks after BMT (mean±SEM, n=14 20% WT-BMT mice [9 weeks HF/HC], n=12 20% KO-BMT mice [9 weeks HF/HC], n=9 20% WT-BMT mice [12 weeks HF/HC], n=10 mice 20% KO-BMT mice [12 weeks HF/HC]. Percentage of apoptotic nuclei within total plaque cells **(a)**, plaque macrophages **(b)** and CD45.2+ macrophages **(c)** were quantified by TUNEL (green) in aortic root sections stained with anti-CD45.2 antibody (white), anti-CD68 antibody (macrophages, red) and DAPI (nuclei, blue). p values in (a) were calculated using a two-way ANOVA. Representative images of the immunofluorescent staining are shown **(d)**. Arrows point to examples of TUNEL-positive macrophages (upper panel, CD45.2+; lower panel, CD45.2-). Scale bars: 25 µm. **e)** Apoptotic cell quantification in cultured *Trp53*-/- and +/+ bone marrow-derived macrophages after 7-ketocholesterol (7KC) treatment for 24h, assessed by propidium iodide staining of cellular DNA content and flow cytometry identification of hypodiploid cells (mean±SEM, n=6 *Trp53*+/+ mice, n=6 *Trp53*-/- mice). **f)** UV irradiation-induced apoptosis was used as positive control. (mean±SEM, n=6 *Trp53*+/+ mice, n=6 *Trp53*-/- mice). A two-way ANOVA with Sidak's multiple comparison test was used for statistical analysis (**p<0.01;***p<0.001).



Supplementary Figure 3. No effect of p53 deficiency on the uptake of modified LDL or apoptotic cells by macrophages. Thioglycolate-elicited peritoneal macrophages were isolated from *Trp53*-/- mice and *Trp53*+/+ controls (n=7 *Trp53*+/+ mice, n=6 *Trp53*-/- mice). **a)** qPCR analysis of the expression of scavenger receptors SRA and CD36 (mean±SEM). **b)** Flow cytometry analysis of fluorescently labeled acetylated low-density lipoprotein (acLDL) uptake by macrophages treated with 5 µg/mL acLDL (mean±SEM). **c)** qPCR analysis of the expression of efferocytosis modulators MerTK and CD47 (mean±SEM). **d)** Flow cytometry analysis of efferocytosis by macrophages, assessed based on the uptake of CellTrace Violet-stained apoptotic thymocytes (mean±SEM).



Supplementary Figure 4. No effect of p53 deficiency on neutrophil functionality. 20% KO-BMT male mice and 20% WT-BMT controls were fed a high-fat/high-cholesterol (HF/HC) diet for 4 weeks, starting 4 weeks after BMT. **a)** Expression levels of several phenotype markers in circulating neutrophils, evaluated by flow cytometry (mean±SEM, n=8 20% WT-BMT mice, n=8 20% KO-BMT mice). **b)** Quantification of reactive oxygen species (ROS) levels by DHR123 staining and flow cytometry analysis of circulating neutrophils in resting conditions and after stimulation with 133 nM phorbol-12-myristate-13-acetate (PMA) for 20 min (mean±SEM, n=8 20% WT-BMT mice [baseline], n=8 20% KO-BMT mice [baseline], n=3 20% WT-BMT mice [PMA], n=3 20% KO-BMT mice [PMA]. Representative histograms are shown.



Supplementary Figure 5. No effect of p53-deficient CHIP on the formation of neutrophil extracellular traps (NETs) in murine atherosclerotic plaques. NETosis was assessed in aortic root sections from 20% KO-BMT male mice and 20% WT-BMT controls fed a HF/HC diet for 9 weeks (n=3 per BM genotype), by immunofluorescent staining with an anti-MPO antibody (green), anti-citrullinated histone 3 (cit H3) antibody (red), anti-CD31 antibody (cyan) and DAPI (nuclei, blue). Lung sections obtained from a mouse model of transfusion-related acute lung injury (TRALI) were used as positive control. Triple-stained events (MPO, cit H3, and DAPI) were considered NETs. No NETosis was observed in atherosclerotic plaques, regardless of BM genotype. Representative images are shown; atherosclerotic plaques are delineated by dashed lines. Triangles in lung sections indicate examples of NETs. Scale bars, 100 μm or 20 μm for magnified fields.

