SUPPLEMENTAL MATERIAL

Prognostic Significance of TET2-Clonal Haematopoiesis of Indeterminate Potential-Mutations with hs-CRP in Patients with STEMI --- from a Prospective Cohort Study Combing Bidirectional Mendelian Randomization

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Details on the study cohort

The diagnosis and classification of AMI followed contemporary guidelines and widely recognized definitions. Assessments included clinical presentations, distinctive electrocardiographic findings, dynamic cardiac enzyme levels, and imaging evidence. The cohort consisted of patients diagnosed with AMI, who were stratified for conservative medical management, PCI, or CABG based on coronary angiography results and individual clinical statuses. Eligibility criteria included adult patients meeting two main conditions: (1) they underwent primary PCI involving stent implantation, thrombus aspiration, or balloon dilation in coronary arteries; and (2) they provided written informed consent. Exclusion criteria applied to individuals if they met any of the following: (1) declined participation; (2) could not be traced during follow-up; (3) lacked the measured CHIP parameters; or (4) had a history of malignancies combined with moderate to severe valvular heart disease, previous cardiac surgeries (except thoracoscopic ablation), moderate liver dysfunction, or chronic kidney disease with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2 These exclusions aimed to reduce potential confounding factors between CHIP and other diseases. Demographic data, medication history, and laboratory test results were comprehensively examined across all study populations. The high-sensitivity C-reactive protein (hs-CRP), fasting glucose, creatinine etc. measurement was meticulously extracted from the electronic medical records, reflecting the most recent available test result pertinent to the date when the study sample was collected. Comorbidities were identified through a triad of methodologies: self-reporting by participants, detailed examination of electronic medical records, or clinical diagnoses based on established measured values. The study protocol was rigorously aligned with the ethical principles articulated in the Declaration of Helsinki and secured endorsement from our institution's ethics committee (No. 2017-866). Written informed consent was duly obtained from all participants involved.

Outcomes and Follow-up

The principal outcome of the present analysis was mortality from all causes. Routine follow-up assessments were conducted following patient discharge. At the conclusion of the first month, patients were invited to return to the medical facility for comprehensive evaluations; for those unable to attend in person, a follow-up was executed via telephone interviews conducted by staff members at the institute's information center, utilizing a standardized questionnaire independent of external influence. Subsequently, all patients were scheduled for additional phone interviews at both six and twelve months post-discharge. For individuals who survived beyond one year, subsequent follow-ups would occur on an annual basis. The research team received monthly updates regarding follow-up data, and all reported adverse events underwent systematic assessment by a dedicated group of physicians.

Supplemental Methods 2.Deep targeted sequencing of clonal hematopoiesis mutations

Peripheral blood specimens were meticulously collected following the acquisition of written informed consent. DNA extraction was conducted on peripheral leukocytes to facilitate the targeted sequencing of 42 genes implicated in clonal hematopoiesis of indeterminate potential. We engineered a bespoke panel (Agilent, USA), encompassing an exhaustive repertoire of hematologic genes and variant loci inspired by insights gleaned from prior scholarly investigations [1]. The ensuing targeted sequencing was executed by a distinguished commercial entity (Tianhao, China), strictly adhering to the comprehensive protocols delineated below. DNA extraction employed whole blood samples procured from either the radial or femoral artery prior to heparinization and percutaneous coronary intervention (PCI). The integrity of genomic DNA was assessed via agarose gel electrophoresis; distinct bands devoid of trailing artifacts signified an absence of degradation. Both concentration and quality metrics for the extracted DNA were quantified utilizing Nanodrop 2000/Qubit systems, conforming to rigorous criteria: concentration $\geq$ 20 ng/μL, total yield $\geq$ 1 μg, and an OD260/280 ratio ranging between 1.8 and 2.0. These exacting standards ensured elevated purity levels for the DNA sample while affirming its freedom from protein or RNA contamination. The isolated DNA underwent several pivotal procedures: size selection, purification, fragmentation, end repair with inherent adenylation at both termini, followed by ligation with unique molecular identifier (UMI) sequencing adapters to construct libraries in preparation for subsequent sequencing endeavors. The Picard software deftly enabled the meticulous analysis of alignment outcomes derived from single-stranded consensus sequences, following a comprehensive and precise UMI correction for each sample. The ANNOVAR tool was judiciously employed to systematically juxtapose all identified single nucleotide variants (SNVs) and insertions/deletions (InDels) against the most up-to-date population databases, as well as functional and disease-related repositories. This exhaustive analysis meticulously evaluated the prevalence of variants, their functional characteristics, conservation status, and associated pathogenicity pertaining to these SNV/InDel alterations. A variant allele fraction (VAF) of $\geq$ 2.0% signified the presence of CHIP mutations [2].

[1] Jaiswal S, Fontanillas P, Flannick J, et al. Agerelated clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488–2498.

[2] Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. Nat Rev Cardiol 2020;17:137–44.

Supplemental Table 1. List of 42 clonal hematopoiesis-associated genes analyzed by targeted sequencing.

ASXL1	*ASXL2*	*BCOR*	*BCORL1*	*BRCC3*	*CEBPA*	*CREBBP*	*CTCF*	*CUX1*	*DNMT3A*
EP300	*ETV6*	*EZH2*	*GATA1*	*GATA2*	*GATA3*	*GNB1*	*IDH2*	*IKZF2*	*IKZF3*
JAK2	*KDM6A*	*MPL*	*NF1*	*PDS5B*	*PHIP*	*PPM1D*	*PRPF40B*	*PTEN*	*RAD21*
RUNX1	*SETD2*	*SETDB1*	*SF1*	*SF3A1*	*SF3B1*	*SMC3*	*STAG1*	*STAG2*	*TET2*
TP53	*ZRSR2*								

Supplemental Table 2 Clinical features according to the of Tet2-CHIP (variant allele fraction ⩾ 2.0%) and PCSK9 in all enrolled cohort.