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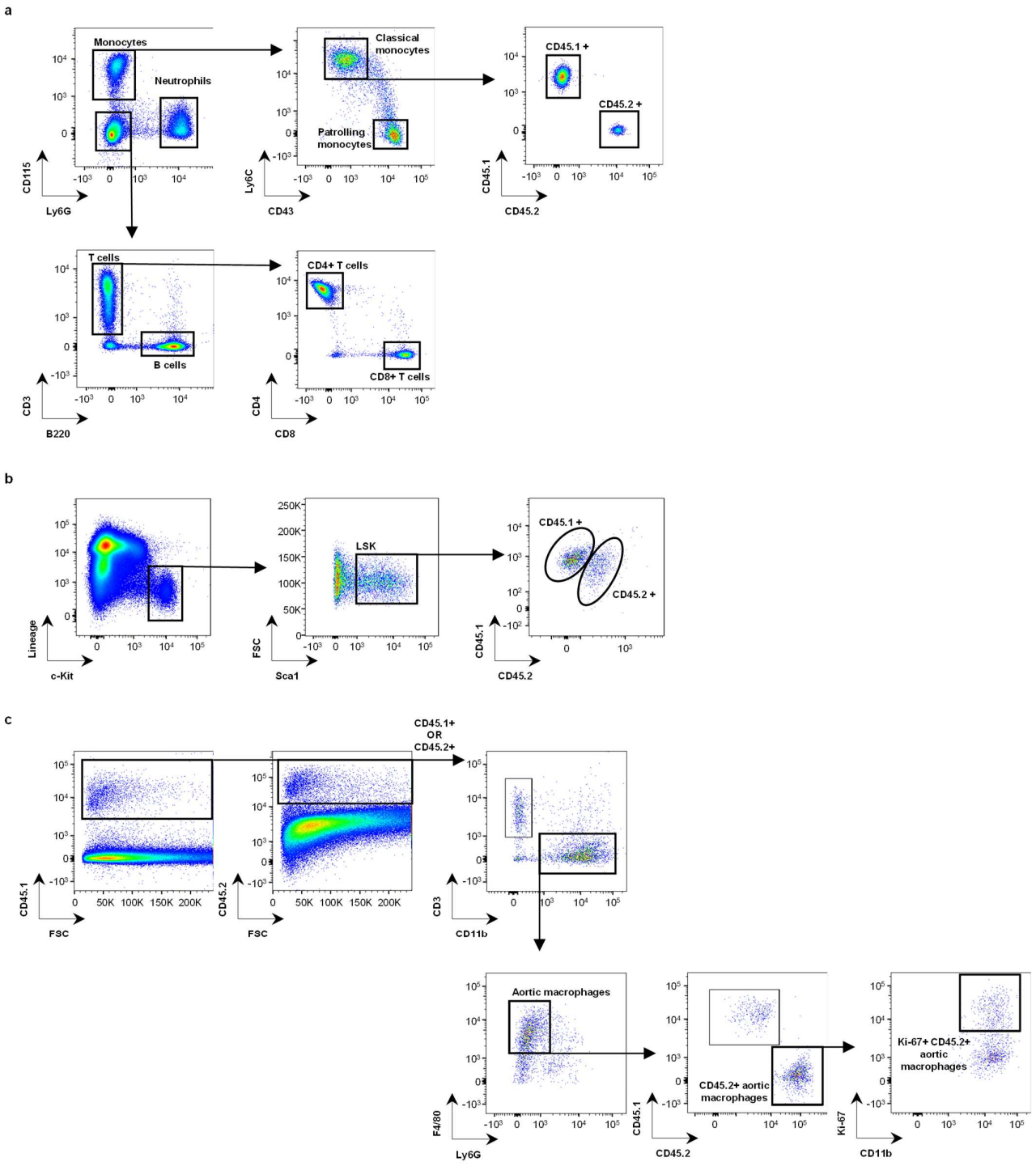