Variables	***Total (N=1286)***	***Tet2(-)/PCSK9(-) (N=625)***	***Tet2(-)/PCSK9(+) (N=625)***	***Tet2(+)/PCSK9(-) (N=18)***	***Tet2(+)/PCSK9(+) (N=18)***	***P***
Age (years)	60.7 ±12.4	60.6 ±11.8	60.2 ±12.7	70.8 ±13.3	69.1 ±13.7	< 0.001*
Male	1037 (80.6)	517 (82.7)	494 (79)	15 (83.3)	11 (61.1)	0.079
Heart rate(beats/min)	76.6 ±21.4	75.3 ±15.4	77.8 ±26.1	78.9 ±17.1	76.3 ±21.7	0.231
SBP (mmHg)	125.4 ±19.9	124.4 ±20.0	126.3 ±19.8	129.1 ±19.9	128.8 ±23.3	0.280
DBP(mmHg)	78.6 ±13.5	78.2 ±13.7	78.9 ±13.2	84.4 ±15.5	78.9 ±11.5	0.220
EF at admission	53.7 ±7.7	54.1 ±7.3	53.2 ±8.0	54.4 ±8.3	53.4 ±8.6	0.285
Hypertension[%(n)]	841 (65.4)	409 (65.4)	410 (65.6)	11 (61.1)	11 (61.1)	0.959
Hyperlipidemia[%(n)]	1164 (90.5)	555 (88.8)	579 (92.6)	17 (94.4)	13 (72.2)	0.011*
Diabetes Mellitus[%(n)]	437 (34.0)	205 (32.8)	218 (34.9)	9 (50)	5 (27.8)	0.395
Smoking[%(n)]	914 (71.6)	458 (73.9)	434 (69.9)	13 (72.2)	9 (50)	0.086
CKD[%(n)]	91 (7.1)	39 (6.2)	48 (7.7)	0 (0)	4 (22.2)	0.055
periphery atherosclerosis[%(n)]	68 (5.3)	29 (4.6)	39 (6.3)	0 (0)	0 (0)	0.451
History of MI [%(n)]	223 (17.3)	97 (15.5)	121 (19.4)	2 (11.1)	3 (16.7)	0.306
History of PCI [%(n)]	227 (17.7)	97 (15.5)	126 (20.2)	2 (11.1)	2 (11.1)	0.142
History of CABG [%(n)]	28 (2.2)	8 (1.3)	17 (2.7)	1 (5.6)	2 (11.1)	0.022*
FABP4 (ng/mL)	7.9 ±7.2	7.9 ±7.3	7.9 ±7.1	9.9 ±8.3	7.5 ±6.3	0.714
RVD (ng/mL)	241.9 ±294.9	281.2 ±363.5	203.3 ±203.8	251.0 ±164.8	209.4 ±241.3	< 0.001*
HDL-C (mg/dl)	1.1 ±0.4	1.1 ±0.3	1.1 ±0.4	1.0 ±0.3	1.0 ±0.2	0.574
LDL-C (mg/dl)	2.8 ±3.9	2.7 ±0.9	2.9 ±5.5	2.5 ±0.9	2.6 ±0.6	0.865
Triglycerides (mmol/L)	1.7 ±1.2	1.6 ±1.1	1.8 ±1.2	1.7 ±0.8	1.8 ±1.3	0.034*
TyG index	9.1 ±0.7	9.1 ±0.7	9.2 ±0.7	9.1 ±0.7	9.2 ±1.0	0.123
TC (mmol/L)	4.3 ±1.8	4.4 ±2.3	4.3 ±1.1	4.1 ±1.1	4.2 ±0.8	0.761
LPA (g/L)	269.4 ±277.9	262.4 ±271.7	277.5 ±284.8	157.8 ±148.1	338.5 ±324.8	0.177
TC/HDL-C	4.3 ±3.9	4.1 ±1.8	4.5 ±5.3	4.1 ±1.1	4.1 ±1.0	0.494
LDL-C/HDL-C	2.7 ±3.9	2.6 ±1.0	2.9 ±5.5	2.6 ±1.0	2.5 ±0.8	0.458
PTX3 (ng/mL)	9.6 ±15.7	8.0 ±18.5	11.2 ±12.4	6.6 ±3.0	12.4 ±8.6	0.003*
LXA4 (ng/mL)	6.6 ±5.4	6.1 ±5.8	6.9 ±5.1	7.1 ±3.5	9.4 ±5.1	0.008*
LL37 (ng/mL)	24.0 ±14.5	21.1 ±11.6	26.8 ±16.5	19.9 ±12.7	27.4 ±12.2	< 0.001*
hs-CRP (mg/L)	6.7 ±8.7	6.2 ±4.7	7.2 ±11.5	6.2 ±4.7	7.8 ±4.1	0.197
Creatinine (mmol/L)	89.6 ±37.2	87.2 ±26.4	92.0 ±45.9	86.4 ±15.4	93.7 ±35.1	0.144
Fasting glucose (mmol/L)	8.4 ±3.8	8.4 ±3.8	8.4 ±3.8	8.5 ±4.1	9.3 ±4.7	0.804
cTnI at baseline level (mmol/L)	6.6 ±15.1	6.9 ±16.2	6.1 ±13.3	6.5 ±23.4	12.7 ±24.5	0.304
cTnI at peak level (mmol/L)	24.0 ±27.3	26.5 ±28.4	21.3 ±25.5	34.8 ±35.9	24.0 ±30.3	0.003*
NT-proBNP at baseline level (mmol/L)	1040.5 ±2514.8	912.7 ±2040.7	1151.0 ±2935.7	1041.4 ±1734.3	1619.8 ±2015.8	0.288
NT-proBNP at peak level (mmol/L)	2963.0 ±5317.3	2997.2 ±5163.0	2719.3 ±4826.0	7696.6 ±13323.8	5493.7 ±9648.0	< 0.001*
Aspirin[%(n)]	1207 (95.2)	584 (94.8)	591 (95.8)	18 (100)	14 (82.4)	0.102
Statin[%(n)]	1210 (95.4)	581 (94.3)	596 (96.6)	17 (94.4)	16 (94.1)	0.174
Clopidogrel[%(n)]	637 (50.2)	287 (46.6)	323 (52.4)	14 (77.8)	13 (76.5)	0.002*
Ticagrelor[%(n)]	613 (48.3)	320 (51.9)	285 (46.2)	4 (22.2)	4 (23.5)	0.004*
Beta-Blockers[%(n)]	1089 (85.9)	531 (86.2)	530 (85.9)	15 (83.3)	13 (76.5)	0.592
proton pump inhibitor[%(n)]	649 (51.3)	314 (51.1)	322 (52.3)	5 (27.8)	8 (47.1)	0.226
Anticoagulants[%(n)]	36 (2.8)	21 (3.4)	14 (2.3)	0 (0)	1 (5.9)	0.351
TIMI score	3.5 ±2.1	3.5 ±2.1	3.5 ±2.0	4.7 ±2.1	5.2 ±3.0	< 0.001*
Diameter of coronary lesion (mm^2)	2.8 ±1.2	2.8 ±1.6	2.9 ±0.8	2.7 ±1.2	3.0 ±0.6	0.818
Length of coronary lesion (mm)	26.4 ±15.7	27.2 ±17.3	25.8 ±14.1	22.1 ±7.6	22.5 ±10.7	0.218
All caused mortality	125 (9.7)	51 (8.2)	64 (10.2)	6 (33.3)	4 (22.2)	0.003*
Cardiac death	72 (5.6)	29 (4.6)	39 (6.2)	3 (16.7)	1 (5.6)	0.108
Recurrence MI	66 (5.1)	31 (5)	32 (5.1)	1 (5.6)	2 (11.1)	0.538
Recurrence HF	39 (3.0)	13 (2.1)	25 (4)	0 (0)	1 (5.6)	0.170
Recurrence revas	223 (17.3)	109 (17.4)	112 (17.9)	2 (11.1)	0 (0)	0.215
Ischemic stroke	66 (5.1)	30 (4.8)	35 (5.6)	0 (0)	1 (5.6)	0.731

Continuous data are presented as median (IQR). Categorical data are presented as number (%). If it is a continuous variable, it can be obtained by Kruskal Wallis rank sum test. If the counting variable is less than 10, it can be obtained by Fisher exact probability test. ***Abbreviations:*** *DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diabetes blood pressure; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TnI, troponin; CK-MB, creatine kinase isoenzymes; LPA, lipse activator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; hs-CRP, high sensitive C-reactive protein; MACE, major adverse cardiovascular events; MI, myocardial i*nfarctio*n. FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide, RVD, Resolvin D1. *P<0.05.*

Supplemental Table 3 Clinical features according to the of Tet2-CHIP (variant allele fraction ⩾ 2.0%) and PCSK9 stratified by the status of DM in all enrolled cohort

Variables	***DM***						***Non-DM***					
	Total DM N=437	***Tet2(-)/PCSK9(-) N=205***	***Tet2(-)/PCSK9(+) N=218***	***Tet2(+)/PCSK9(-) N=9***	***Tet2(+)/PCSK9(+) N=5***	***P1***	***Total Non-DM N=849***	***Tet2(-)/PCSK9(-) N=420***	***Tet2(-)/PCSK9(+) N=407***	***Tet2(+)/PCSK9(-) N=9***	***Tet2(+)/PCSK9(+) N=13***	***P2***
Age (years)	62.2 ± 11.3	61.2 ± 10.3	62.7 ± 11.7	67.7 ± 17.7	69.2 ± 17.9	0.110	59.9 ± 12.8	60.3 ± 12.4	58.8 ± 13.1	73.8 ± 6.6	69.0 ± 12.6	< 0.001*
Male	328 (75.1)	168 (82)	151 (69.3)	7 (77.8)	2 (40)	0.005*	709 (83.5)	349 (83.1)	343 (84.3)	8 (88.9)	9 (69.2)	0.484
Heart rate(beats/min)	77.6 ± 15.4	75.9 ± 15.8	79.1 ± 14.9	86.6 ± 18.1	72.0 ± 3.5	0.043*	76.0 ± 23.9	75.1 ± 15.2	77.1 ± 30.5	71.3 ± 12.6	77.9 ± 25.5	0.589
SBP (mmHg)	127.2 ± 19.2	126.5 ± 19.8	127.6 ± 18.7	128.1 ± 18.4	140.0 ± 16.6	0.450	124.5 ± 20.3	123.4 ± 20.0	125.5 ± 20.4	130.0 ± 22.4	124.5 ± 24.6	0.401
DBP(mmHg)	78.9 ± 12.7	78.9 ± 12.7	78.6 ± 12.9	84.2 ± 11.9	82.2 ± 8.5	0.572	78.5 ± 13.8	77.8 ± 14.2	79.1 ± 13.3	84.7 ± 19.2	77.6 ± 12.5	0.303
EF at admission	53.0 ± 7.7	53.6 ± 7.2	52.3 ± 8.1	50.9 ± 8.7	55.6 ± 8.3	0.240	54.0 ± 7.6	54.3 ± 7.3	53.7 ± 7.9	58.0 ± 6.6	52.5 ± 8.9	0.259
Hypertension[%(n)]	313 (71.6)	144 (70.2)	158 (72.5)	8 (88.9)	3 (60)	0.617	528 (62.2)	265 (63.1)	252 (61.9)	3 (33.3)	8 (61.5)	0.377
Hyperlipidemia[%(n)]	408 (93.4)	188 (91.7)	207 (95)	9 (100)	4 (80)	0.228	756 (89.0)	367 (87.4)	372 (91.4)	8 (88.9)	9 (69.2)	0.033
Smoking[%(n)]	295 (68.0)	156 (76.8)	132 (60.8)	6 (66.7)	1 (20)	< 0.001*	619 (73.4)	302 (72.4)	302 (74.8)	7 (77.8)	8 (61.5)	0.639
CKD[%(n)]	35 (8.0)	15 (7.3)	18 (8.3)	0 (0)	2 (40)	0.125	56 (6.6)	24 (5.7)	30 (7.4)	0 (0)	2 (15.4)	0.333
periphery atherosclerosis[%(n)]	27 (6.2)	10 (4.9)	17 (7.8)	0 (0)	0 (0)	0.543	41 (4.8)	19 (4.5)	22 (5.4)	0 (0)	0 (0)	0.877
History of MI [%(n)]	90 (20.6)	39 (19)	50 (22.9)	1 (11.1)	0 (0)	0.562	133 (15.7)	58 (13.8)	71 (17.4)	1 (11.1)	3 (23.1)	0.389
History of PCI [%(n)]	92 (21.1)	40 (19.5)	52 (23.9)	0 (0)	0 (0)	0.218	135 (15.9)	57 (13.6)	74 (18.2)	2 (22.2)	2 (15.4)	0.228
History of CABG [%(n)]	15 (3.4)	5 (2.4)	8 (3.7)	1 (11.1)	1 (20)	0.084	13 (1.5)	3 (0.7)	9 (2.2)	0 (0)	1 (7.7)	0.070
FABP4 (ng/mL)	8.4 ± 7.6	7.4 ± 6.8	9.4 ± 8.3	9.7 ± 8.2	6.2 ± 4.4	0.037	7.7 ± 6.9	8.1 ± 7.5	7.1 ± 6.2	10.0 ± 8.8	8.1 ± 7.0	0.136
RVD (ng/mL)	248.2 ± 256.9	279.5 ± 293.5	218.1 ± 216.1	241.3 ± 182.9	293.9 ± 314.9	0.102	238.7 ± 312.8	282.1 ± 393.6	195.4 ± 196.6	260.7 ± 155.1	176.8 ± 212.8	< 0.001*
HDL-C (mg/dl)	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.2	1.1 ± 0.1	0.765	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.2	0.314
LDL-C (mg/dl)	2.6 ± 0.9	2.6 ± 0.9	2.6 ± 1.0	2.6 ± 1.0	2.7 ± 0.8	0.973	2.9 ± 4.8	2.7 ± 0.9	3.0 ± 6.8	2.5 ± 1.0	2.5 ± 0.6	0.837
TyG index	9.5 ± 0.7	9.4 ± 0.7	9.5 ± 0.7	9.5 ± 0.6	10.2 ± 1.0	0.051	8.9 ± 0.6	8.9 ± 0.6	9.0 ± 0.6	8.8 ± 0.6	8.8 ± 0.7	0.323
TC (mmol/L)	4.2 ± 1.1	4.2 ± 1.0	4.2 ± 1.1	4.1 ± 1.1	4.6 ± 1.1	0.806	4.4 ± 2.0	4.5 ± 2.7	4.3 ± 1.0	4.1 ± 1.1	4.1 ± 0.7	0.616
LPA (g/L)	273.6 ± 286.8	271.7 ± 289.3	282.1 ± 290.6	100.5 ± 98.5	294.0 ± 153.4	0.321	267.2 ± 273.3	257.9 ± 262.9	275.0 ± 281.9	215.1 ± 171.9	355.6 ± 374.8	0.477
TC/HDL-C	4.2 ± 1.2	4.2 ± 1.2	4.2 ± 1.3	4.1 ± 0.9	4.2 ± 1.4	0.982	4.4 ± 4.7	4.1 ± 2.1	4.6 ± 6.5	4.1 ± 1.3	4.1 ± 1.0	0.479
LDL-C/HDL-C	2.6 ± 1.0	2.7 ± 1.0	2.6 ± 1.0	2.5 ± 0.9	2.5 ± 0.9	0.826	2.8 ± 4.8	2.5 ± 0.9	3.1 ± 6.8	2.6 ± 1.1	2.5 ± 0.8	0.369
PTX3 (ng/mL)	10.1 ± 12.2	7.5 ± 6.6	12.5 ± 15.5	6.6 ± 3.4	14.8 ± 12.7	< 0.001*	9.4 ± 17.2	8.3 ± 22.2	10.5 ± 10.3	6.5 ± 2.8	11.5 ± 7.0	0.262
LXA4 (ng/mL)	6.7 ± 5.6	6.4 ± 6.5	6.9 ± 4.6	7.2 ± 4.0	10.1 ± 5.9	0.416	6.5 ± 5.3	6.0 ± 5.4	7.0 ± 5.3	7.0 ± 3.0	9.1 ± 5.0	0.022*
LL37 (ng/mL)	23.2 ± 15.1	20.2 ± 11.3	26.2 ± 17.7	18.6 ± 11.4	26.0 ± 10.9	< 0.001*	24.3 ± 14.2	21.5 ± 11.8	27.2 ± 15.9	21.2 ± 14.5	28.0 ± 13.0	< 0.001*
hs-CRP (mg/L)	6.9 ± 4.7	6.3 ± 4.6	7.4 ± 4.8	8.4 ± 4.3	8.2 ± 3.9	0.065	6.6 ± 10.2	6.1 ± 4.8	7.1 ± 13.8	4.0 ± 4.2	7.7 ± 4.4	0.458
Creatinine (mmol/L)	90.7 ± 32.7	88.2 ± 25.4	93.2 ± 38.8	88.8 ± 17.1	84.9 ± 21.0	0.434	89.1 ± 39.4	86.8 ± 26.9	91.3 ± 49.2	84.1 ± 14.0	97.1 ± 39.4	0.336
Fasting glucose (mmol/L)	11.0 ± 4.5	10.9 ± 4.6	10.9 ± 4.4	10.7 ± 4.5	13.7 ± 5.9	0.602	7.1 ± 2.6	7.2 ± 2.6	7.0 ± 2.5	6.4 ± 2.0	7.6 ± 2.9	0.501
cTnI at baseline level (mmol/L)	7.2 ± 14.9	7.5 ± 15.9	6.7 ± 12.7	11.9 ± 33.0	7.9 ± 16.7	0.750	6.3 ± 15.3	6.5 ± 16.4	5.8 ± 13.6	1.0 ± 1.8	14.5 ± 27.3	0.150
cTnI at peak level (mmol/L)	25.5 ± 28.2	28.2 ± 28.9	21.9 ± 26.0	56.5 ± 38.6	17.0 ± 26.2	< 0.001*	23.3 ± 26.8	25.6 ± 28.2	21.0 ± 25.2	13.1 ± 13.7	26.6 ± 32.3	0.052
NT-proBNP at baseline level (mmol/L)	1376.3 ± 3289.6	992.8 ± 1788.0	1760.9 ± 4283.8	851.6 ± 1336.2	1350.3 ± 1759.3	0.112	867.3 ± 1981.4	873.3 ± 2155.3	825.8 ± 1776.8	1231.1 ± 2127.3	1723.4 ± 2164.0	0.406
NT-proBNP at peak level (mmol/L)	3448.0 ± 6070.5	3199.8 ± 5677.5	3454.8 ± 5961.7	9401.2 ± 13300.4	2612.0 ± 2675.7	0.028*	2712.5 ± 4868.0	2897.9 ± 4895.1	2324.3 ± 4041.8	5992.1 ± 13921.2	6602.0 ± 11166.5	0.001*
Aspirin[%(n)]	411 (95.4)	193 (94.6)	207 (96.7)	9 (100)	2 (50)	0.015*	796 (95.1)	391 (94.9)	384 (95.3)	9 (100)	12 (92.3)	0.739
Statin[%(n)]	416 (96.5)	194 (95.1)	210 (98.1)	8 (88.9)	4 (100)	0.139	794 (94.9)	387 (93.9)	386 (95.8)	9 (100)	12 (92.3)	0.494
Clopidogrel[%(n)]	237 (55.0)	100 (49)	127 (59.3)	7 (77.8)	3 (75)	0.061	400 (47.8)	187 (45.4)	196 (48.6)	7 (77.8)	10 (76.9)	0.035*

Ticagrelor[%(n)]	190 (44.1)	101 (49.5)	86 (40.2)	2 (22.2)	1 (25)	0.100	423 (50.5)	219 (53.2)	199 (49.4)	2 (22.2)	3 (23.1)	0.041*
Beta-Blockers[%(n)]	379 (87.9)	177 (86.8)	191 (89.3)	8 (88.9)	3 (75)	0.460	710 (84.8)	354 (85.9)	339 (84.1)	7 (77.8)	10 (76.9)	0.502
proton pump inhibitor[%(n)]	229 (53.3)	107 (52.7)	118 (55.1)	1 (11.1)	3 (75)	0.044*	420 (50.2)	207 (50.2)	204 (50.7)	4 (44.4)	5 (38.5)	0.839
Anticoagulants[%(n)]	13 (3.0)	6 (3)	6 (2.8)	0 (0)	1 (25)	0.176	23 (2.8)	15 (3.6)	8 (2)	0 (0)	0 (0)	0.533
TIMI score	3.7 ±2.0	3.5 ±1.9	3.8 ±2.1	4.9 ±2.0	4.8 ±2.6	0.095	3.5 ±2.1	3.5 ±2.2	3.3 ±2.0	4.6 ±2.3	5.4 ±3.2	0.001*
Diameter of coronary lesion (mm^2)	2.8 ±1.7	2.9 ±2.4	2.7 ±0.9	3.0 ±0.5	3.0 ±0.9	0.867	2.8 ±0.9	2.8 ±1.0	2.9 ±0.8	2.4 ±1.6	3.0 ±0.5	0.072
Length of coronary lesion (mm)	27.9 ± 15.7	28.4 ± 16.8	27.4 ±15.0	26.3 ±6.0	32.3 ± 15.3	0.884	25.6 ± 15.6	26.7 ± 17.6	24.9 ± 13.6	18.4 ±7.1	19.5 ±7.6	0.126
All caused mortality	53 (12.1)	15 (7.3)	32 (14.7)	3 (33.3)	3 (60)	< 0.001*	72 (8.5)	36 (8.6)	32 (7.9)	3 (33.3)	1 (7.7)	0.102
Cardiac death	32 (7.3)	9 (4.4)	21 (9.6)	2 (22.2)	0 (0)	0.054	40 (4.7)	20 (4.8)	18 (4.4)	1 (11.1)	1 (7.7)	0.410
Recurrence MI	17 (3.9)	9 (4.4)	7 (3.2)	1 (11.1)	0 (0)	0.408	49 (5.8)	22 (5.2)	25 (6.1)	0 (0)	2 (15.4)	0.338
Recurrence HF	16 (3.7)	4 (2)	12 (5.5)	0 (0)	0 (0)	0.250	23 (2.7)	9 (2.1)	13 (3.2)	0 (0)	1 (7.7)	0.375
Recurrence revas	80 (18.3)	44 (21.5)	35 (16.1)	1 (11.1)	0 (0)	0.391	143 (16.8)	65 (15.5)	77 (18.9)	1 (11.1)	0 (0)	0.202
Ischemic stroke	35 (8.0)	17 (8.3)	18 (8.3)	0 (0)	0 (0)	1.000	31 (3.7)	13 (3.1)	17 (4.2)	0 (0)	1 (7.7)	0.500