Supplementary Figure 6. Summary of gating strategies in flow cytometry experiments. a) Gating strategy for white blood cell lineages (initially gated as single, live CD45+ cells). The final CD45.1/CD45.2 gating is shown exclusively for classical monocytes for simplicity, but the same gating was applied to other white blood cell lineages. **b**) Gating strategy for bone marrow hematopoietic stem and progenitor (LSK) cells (initially gated as single, live cells). **c**) Gating strategy for aortic macrophages (initially gated as single, live cells).

	UKBB (N=37,657)		*MGBB (N=12,465)*	
	All CHIP	Large CHIP	All CHIP	Large CHIP
CHIP (%)	2194 (5.8)	911 (2.4)	657 (5.3)	314 (2.5)
>1 CHIP Mutation (%)	191 (0.5)	70 (0.2)	55 (0.4)	16 (0.1)
DNMT3A (%)	1401 (3.8)	489 (1.4)	311 (2.6)	144 (1.2)
TET2 (%)	347 (1.0)	181 (0.5)	132 (1.1)	61 (0.5)
JAK2 (%)	17 (0.0)	17 (0.0)	5 (0.0)	5 (0.0)
ASXL1 (%)	152 (0.4)	100 (0.3)	47 (0.4)	21 (0.2)
Splicing Factor Mutation (%)	49 (0.1)	28 (0.1)	17 (0.1)	8 (0.1)
TP53 (%)	36 (0.1)	11 (0.0)	20 (0.2)	12 (0.1)
PPM1D (%)	32 (0.1)	12 (0.0)	32 (0.3)	13 (0.1)
TP53 or PPM1D (%)	68 (0.2)	23 (0.1)	52 (0.4)	25 (0.2)

Supplementary Table 1. CHIP gene carrier count by cohort. Splicing Factor Mutations refer to the following CHIP genes: *LUC7L2, PRPF8, SF3B1, SRSF2, U2AF1,* and *ZRSR2.* Large CHIP refers to mutations with variant allele frequency > 10%.

	UK Biobank			*MGB Biobank*		
	-CHIP	**+CHIP**	**p**	**-CHIP**	**+CHIP**	**p**
n	35463	2194		11808	657	
age (mean (SD))	56.81 (7.84)	60.59 (6.57)	<0.001	46.13 (14.65)	60.12 (12.05)	<0.001
Sex = Male (%)	16379 (46.2)	1042 (47.5)	0.242	4937 (41.8)	304 (46.3)	0.027
Race (%)			NA			0.002
White	35463 (100.0)	2194 (100.0)		9449 (80.0)	566 (86.1)	
Black				723 (6.1)	27 (4.1)	
Asian				465 (3.9)	19 (2.9)	
Other				474 (4.0)	12 (1.8)	
Unknown				697 (5.9)	33 (5.0)	
Smoking Status (%)			<0.001			<0.001
Current	3027 (8.5)	220 (10.0)		288 (2.4)	17 (2.6)	
Previous	12664 (35.7)	900 (41.0)		3662 (31.0)	261 (39.7)	
Never	19772 (55.8)	1074 (49.0)		7183 (60.8)	351 (53.4)	
Alcohol intake (drinks in last 4wk) (mean (SD))	11.37 (9.89)	11.67 (10.11)	0.156			
Exercise frequency (days in last 4wk) (mean (SD))	8.34 (6.38)	8.45 (6.43)	0.591			
Townsend Deprivation Index (mean (SD))	-1.55 (2.81)	-1.65 (2.75)	0.137			
Significant life stressor in last 2y (%)	16915 (47.8)	1030 (47.1)	0.535			
Handfulls of sweets/day (mean (SD))	1.09 (1.17)	0.93 (1.19)	0.399			
Vegetable servings/day (mean (SD))	1.08 (0.54)	1.02 (0.49)	0.283			
BMI (mean (SD))	27.39 (4.76)	27.48 (4.55)	0.414	28.14 (6.35)	28.55 (6.33)	0.132
Prevalent Type 2 Diabetes Mellitus (%)	956 (2.7)	70 (3.2)	0.189	505 (4.3)	40 (6.1)	0.035
Prevalent Coronary Artery Disease (%)	2040 (5.8)	171 (7.8)	<0.001	378 (3.2)	42 (6.4)	<0.001
Prevalent Hypertension (%)	10650 (30.0)	782 (35.6)	<0.001	1893 (16.0)	193 (29.4)	<0.001
Prevalent Hypercholesterolemia (%)	6159 (17.4)	448 (20.4)	<0.001	1739 (14.7)	172 (26.2)	<0.001