Continuous data are presented as median (IQR). Categorical data are presented as number (%). If it is a continuous variable, it can be obtained by Kruskal Wallis rank sum test. If the counting variable is less than 10, it can be obtained by Fisher exact probability test

Abbreviations: *DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diabetes blood pressure; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TnI, troponin; CK-MB, creatine kinase isoenzymes; LPA, lipse activator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; hs-CRP, high sensitive C-reactive protein; MACE, major adverse cardiovascular events; MI, myocardial* infarction*. FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide, RVD, Resolvin D1.*

**P<0.05.*

Supplemental Table 4 Clinical features according to the of Tet2-CHIP (variant allele fraction ⩾ 2.0%) and PCSK9 stratified by the status of mortality and survival in all enrolled cohort

Variables	***Mortality***						***Survival***					
	N=125	***Tet2(-)/PCSK9(-) N=51***	***Tet2(-)/PCSK9(+) N=64***	***Tet2(+)/PCSK9(-) N=6***	***Tet2(+)/PCSK9(+) N=4***	***P1***	***N=1161***	***Tet2(-)/PCSK9(-) N=574***	***Tet2(-)/PCSK9(+) N=561***	***Tet2(+)/PCSK9(-) N=12***	***Tet2(+)/PCSK9(+) N=14***	***P2***
Age (years)	69.5 ± 13.0	69.7 ± 12.0	68.4 ± 14.3	74.1 ± 7.9	79.8 ± 3.3	0.294	59.7 ± 11.9	59.8 ± 11.4	59.2 ± 12.2	69.1 ± 15.4	66.0 ± 14.1	0.006
Male	90 (72.0)	42 (82.4)	42 (65.6)	4 (66.7)	2 (50)	0.110	947 (81.6)	475 (82.8)	452 (80.6)	11 (91.7)	9 (64.3)	0.223
Heart rate(beats/min)	84.4 ± 20.6	81.5 ± 20.1	86.6 ± 20.3	81.3 ± 20.5	90.8 ± 32.8	0.537	75.7 ± 21.3	74.8 ± 14.8	76.8 ± 26.5	77.8 ± 15.9	72.1 ± 16.8	0.400
SBP (mmHg)	124.2 ± 23.2	124.1 ± 24.1	123.4 ± 23.2	133.8 ± 22.7	122.8 ± 17.4	0.774	125.6 ± 19.6	124.4 ± 19.6	126.6 ± 19.4	126.7 ± 19.0	130.6 ± 25.0	0.219
DBP(mmHg)	76.4 ± 14.2	77.4 ± 15.1	75.0 ± 14.2	80.7 ± 8.4	78.0 ± 3.7	0.703	78.9 ± 13.4	78.2 ± 13.6	79.4 ± 13.0	86.3 ± 18.1	79.1 ± 13.0	0.119
EF at admission	47.7 ± 9.7	48.0 ± 10.3	47.1 ± 9.6	49.0 ± 9.7	52.0 ± 5.4	0.755	54.3 ± 7.1	54.6 ± 6.7	54.0 ± 7.5	57.2 ± 6.3	53.8 ± 9.4	0.227
Hypertension[%(n)]	96 (76.8)	38 (74.5)	51 (79.7)	5 (83.3)	2 (50)	0.495	745 (64.2)	371 (64.6)	359 (64)	6 (50)	9 (64.3)	0.756
Hyperlipidemia[%(n)]	111 (88.8)	40 (78.4)	61 (95.3)	6 (100)	4 (100)	0.038	1053 (90.7)	515 (89.7)	518 (92.3)	11 (91.7)	9 (64.3)	0.011
Smoking[%(n)]	81 (64.8)	35 (68.6)	42 (65.6)	3 (50)	1 (25)	0.284	833 (72.3)	423 (74.3)	392 (70.4)	10 (83.3)	8 (57.1)	0.198
CKD[%(n)]	26 (20.8)	9 (17.6)	16 (25)	0 (0)	1 (25)	0.458	65 (5.6)	30 (5.2)	32 (5.7)	0 (0)	3 (21.4)	0.124
periphery atherosclerosis[%(n)]	12 (9.7)	5 (9.8)	7 (11.1)	0 (0)	0 (0)	1.000	56 (4.8)	24 (4.2)	32 (5.7)	0 (0)	0 (0)	0.596
History of MI [%(n)]	38 (30.4)	11 (21.6)	25 (39.1)	2 (33.3)	0 (0)	0.117	185 (15.9)	86 (15)	96 (17.1)	0 (0)	3 (21.4)	0.309
History of PCI [%(n)]	34 (27.2)	14 (27.5)	17 (26.6)	2 (33.3)	1 (25)	0.977	193 (16.6)	83 (14.5)	109 (19.4)	0 (0)	1 (7.1)	0.031
History of CABG [%(n)]	3 (2.4)	0 (0)	2 (3.1)	1 (16.7)	0 (0)	0.123	25 (2.2)	8 (1.4)	15 (2.7)	0 (0)	2 (14.3)	0.032
FABP4 (ng/mL)	11.6 ± 9.0	10.3 ± 9.0	12.6 ± 9.2	13.6 ± 9.0	6.7 ± 4.6	0.353	7.5 ± 6.8	7.7 ± 7.1	7.4 ± 6.6	8.0 ± 7.5	7.8 ± 6.9	0.916
RVD (ng/mL)	281.1 ± 387.5	311.0 ± 523.9	261.8 ± 266.3	279.0 ± 215.7	211.1 ± 193.8	0.901	237.7 ± 283.0	278.6 ± 346.2	196.6 ± 194.5	237.0 ± 142.1	208.8 ± 259.8	< 0.001
HDL-C (mg/dl)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.2	1.1 ± 0.2	0.796	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	1.0 ± 0.2	0.709
LDL-C (mg/dl)	2.5 ± 1.0	2.6 ± 1.0	2.4 ± 1.1	2.4 ± 0.9	2.4 ± 0.6	0.892	2.8 ± 4.1	2.7 ± 0.9	2.9 ± 5.8	2.6 ± 1.0	2.6 ± 0.7	0.84
TyG index	9.2 ± 0.8	8.9 ± 0.8	9.4 ± 0.8	9.4 ± 0.8	9.7 ± 1.1	0.024	9.1 ± 0.7	9.1 ± 0.7	9.1 ± 0.7	9.0 ± 0.6	9.0 ± 0.9	0.484
TC (mmol/L)	4.1 ± 1.2	4.2 ± 1.2	4.1 ± 1.2	4.0 ± 1.0	4.0 ± 1.0	0.983	4.4 ± 1.8	4.4 ± 2.3	4.3 ± 1.0	4.2 ± 1.2	4.2 ± 0.8	0.853
LPA (g/L)	283.4 ± 310.7	233.5 ± 237.9	340.4 ± 364.4	96.8 ± 147.9	267.0 ± 136.5	0.143	268.0 ± 274.5	264.8 ± 274.3	270.6 ± 274.2	188.3 ± 144.6	358.9 ± 362.9	0.444
TC/HDL-C	4.0 ± 1.3	3.9 ± 1.3	4.1 ± 1.4	3.9 ± 0.9	3.9 ± 1.3	0.933	4.3 ± 4.1	4.2 ± 1.9	4.5 ± 5.5	4.2 ± 1.2	4.2 ± 1.0	0.518
LDL-C/HDL-C	2.4 ± 1.1	2.4 ± 1.1	2.4 ± 1.2	2.4 ± 0.9	2.4 ± 0.8	1.000	2.8 ± 4.1	2.6 ± 1.0	3.0 ± 5.8	2.6 ± 1.1	2.6 ± 0.8	0.437
PTX3 (ng/mL)	14.6 ± 20.1	7.7 ± 6.7	21.0 ± 25.8	4.1 ± 2.3	17.0 ± 11.6	0.002	9.1 ± 15.0	8.1 ± 19.3	10.1 ± 9.1	7.8 ± 2.6	11.1 ± 7.6	0.135
LXA4 (ng/mL)	7.2 ± 5.6	5.9 ± 5.2	8.2 ± 6.0	5.9 ± 3.3	11.0 ± 5.6	0.071	6.5 ± 5.4	6.2 ± 5.8	6.8 ± 4.9	7.7 ± 3.5	9.0 ± 5.1	0.063
LL37 (ng/mL)	22.2 ± 14.9	19.3 ± 12.2	24.8 ± 17.5	19.1 ± 4.0	20.6 ± 3.3	0.251	24.1 ± 14.5	21.2 ± 11.6	27.1 ± 16.4	20.3 ± 15.6	29.4 ± 13.2	< 0.001
hs-CRP (mg/L)	10.6 ± 24.0	6.3 ± 4.4	14.2 ± 32.6	6.9 ± 3.4	9.8 ± 2.7	0.396	6.3 ± 5.0	6.2 ± 4.8	6.5 ± 5.2	5.8 ± 5.4	7.3 ± 4.4	0.68
Creatinine (mmol/L)	117.2 ± 67.0	106.8 ± 51.3	128.5 ± 78.9	86.4 ± 12.0	115.6 ± 67.0	0.229	86.6 ± 31.0	85.5 ± 22.2	87.8 ± 38.4	86.4 ± 17.3	87.5 ± 19.6	0.668
Fasting glucose (mmol/L)	10.2 ± 5.4	8.9 ± 5.1	11.1 ± 5.4	9.5 ± 5.6	13.4 ± 6.3	0.102	8.2 ± 3.6	8.4 ± 3.7	8.1 ± 3.5	8.1 ± 3.2	8.1 ± 3.6	0.538
cTnI at baseline level (mmol/L)	10.5 ± 20.8	11.5 ± 23.5	11.0 ± 20.0	0.6 ± 0.5	3.0 ± 4.9	0.567	6.2 ± 14.3	6.4 ± 15.4	5.6 ± 12.2	9.4 ± 28.6	15.4 ± 27.3	0.055
cTnI at peak level (mmol/L)	38.3 ± 37.8	44.5 ± 40.1	35.2 ± 36.4	37.5 ± 38.4	10.3 ± 8.2	0.266	22.5 ± 25.5	24.9 ± 26.6	19.7 ± 23.4	33.5 ± 36.3	27.9 ± 33.3	0.002
NT-proBNP at baseline	3108.8 ±	1645.8	4390.2 ±	1942.6	2275.7	0.052	820.9 ±	849.9 ±	780.8 ±	590.7 ±	1432.3	0.551

level (mmol/L)	5383.3 ± 2363.9	6907.4 ± 2398.4	± 1978.3			1854.2	2000.5	1699.8	1170.1 ± 2059.2		
NT-proBNP at peak level (mmol/L)	8176.5 ± 10349.2	6734.9 ± 9338.0	8628.0 ± 9980.3	18190.3 ± 19046.1	3952.7 ± 2732.6	0.059	2405.2 ± 4086.9	2671.1 ± 4493.2	2044.0 ± 3205.8	2449.8 ± 4401.3	5933.9 ± 10911.6	< 0.001
Aspirin[%(n)]	97 (89.8)	38 (88.4)	52 (92.9)	6 (100)	1 (33.3)	0.058	1110 (95.7)	546 (95.3)	539 (96.1)	12 (100)	13 (92.9)	0.644
Statin[%(n)]	101 (93.5)	39 (90.7)	54 (96.4)	6 (100)	2 (66.7)	0.204	1109 (95.6)	542 (94.6)	542 (96.6)	11 (91.7)	14 (100)	0.237
Clopidogrel[%(n)]	73 (67.6)	23 (53.5)	41 (73.2)	6 (100)	3 (100)	0.025	564 (48.6)	264 (46.1)	282 (50.3)	8 (66.7)	10 (71.4)	0.087
Ticagrelor[%(n)]	32 (29.6)	17 (39.5)	15 (26.8)	0 (0)	0 (0)	0.115	581 (50.1)	303 (52.9)	270 (48.1)	4 (33.3)	4 (28.6)	0.086
Beta-Blockers[%(n)]	88 (81.5)	34 (79.1)	45 (80.4)	6 (100)	3 (100)	0.786	1001 (86.3)	497 (86.7)	485 (86.5)	9 (75)	10 (71.4)	0.191
proton pump inhibitor[%(n)]	60 (56.1)	23 (54.8)	34 (60.7)	1 (16.7)	2 (66.7)	0.219	589 (50.8)	291 (50.8)	288 (51.4)	4 (33.3)	6 (42.9)	0.592
Anticoagulants[%(n)]	5 (4.7)	0 (0)	4 (7.1)	0 (0)	1 (33.3)	0.065	31 (2.7)	21 (3.7)	10 (1.8)	0 (0)	0 (0)	0.252
TIMI score	5.3 ± 2.6	5.4 ± 2.7	5.1 ± 2.6	5.7 ± 2.3	6.8 ± 1.7	0.579	3.4 ± 2.0	3.4 ± 2.0	3.3 ± 1.9	4.2 ± 1.8	4.8 ± 3.2	0.029
Diameter of coronary lesion (mm^2)	2.9 ± 0.7	3.0 ± 0.6	2.8 ± 0.8	3.5 ± 0.5	3.0 ± 0.9	0.421	2.8 ± 1.3	2.8 ± 1.6	2.9 ± 0.8	2.4 ± 1.3	3.0 ± 0.5	0.609
Length of coronary lesion (mm)	24.3 ± 12.8	22.7 ± 12.7	25.2 ± 13.4	28.7 ± 2.3	22.3 ± 2.1	0.727	26.6 ± 15.9	27.6 ± 17.6	25.8 ± 14.2	20.4 ± 7.6	22.5 ± 12.3	0.137
Recurrence MI	9 (7.2)	3 (5.9)	6 (9.4)	0 (0)	0 (0)	0.873	57 (4.9)	28 (4.9)	26 (4.6)	1 (8.3)	2 (14.3)	0.224
Recurrence HF	5 (4.0)	1 (2)	4 (6.2)	0 (0)	0 (0)	0.603	34 (2.9)	12 (2.1)	21 (3.7)	0 (0)	1 (7.1)	0.205
Recurrence revas	7 (5.6)	2 (3.9)	5 (7.8)	0 (0)	0 (0)	0.700	216 (18.6)	107 (18.6)	107 (19.1)	2 (16.7)	0 (0)	0.335
Ischemic stroke	8 (6.4)	3 (5.9)	5 (7.8)	0 (0)	0 (0)	1.000	58 (5.0)	27 (4.7)	30 (5.3)	0 (0)	1 (7.1)	0.793

Continuous data are presented as median (IQR). Categorical data are presented as number (%). If it is a continuous variable, it can be obtained by Kruskal Wallis rank sum test. If the counting variable is less than 10, it can be obtained by Fisher exact probability test

Abbreviations: *DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diabetes blood pressure; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TnI, troponin; CK-MB, creatine kinase isoenzymes; LPA, lipse activator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; hs-CRP, high sensitive C-reactive protein; MACE, major adverse cardiovascular events; MI, myocardial* infarction*. FABP4, Fatty acid-binding protein 4, PCSK9, proprotein convertase subtilisin/kexin type 9, PTX3, pentraxin 3, LXA4, Lipoxin A4, LL-37, Antimicrobial peptide, RVD, Resolvin D1.*

**P<0.05.*

Supplemental Table 5 Multivariable-Adjusted Associations of CHIP with CRP for all-cause mortality