Supplementary Table 2 - Demographic and clinical characteristics for CHIP carriers and controls in the UK and Mass General Brigham Biobanks. P-values reflect chi-square tests comparing CHIP carriers to controls across each phenotypic category.

CHIP Status	HR	SE	P
All CHIP	1.72	0.19	0.0033
Large CHIP	2.54	0.23	0.000034
DDR CHIP	3.09	0.71	0.11

Supplementary Table 3. PAD association results when removing prevalent CAD from the analysis

CHIP Status	HR	SE	P
All CHIP	1.61	0.18	0.00772
Large CHIP	2.24	0.22	0.0003
DDR CHIP	4.24	0.58	0.013

Supplementary Table 4 - PAD association results when adding CAD as a covariate to the model for analysis

	UK Biobank			*MGB Biobank*		
	No CHIP	**CHIP**	**p**	**No CHIP**	**CHIP**	**p**
Composite Atherosclerosis (%)	1697 (100.0)	178 (100.0)	NA	878 (100.0)	75 (100.0)	NA
Coronary Artery Disease (%)	917 (54.0)	94 (52.8)	0.815	666 (75.9)	59 (78.7)	0.684
Peripheral Artery Disease (%)	224 (13.2)	33 (18.5)	0.063	234 (26.7)	19 (25.3)	0.911
Cerebral Atherosclerosis (%)	526 (31.0)	39 (21.9)	0.015	158 (18.0)	19 (25.3)	0.157
Abdominal Aortic Aneurysm (%)	76 (4.5)	13 (7.3)	0.133	18 (2.1)	0 (0.0)	0.418
Aortic Aneurysm (%)	143 (8.4)	24 (13.5)	0.034	55 (6.3)	4 (5.3)	0.943
Other Aneurysm (%)	180 (10.6)	30 (16.9)	0.017	99 (11.3)	8 (10.7)	1
Chronic Mesenteric Ischemia (%)	3 (0.2)	0 (0.0)	1	6 (0.7)	1 (1.3)	1
Acute Mesenteric Ischemia (%)	37 (2.2)	8 (4.5)	0.097	1 (0.1)	0 (0.0)	1
Renal Artery Atherosclerosis (%)	1 (0.1)	0 (0.0)	1	14 (1.6)	0 (0.0)	0.547

Supplementary Table 5. Breakdown of composite incident atherosclerosis events by disease in the UK Biobank and MGB Biobank.

Gene	HR	95% CI	P
DNMT3A	1.08	0.86-1.35	0.5
TET2	2.05	1.54-2.71	6.30E-07
TP53	2.31	1.03-5.16	0.042
PPM1D	2.63	1.40-4.95	0.0027
ASXL1	1.73	1.09-2.76	0.021
Splicing Factor Mutation	1.62	0.72-3.66	0.24
Multiple Mutations	1.70	1.06-2.71	0.026
TP53 or PPM1D	2.51	1.52-4.13	0.00032

Supplementary Table 6. Association of CHIP carrier state, stratified by CHIP gene, with incident CAD events in the UK Biobank (UKB) and Mass General Brigham Biobank (MGBB). Results were combined using an inverse-variance weighted fixed effects meta-analysis.

Supplementary Tables 7-9 are provided in a separate Excel file.