Variable	*Total*	*Events (N%)*	*Crude HR 95%CI*	*Crude P value*	*Adjusted HR 95%CI*	*Adjusted P value*	*P_1 for interaction*	*P_2 for interaction*
Group of any CHIP mutation and CRP								
							0.164	0.042*
Subgroup of non-DM cohort								
Any CHIP (-)/CRP (-)	379	24 (6.3)	1(Ref)		1(Ref)			
Any CHIP (-)/CRP (+)	346	35 (10.1)	1.59 (0.95~2.68)	0.080	1.49 (0.87~2.57)	0.148		
Any CHIP (+)/CRP (-)	68	7 (10.3)	1.67 (0.72~3.86)	0.235	1.48 (0.62~3.52)	0.376		
Any CHIP (+)/CRP (+)	56	6 (10.7)	1.75 (0.72~4.29)	0.219	1.20 (0.47~3.03)	0.704		
Trend.test	849	72 (8.5)	1.24 (0.97~1.59)	0.087	1.11 (0.86~1.43)	0.435		
Subgroup of DM cohort								
Any CHIP (-)/CRP (-)	175	10 (5.7)	1(Ref)		1(Ref)			
Any CHIP (-)/CRP (+)	192	28 (14.6)	2.82 (1.37~5.80)	0.005**	2.46 (1.16~5.19)	0.019*		
Any CHIP (+)/CRP (-)	25	2 (8.0)	1.45 (0.32~6.61)	0.633	0.97 (0.20~4.72)	0.972		
Any CHIP (+)/CRP (+)	45	13 (28.9)	6.06 (2.65~13.84)	＜0.001***	3.82 (1.54~9.50)	0.004**		
Trend.test	437	53 (12.1)	1.67 (1.30~2.13)	＜0.001***	1.43 (1.08~1.88)	0.012**		
Group of commonly CHIP mutation and CRP								
							0.108	0.087
Subgroup of non-DM cohort								
Commonly CHIP (-)/CRP (-)	408	24 (5.9)	1(Ref)		1(Ref)			
Commonly CHIP (-)/CRP (+)	375	37 (9.9)	1.68 (1~2.8)	0.049*	1.58 (0.93~2.71)	0.093		
Commonly CHIP (+)/CRP (-)	39	7 (17.9)	3.21 (1.38~7.45)	0.007**	2.59 (1.07~6.26)	0.034*		
Commonly CHIP (+)/CRP (+)	27	4 (14.8)	2.66 (0.92~7.67)	0.070	1.43 (0.47~4.38)	0.529		
Trend.test	849	72 (8.5)	1.52 (1.16~1.99)	0.003**	1.28 (0.97~1.7)	0.085		
Subgroup of DM cohort								
Commonly CHIP (-)/CRP (-)	183	11 (6)	1(Ref)		1(Ref)			
Commonly CHIP (-)/CRP (+)	207	30 (14.5)	2.66 (1.33~5.31)	0.006**	2.28 (1.1~4.69)	0.026*		
Commonly CHIP (+)/CRP (-)	17	1 (5.9)	0.97 (0.13~7.51)	0.976	0.64 (0.08~5.26)	0.680		
Commonly CHIP (+)/CRP (+)	30	11 (36.7)	7.39 (3.2~17.07)	＜0.001***	4.37 (1.74~10.96)	0.002**		
Trend.test	437	53 (12.1)	1.8 (1.39~2.34)	＜0.001***	1.52 (1.14~2.04)	0.004**		
Group of DTA CHIP mutation and CRP								
							0.061	0.080
Subgroup of non-DM cohort								
DTA CHIP (-)/CRP (-)	411	26 (6.3)	1(Ref)		1(Ref)			
DTA CHIP (-)/CRP (+)	376	37 (9.8)	1.55 (0.94~2.56)	0.088	1.44 (0.86~2.44)	0.168		
DTA CHIP(+)/CRP (-)	36	5 (13.9)	2.24 (0.86~5.84)	0.098	1.72 (0.64~4.64)	0.282		
DTA CHIP (+)/CRP (+)	26	4 (15.4)	2.6 (0.91~7.44)	0.076	1.35 (0.44~4.11)	0.598		
Trend.test	849	72 (8.5)	1.43 (1.08~1.89)	0.013*	1.19 (0.89~1.6)	0.234		
Subgroup of DM cohort								
DTA CHIP (-)/CRP (-)	188	12 (6.4)	1(Ref)		1(Ref)			
DTA CHIP (-)/CRP (+)	209	31 (14.8)	2.55 (1.31~4.97)	0.006**	2.14 (1.06~4.3)	0.033*		
DTA CHIP(+)/CRP (-)	12	0 (0)	0 (0~Inf)	0.996	0 (0~Inf)	0.995		
DTA CHIP (+)/CRP (+)	28	10 (35.7)	6.83 (2.95~15.84)	＜0.001***	4.21 (1.66~10.71)	0.003**		
Trend.test	437	53 (12.1)	1.76 (1.35~2.3)	＜0.001***	1.51 (1.12~2.04)	0.007**		
Group of DT CHIP mutation and CRP								
							0.137	0.144
Subgroup of non-DM cohort								
DT CHIP (-)/CRP (-)	415	27 (6.5)	1(Ref)		1(Ref)			
DT CHIP (-)/CRP (+)	381	37 (9.7)	1.48 (0.9~2.44)	0.119	1.38 (0.82~2.33)	0.219		
DT CHIP(+)/CRP (-)	32	4 (12.5)	1.94 (0.68~5.54)	0.217	1.48 (0.5~4.39)	0.476		
DT CHIP (+)/CRP (+)	21	4 (19)	3.16 (1.11~9.04)	0.032	1.55 (0.5~4.77)	0.449		
Trend.test	849	72 (8.5)	1.45 (1.08~1.95)	0.013	1.2 (0.89~1.63)	0.231		
Subgroup of DM cohort								
DT CHIP (-)/CRP (-)	191	12 (6.3)	1(Ref)		1(Ref)			
DT CHIP (-)/CRP (+)	217	34 (15.7)	2.75 (1.43~5.32)	0.003**	2.32 (1.17~4.64)	0.017		
DT CHIP(+)/CRP (-)	9	0 (0)	0 (0~Inf)	0.996	0 (0~Inf)	0.995		
DT CHIP (+)/CRP (+)	20	7 (35)	6.67 (2.62~16.95)	＜0.001***	3.9 (1.32~11.53)	0.014*		
Trend.test	437	53 (12.1)	1.77 (1.33~2.35)	＜0.001***	1.52 (1.09~2.14)	0.014*		
Group of TA CHIP mutation and CRP								
							0.031*	0.023*
Subgroup of non-DM cohort								
TA CHIP (-)/CRP (-)	430	28 (6.5)	1(Ref)		1(Ref)			
TA CHIP (-)/CRP (+)	384	39 (10.2)	1.56 (0.96~2.53)	0.073	1.44 (0.87~2.39)	0.161		
TA CHIP(+)/CRP (-)	17	3 (17.6)	2.96 (0.9~9.75)	0.074	1.82 (0.54~6.19)	0.335		
TA CHIP (+)/CRP (+)	18	2 (11.1)	1.8 (0.43~7.56)	0.422	0.87 (0.19~3.94)	0.859		

Trend.test	849	72 (8.5)	1.4 (1.02~1.92)	0.036	1.16 (0.84~1.6)	0.383		
Subgroup of DM cohort								
TA CHIP (-)/CRP (-)	194	12 (6.2)	1(Ref)		1(Ref)			
TA CHIP (-)/CRP (+)	218	32 (14.7)	2.61 (1.34~5.06)	0.005**	2.3 (1.15~4.59)	0.018*		
TA CHIP(+)/CRP (-)	6	0 (0)	-	0.996	-	0.996		
TA CHIP (+)/CRP (+)	19	9 (47.4)	10.11 (4.24~24.11)	＜0.001***	6.28 (2.35~16.76)	＜0.001**		
Trend.test	437	53 (12.1)	2.06 (1.56~2.71)	＜0.001***	1.75 (1.28~2.39)	＜0.001**		
Group of DNMAT3A CHIP mutation and CRP								
							0.158	0.828
Subgroup of non-DM cohort								
DNMAT3A CHIP (-)/CRP (-)	423	29 (6.9)	1(Ref)		1(Ref)			
DNMAT3A CHIP (-)/CRP (+)	392	39 (9.9)	1.44 (0.89~2.33)	0.136	1.31 (0.79~2.16)	0.294		
DNMAT3A CHIP (+)/CRP (-)	24	2 (8.3)	1.16 (0.28~4.87)	0.838	0.99 (0.23~4.26)	0.990		
DNMAT3A CHIP (+)/CRP (+)	10	2 (20)	3.21 (0.76~13.44)	0.111	1.94 (0.44~8.64)	0.382		
Trend.test	849	72 (8.5)	1.37 (0.97~1.93)	0.078	1.21 (0.85~1.73)	0.293		
Subgroup of DM cohort								
DNMAT3A CHIP (-)/CRP (-)	194	12 (6.2)	1(Ref)		1(Ref)			
DNMAT3A CHIP (-)/CRP (+)	228	40 (17.5)	3.17 (1.66~6.04)	＜0.001***	2.55 (1.29~5.03)	0.007**		
DNMAT3A CHIP (+)/CRP (-)	6	0 (0)	-	0.997	-	0.996		
DNMAT3A CHIP (+)/CRP (+)	9	1 (11.1)	1.91 (0.25~14.72)	0.533	1.59 (0.2~12.55)	0.661		
Trend.test	437	53 (12.1)	1.61 (1.13~2.29)	0.009**	1.39 (0.93~2.08)	0.108		
Group of ASXL1 CHIP mutation and CRP								
							0.103	0.097
Subgroup of non-DM cohort								
ASXL1 CHIP (-)/CRP (-)	441	30 (6.8)	1(Ref)		1(Ref)			
ASXL1 CHIP (-)/CRP (+)	393	40 (10.2)	1.49 (0.93~2.39)	0.098	1.37 (0.83~2.24)	0.214		
ASXL1 CHIP (+)/CRP (-)	6	1 (16.7)	2.53 (0.34~18.57)	0.362	1.3 (0.17~9.85)	0.800		
ASXL1 CHIP (+)/CRP (+)	9	1 (11.1)	1.82 (0.25~13.38)	0.554	0.68 (0.09~5.34)	0.715		
Trend.test	849	72 (8.5)	1.4 (0.97~2.03)	0.075	1.13 (0.79~1.63)	0.497		
Subgroup of DM cohort								
ASXL1 CHIP (-)/CRP (-)	196	12 (6.1)	1(Ref)		1(Ref)			
ASXL1 CHIP (-)/CRP (+)	229	38 (16.6)	3.01 (1.57~5.75)	0.001**	2.51 (1.27~4.95)	0.008**		
ASXL1 CHIP (+)/CRP (-)	4	0 (0)	-	0.996	-	0.995		
ASXL1 CHIP (+)/CRP (+)	8	3 (37.5)	7.89 (2.21~28.08)	0.001**	5.38 (1.46~19.88)	0.012*		
Trend.test	437	53 (12.1)	2.01 (1.42~2.85)	＜0.001***	1.75 (1.2~2.54)	0.004**		

Adjusted for age, sex, smoking, hypertension, hyperlipidemia, history of MI, peripheral artery atherosclerosis, history of PCI, history of CABG, height, weight, heart rate, systolic blood pressure, diastolic blood pressure; Any CHIP was identified by Variant allele fraction ≥2%; Commonly CHIP mutations included DNMAT3A, TET2 and ASXL1 CHIP mutations; * p＜0.05, ** p＜0.01,*** p＜0.001

Abbreviations: *hs-CRP, high sensitive C-reactive protein; CHIP, clonal hematopoiesis of indeterminate potential; HR, hazard ratio; CI, confidential interval; MR, Mendelian randomization; DM, diabetes mellitus; DTA, combination of DNMAT3A, TET2 and ASXL1 CHIP mutation; TA, combination of TET2 and ASXL1 CHIP mutation; DT, combination of DNMAT3A and TET2 CHIP mutation.*

Supplemental Table 6 Multivariable-Adjusted Associations of CHIP with PCSK9 for all-cause mortality

Variable	*Total*	*Events (N%)*	*Crude HR 95%CI*	*Crude P value*	*Adjusted HR 95%CI*	*Adjusted P value*	*P_1 for interaction*	*P_2 for interaction*
All enrolled								
TET2(-)/PCSK9(-)	625	51 (8.2)	1(Ref)		1(Ref)			
TET2(-)/PCSK9(+)	625	64 (10.2)	1.32 (0.91~1.9)	0.143	1.25 (0.84~1.86)			
TET2(+)/PCSK9(-)	18	6 (33.3)	4.7 (2.02~10.95)	<0.001**	3.34 (1.32~8.46)	0.909		
TET2(+)/PCSK9(+)	18	4 (22.2)	3.06 (1.11~8.47)	0.031*	1.93 (0.65~5.72)	0.058		
Trend.test	1286	125 (9.7)	1.51 (1.17~1.96)	0.002*	1.33 (1.02~1.74)	0.491		
Group of any CHIP mutation and PCSK9								
							0.022*	0.008**
Subgroup of non-DM cohort								
Any CHIP (-)/PCSKP (-)	372	29 (7.8)	1(Ref)		1(Ref)			
Any CHIP (-)/PCSKP (+)	353	30 (8.5)	1.13 (0.68~1.88)	0.645	1.32 (0.77~2.24)	0.309		
Any CHIP (+)/PCSKP (-)	57	10 (17.5)	2.44 (1.19~5.02)	0.015*	2.18 (1.03~4.59)	0.041*		
Any CHIP (+)/PCSKP (+)	67	3 (4.5)	0.59 (0.18~1.92)	0.377	0.48 (0.14~1.59)	0.229		
Trend.test	849	72 (8.5)	1.06 (0.82~1.37)	0.661	1.01 (0.78~1.3)	0.949		
Subgroup of DM cohort								
Any CHIP (-)/PCSKP (-)	178	13 (7.3)	1(Ref)		1(Ref)			
Any CHIP (-)/PCSKP (+)	189	25 (13.2)	2 (1.02~3.91)	0.043*	1.41 (0.69~2.86)	0.348		
Any CHIP (+)/PCSKP (-)	36	5 (13.9)	2.03 (0.72~5.7)	0.178	0.95 (0.29~3.15)	0.937		
Any CHIP (+)/PCSKP (+)	34	10 (29.4)	4.87 (2.13~11.13)	＜0.001***	2.93 (1.18~7.28)	0.020*		
Trend.test	437	53 (12.1)	1.62 (1.25~2.1)	＜0.001***	1.35 (1~1.82)	0.051*		
Group of commonly CHIP mutation and PCSK9								
							0.105	0.044*
Subgroup of non-DM cohort								
Commonly CHIP (-)/PCSKP (-)	395	31 (7.8)	1(Ref)		1(Ref)			
Commonly CHIP (-)/PCSKP (+)	388	30 (7.7)	1.01 (0.61~1.67)	0.959	1.17 (0.7~1.97)	0.552		
Commonly CHIP (+)/PCSKP (-)	34	8 (23.5)	3.32 (1.52~7.22)	0.002**	2.74 (1.22~6.16)	0.015*		
Commonly CHIP (+)/PCSKP (+)	32	3 (9.4)	1.23 (0.38~4.03)	0.729	0.77 (0.23~2.62)	0.678		
Trend.test	849	72 (8.5)	1.24 (0.93~1.66)	0.140	1.13 (0.86~1.49)	0.394		
Subgroup of DM cohort								
Commonly CHIP (-)/PCSKP (-)	191	14 (7.3)	1(Ref)		1(Ref)			
Commonly CHIP (-)/PCSKP (+)	199	27 (13.6)	2.04 (1.07~3.89)	0.031*	1.45 (0.73~2.89)	0.292		
Commonly CHIP (+)/PCSKP (-)	23	4 (17.4)	2.48 (0.82~7.54)	0.109	1.11 (0.3~4.08)	0.881		
Commonly CHIP (+)/PCSKP (+)	24	8 (33.3)	5.44 (2.28~13.01)	＜0.001***	3.44 (1.34~8.83)	0.010*		
Trend.test	437	53 (12.1)	1.71 (1.3~2.25)	＜0.001***	1.43 (1.05~1.97)	0.025*		
Group of DTA CHIP mutation and PCSK9								
							0.095	0.031*
Subgroup of non-DM cohort								
DTA CHIP (-)/PCSKP (-)	399	33 (8.3)	1(Ref)		1(Ref)			
DTA CHIP (-)/PCSKP (+)	388	30 (7.7)	0.96 (0.58~1.57)	0.869	1.1 (0.66~1.84)	0.705		
DTA CHIP(+)/PCSKP (-)	30	6 (20)	2.62 (1.1~6.26)	0.030*	2.05 (0.84~5.05)	0.116		
DTA CHIP (+)/PCSKP (+)	32	3 (9.4)	1.17 (0.36~3.81)	0.797	0.72 (0.21~2.45)	0.604		
Trend.test	849	72 (8.5)	1.15 (0.85~1.55)	0.358	1.05 (0.79~1.4)	0.734		
Subgroup of DM cohort								
DTA CHIP (-)/PCSKP (-)	193	15 (7.8)	1(Ref)		1(Ref)			
DTA CHIP (-)/PCSKP (+)	204	28 (13.7)	1.94 (1.04~3.64)	0.038*	1.34 (0.68~2.64)	0.398		
DTA CHIP(+)/PCSKP (-)	21	3 (14.3)	1.91 (0.55~6.59)	0.307	0.75 (0.17~3.25)	0.700		
DTA CHIP (+)/PCSKP (+)	19	7 (36.8)	5.76 (2.34~14.16)	＜0.001***	3.54 (1.35~9.28)	0.010*		
Trend.test	437	53 (12.1)	1.72 (1.29~2.29)	＜0.001***	1.41 (1.01~1.97)	0.042*		
Group of DT CHIP mutation and PCSK9								
							0.201	0.07
Subgroup of non-DM cohort								
DT CHIP (-)/PCSKP (-)	404	34 (8.4)	1(Ref)		1(Ref)			
DT CHIP (-)/PCSKP (+)	392	30 (7.7)	0.93 (0.57~1.52)	0.774	1.06 (0.64~1.77)	0.823		
DT CHIP(+)/PCSKP (-)	25	5 (20)	2.52 (0.99~6.45)	0.053	1.86 (0.7~4.94)	0.210		
DT CHIP (+)/PCSKP (+)	28	3 (10.7)	1.32 (0.41~4.31)	0.641	0.82 (0.24~2.77)	0.743		
Trend.test	849	72 (8.5)	1.15 (0.84~1.56)	0.391	1.05 (0.78~1.41)	0.758		
Subgroup of DM cohort								
DT CHIP (-)/PCSKP (-)	198	15 (7.6)	1(Ref)		1(Ref)			
DT CHIP (-)/PCSKP (+)	210	31 (14.8)	2.15 (1.16~3.99)	0.015*	1.49 (0.77~2.89)	0.239		
DT CHIP(+)/PCSKP (-)	16	3 (18.8)	2.57 (0.74~8.87)	0.136	0.87 (0.19~4.05)	0.862		
DT CHIP (+)/PCSKP (+)	13	4 (30.8)	4.8 (1.59~14.47)	0.005**	3.36 (1.03~10.93)	0.044*		
Trend.test	437	53 (12.1)	1.69 (1.24~2.32)	0.001**	1.39 (0.94~2.03)	0.095		
Group of TA CHIP mutation and PCSK9								