Antibody	Clone	Supplier	Ref	Dilution
Alkaline phosphatase-conjugated mouse anti-smooth muscle α-actin	1A4	Sigma	A6691	1/50
Anti-Mouse/Human Mac-2 (Galectin-3), Purified monoclonal antibody (rat IgG2a)	M3/38	Cedarlane Labs	CL8942AP	1/300
Rabbit anti-Ki-67 monoclonal antibody	SP6	Abcam	ab16667	1/100
Rat anti mouse CD68 primary antibody	FA-11	BioRad	MCA1957	1/100
Alexa Fluor 647-conjugated anti-CD45.2 antibody	104	BioLegend	109817	1/200
Recombinant Anti-Histone H3 (citrulline R2 + R8 + R17) antibody	RM1001	Abcam	ab5103	1/200
CD31 monoclonal antibody	2H8	ThermoFisher	MA3105	1/200
(Biotinylated)- Human/Mouse Myeloperoxidase/MPO Antibody	Polyclonal	R&D Systems (biotinylated in house)	AF3667	1/200
BrdU Monoclonal Antibody	MoBV-1	ThermoFisher	B35128	1/100
Biotin-conjugated goat anti-rat secondary antibody IgG	-	Vector Laboratories	BA9401	1/400
Biotin-conjugated horse anti-rabbit secondary antibody IgG	-	Vector Laboratories	BA1100	1/400
Alexa Fluor 568-conjugated goat anti-rat IgG (H+L) antibody	Polyclonal	ThermoFisher	A-11077	1/500
Alexa Fluor 568-conjugated goat anti-rabbit IgG (H+L) antibody	Polyclonal	ThermoFisher	A-11011	1/500
Alexa Fluor 488-conjugated goat anti-mouse IgG secondary (H+L) antibody	Polyclonal	ThermoFisher	A-11029	1/500
Alexa Fluor 647-conjugated goat anti-hamster IgG secondary antibody	Polyclonal	Jackson Immunoresearch	127-605-099	1/500
Alexa fluor-488 conjugated Streptavidin antibody	-	BioLegend	405235	1/500
Biotin rat anti mouse-CD11b antibody	M1/70	BD Biosciences	559971	1/50
Biotin rat anti mouse Gr-1 antibody	RB6-8C5	BD Biosciences	559971	1/50
Biotin rat anti mouse Ter119 antibody	TER-119	BD Biosciences	559971	1/50
Biotin rat anti mouse B220 (CD45R) antibody	RA3-6B2	BD Biosciences	559971	1/50
Biotin hamster anti mouse CD3e antibody	145-2C11	BD Biosciences	559971	1/50
Biotin anti mouse CD127 (IL-7Rα) antibody	A7R34	BioLegend	135005	1/100
BV421-conjugated Streptavidin	-	BD Biosciences	563259	1/500
APC-Cy7-conjugated anti-CD45 antibody	30-F11	BioLegend	103116	1/200
PE-Cy7-conjugated anti-CD45.1 antibody	A20	eBioscience	25-0453-82	1/100
PE-Cy7-conjugated anti-CD45.1 antibody	A20	BioLegend	110730	1/200
PerCP-Cy5.5-conjugated anti-CD45.1	A20	BioLegend	110728	1/100
eFluor450-conjugated anti-CD45.2 antibody	104	eBioscience	48-0454-82	1/100
FITC-conjugated anti-CD45.2 antibody	104	eBioscience	11-0454-82	1/100
FITC-conjugated anti-CD45.2 antibody	104	BioLegend	109806	1/200
APC-conjugated anti-CD45.2 antibody	104	BioLegend	109814	1/200
FITC-conjugated anti-CD11b antibody	M1/70	eBioscience	11-0112-82	1/100
eFluor450-conjugated anti-CD11b antibody	M1/70	eBioscience	48-0112-82	1/100
FITC-conjugated anti-CD11b antibody	M1/70	Invitrogen	11-0112-82	1/100
PE-conjugated anti-CD11b antibody	M1/70	Tonbo Biosciences	50-0112-U100	1/200
BV510-conjugated anti-CD11b antibody	M1/70	BioLegend	101245	1/200
PE-conjugated anti-F4/80 antibody	521204	R&D Systems	FAB5580P	1/100
PE-conjugated anti-F4/80 antibody	BM8.1	Tonbo bioscience	50-4801-v025	1/100
PE-conjugated anti-CD115 (c-fms) antibody	AFS98	eBioscience	12-1152-82	1/100
PerCP-Cy5.5-conjugated anti-Ly6G antibody	1A8	BD Biosciences	560602	1/100
BV510-conjugated anti-Ly6G antibody	1A8	BD Biosciences	740157	1/100
BUV737-conjugated anti-Ly6G antibody	1A8	BD Biosciences	741813	1/200
APC-Cy7-conjugated anti-B220 antibody	RA3-6B2	BD Biosciences	552094	1/100
PE-eFluor610-conjugated anti-CD3 antibody	145-2C11	eBioscience	61-0031-82	1/100
FITC-conjugated anti-CD4 antibody	RM4-5	eBioscience	11-0042-82	1/100
BV510-conjugated anti-CD8a antibody	53-6.7	BioLegend	10752	1/100
BV711-conjugated anti-CD43 antibody	S7	BD Biosciences	740668	1/100
PE-Cy7-conjugated anti-c-Kit (CD117) antibody	2B8	BD Biosciences	553355	1/50
AlexaFluor647-conjugated anti-Sca1 (Ly-6A/E) antibody	D7	BD Biosciences	558162	1/50

PerCP-Cy5.5-conjugated anti-mouse Ki-67 antibody	16A8	BioLegend	652424	1/300
PE-conjugated anti-CD62L antibody	MEL-14	eBioscience	12-0621-83	1/200
PerCP-Cy5.5-conjugated anti-CXCR2 antibody	SA044g4	BioLegend	149308	1/200
PECy7-conjugated anti-CD101 antibody	Moushi101	ThermoFisher	25-1011-82	1/200
AlexaFluor 647-conjugated anti-CD54 antibody	YN1/1.7.4	BioLegend	116114	1/200
Anti-p53 (D2H90) Rabbit mAb (Rodent Specific)	D2H90	Cell Signaling	32532S	1/1000
HRP-conjugated anti-alpha tubulin	DM1A	Abcam	ab40742	1/2000
Goat anti-rabbit HRP antibody	Polyclonal	Life Technologies	A18871	1/2000

Supplementary Table 10. Antibodies used for immunostaining in experimental studies.

Gene	**FW primer**	**RV primer**
Actb (β-actin)	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT
18S	AGTTCCAGCACATTTTGCGAG	TCATCCTCCGTGAGTTCTCCA
Rplp0 (36B4)	GCTCCAAGCAGATGCAGCA	CCGGATGTGAGGCAGCAG
Trp53	GTCACAGCACATGACGGAGG	TCTTCCAGATGCTCGGGATAC
Cdkn1a	CCTGGTGATGTCCGACCTG	CCATGAGCGCATCGCAATC
Ccnb1	AAGGTGCCTGTGTGTGAAC	GTCAGCCCCATCATCTGCG
Il1b	TGACAGTGATGAGAATGACCTGTTC	TTGGAAGCAGCCCTTCATCT
Il6	GCTACCAAACTGGATATAATCAGGA	CCAGGTAGCTATGGTACTCCAGAA
Nlrp3	ATTACCCGCCCGAGAAAGG	TCGCAGCAAAGATCCACAC
Msr1 (SRA)	TCAGACTGAAGGACTGGGA	GGAGGCCCTTGAATGAAGGT
CD36	TGCCCATGCCGAGAGTCT	CAGAGGCGCACCAAACCT
Mertk	TGCGTTTAATCACACCATT	TGCCCCGAGCAATTCCTTTC
CD47	TGCGGTTCAGCTCAACTACTG	GCTTTGCGCCTCCACATTAC

Supplementary Table 11. Oligonucleotides used as primers in quantitative PCR analyses in experimental studies.