							0.021*	0.012*
Subgroup of non-DM cohort								
TA CHIP (-)/PCSKP (-)	412	35 (8.5)	1(Ref)		1(Ref)			
TA CHIP (-)/PCSKP (+)	402	32 (8)	0.96 (0.59~1.55)	0.869	1.09 (0.66~1.8)	0.728		
TA CHIP(+)/PCSKP (-)	17	4 (23.5)	3.15 (1.12~8.86)	0.030*	2.12 (0.72~6.23)	0.170		
TA CHIP (+)/PCSKP (+)	18	1 (5.6)	0.68 (0.09~4.98)	0.707	0.34 (0.05~2.63)	0.305		
Trend.test	849	72 (8.5)	1.08 (0.76~1.53)	0.682	0.99 (0.71~1.38)	0.966		
Subgroup of DM cohort								
TA CHIP (-)/PCSKP (-)	200	15 (7.5)	1(Ref)		1(Ref)			
TA CHIP (-)/PCSKP (+)	212	29 (13.7)	2.01 (1.08~3.76)	0.028*	1.45 (0.74~2.82)	0.278		
TA CHIP(+)/PCSKP (-)	14	3 (21.4)	3.1 (0.9~10.71)	0.074	1.32 (0.31~5.6)	0.702		
TA CHIP (+)/PCSKP (+)	11	6 (54.5)	9.63 (3.72~24.93)	＜0.001***	6.31 (2.29~17.36)	＜0.001**		
Trend.test	437	53 (12.1)	2.06 (1.51~2.81)	＜0.001***	1.71 (1.2~2.43)	0.003**		
Group of DNMAT3A CHIP mutation and PCSK9								
							0.215	0.996
Subgroup of non-DM cohort								
DNMAT3A CHIP (-)/PCSKP (-)	411	37 (9)	1(Ref)		1(Ref)			
DNMAT3A CHIP (-)/PCSKP (+)	404	31 (7.7)	0.87 (0.54~1.4)	0.567	0.96 (0.59~1.57)	0.867		
DNMAT3A CHIP (+)/PCSKP (-)	18	2 (11.1)	1.23 (0.3~5.1)	0.776	1.06 (0.25~4.48)	0.938		
DNMAT3A CHIP (+)/PCSKP (+)	16	2 (12.5)	1.42 (0.34~5.88)	0.632	1.14 (0.27~4.89)	0.856		
Trend.test	849	72 (8.5)	1 (0.69~1.44)	0.995	1.01 (0.7~1.44)	0.971		
Subgroup of DM cohort								
DNMAT3A CHIP (-)/PCSKP (-)	207	18 (8.7)	1(Ref)		1(Ref)			
DNMAT3A CHIP (-)/PCSKP (+)	215	34 (15.8)	2.01 (1.13~3.56)	0.017	1.55 (0.83~2.89)	0.166		
DNMAT3A CHIP (+)/PCSKP (-)	7	0 (0)	0 (0~Inf)	0.996	0 (0~Inf)	0.995		
DNMAT3A CHIP (+)/PCSKP (+)	8	1 (12.5)	1.57 (0.21~11.76)	0.661	0.96 (0.12~7.59)	0.970		
Trend.test	437	53 (12.1)	1.38 (0.94~2.03)	0.097	1.11 (0.72~1.71)	0.639		
Group of TET2 CHIP mutation and PCSK9								
Subgroup of non-DM cohort								
TET2(-)/PCSK9(-)	420	36 (8.6)	1(Ref)		1(Ref)		0.025*	0.009**
TET2(-)/PCSK9(+)	407	32 (7.9)	0.94 (0.58~1.51)	0.793	1.07 (0.65~1.75)	0.795		
TET2(+)/PCSK9(-)	9	3 (33.3)	4.55 (1.4~14.78)	0.012*	2.94 (0.86~10.09)	0.087		
TET2(+)/PCSK9(+)	13	1 (7.7)	0.96 (0.13~7)	0.967	0.45 (0.06~3.55)	0.451		
Trend.test	849	72 (8.5)	1.09 (0.75~1.6)	0.643	1.03 (0.72~1.46)	0.868		
Subgroup of DM cohort								
TET2(-)/PCSK9(-)	205	15 (7.3)	1(Ref)		1(Ref)			
TET2(-)/PCSK9(+)	218	32 (14.7)	2.22 (1.2~4.1)	0.0110	1.62 (0.84~3.1)	0.149		
TET2(+)/PCSK9(-)	9	3 (33.3)	5.06 (1.46~17.47)	0.010*	1.89 (0.4~8.9)	0.423		
TET2(+)/PCSK9(+)	5	3 (60)	11.1 (3.2~38.49)	＜0.001**	15.96 (3.74~68.09)	＜0.001**		
Trend.test	437	53 (12.1)	2.23 (1.55~3.21)	＜0.001**	1.97 (1.23~3.15)	0.005**		
Group of ASXL1 CHIP mutation and PCSK9								
							0.155	0.135
Subgroup of non-DM cohort								
ASXL1 CHIP (-)/PCSKP (-)	421	38 (9)	1(Ref)		1(Ref)			
ASXL1 CHIP (-)/PCSKP (+)	413	32 (7.7)	0.88 (0.55~1.4)	0.584	0.99 (0.61~1.61)	0.963		
ASXL1 CHIP (+)/PCSKP (-)	8	1 (12.5)	1.52 (0.21~11.07)	0.679	1.07 (0.14~8.03)	0.950		
ASXL1 CHIP (+)/PCSKP (+)	7	1 (14.3)	1.73 (0.24~12.59)	0.589	0.57 (0.07~4.46)	0.593		
Trend.test	849	72 (8.5)	0.97 (0.64~1.48)	0.900	0.94 (0.64~1.37)	0.741		
Subgroup of DM cohort								
ASXL1 CHIP (-)/PCSKP (-)	208	18 (8.7)	1(Ref)		1(Ref)			
ASXL1 CHIP (-)/PCSKP (+)	217	32 (14.7)	1.88 (1.05~3.35)	0.033*	1.48 (0.79~2.77)	0.221		
ASXL1 CHIP (+)/PCSKP (-)	6	0 (0)	-	0.996	-	0.996		
ASXL1 CHIP (+)/PCSKP (+)	6	3 (50)	7.42 (2.18~25.31)	0.001**	3.82 (1.06~13.79)	0.041*		
Trend.test	437	53 (12.1)	1.78 (1.21~2.6)	0.003**	1.45 (0.97~2.18)	0.071		

Adjusted for age, sex, smoking, hypertension, hyperlipidemia, history of MI, peripheral artery atherosclerosis, history of PCI, history of CABG, height, weight, heart rate, systolic blood pressure, diastolic blood pressure; Any CHIP was identified by Variant allele fraction ≥2%; Commonly CHIP mutations included DNMAT3A, TET2 and ASXL1 CHIP mutations; * p＜0.05, ** p＜0.01,*** p＜0.001

Abbreviations: *hs-CRP, high sensitive C-reactive protein; CHIP, clonal hematopoiesis of indeterminate potential; HR, hazard ratio; CI, confidential interval; MR, Mendelian randomization; DM, diabetes mellitus; DTA, combination of DNMAT3A, TET2 and ASXL1 CHIP mutation; TA, combination of TET2 and ASXL1 CHIP mutation; DT, combination of DNMAT3A and TET2 CHIP mutation.*

Supplemental Table 7. Heterogeneity estimates of the effect of CRP on TET2-CHIP mutation

ID. exposure	***ID. outcome***	***Outcome***	***Exposure***	***Method***	***Q***	***Q value***
GCST90018950_buildGRCh37	ixnWIj	GCST90102620	GCST90018950_buildGRCh37	MR Egger	215.2087	0.281656
GCST90018950_buildGRCh37	ixnWIj	GCST90102620	GCST90018950_buildGRCh37	Inverse variance weighted	215.871	0.287582

Supplemental Table 8. Horizontal pleiotropy estimates of the effect of T2DM on TET2-CHIP mutation by MR-PRESSO

MR-PRESSO main results				
Exposure	***MR Analysis***	***Causal Estimate***	***SD***	***T-stat***
Beta. exposure	***Raw***	0.002447	0.00098	2.496903
Beta. exposure	***Outlier-corrected***	--	--	--
MR-PRESSO Global test				
RSSobs	261.6887			
P value	0.564			

Abbreviations: *MR，Mendelian randomization，SD, standard deviation；RSSobs, observed residual sum of squares*

Supplemental Table 9 Mendelian randomization estimates of the effect of *TET2*-CHIP mutation on CRP

Exposure	***ID. outcome***	***Outcome***	***Method***	***SNP***	***B***	***SE***	***P value***	***Lower CI***	***Upper CI***	***OR***	***Lower CI 95%***	***Upper CI 95%***
TET2 CHIP mutations												
GCST90102620	XGgokE	GCST90018950_buildGRCh37	MR Egger	19	-0.2509	0.8164	0.7624	-1.8510	1.3493	0.7781	0.1571	3.8546
GCST90102620	XGgokE	GCST90018950_buildGRCh37	Weighted median	19	-0.5289	0.4289	0.2175	-1.3695	0.3117	0.5892	0.2542	1.3657
GCST90102620	XGgokE	GCST90018950_buildGRCh37	Inverse variance weighted	19	-0.4626	0.3356	0.1680	-1.1204	0.1951	0.6296	0.3262	1.2154
GCST90102620	XGgokE	GCST90018950_buildGRCh37	Simple mode	19	-0.5127	0.7890	0.5240	-2.0592	1.0338	0.5989	0.1276	2.8118
GCST90102620	XGgokE	GCST90018950_buildGRCh37	Weighted mode	19	-0.6940	0.6020	0.2641	-1.8740	0.4860	0.4996	0.1535	1.6258

Abbreviations: *CRP, C-reaction protein; CHIP, clonal hematopoiesis of indeterminate potential; OR, odds ratio; CI, confidential interval; SNP, single nucleotide polymorphisms; MR，Mendelian randomization*

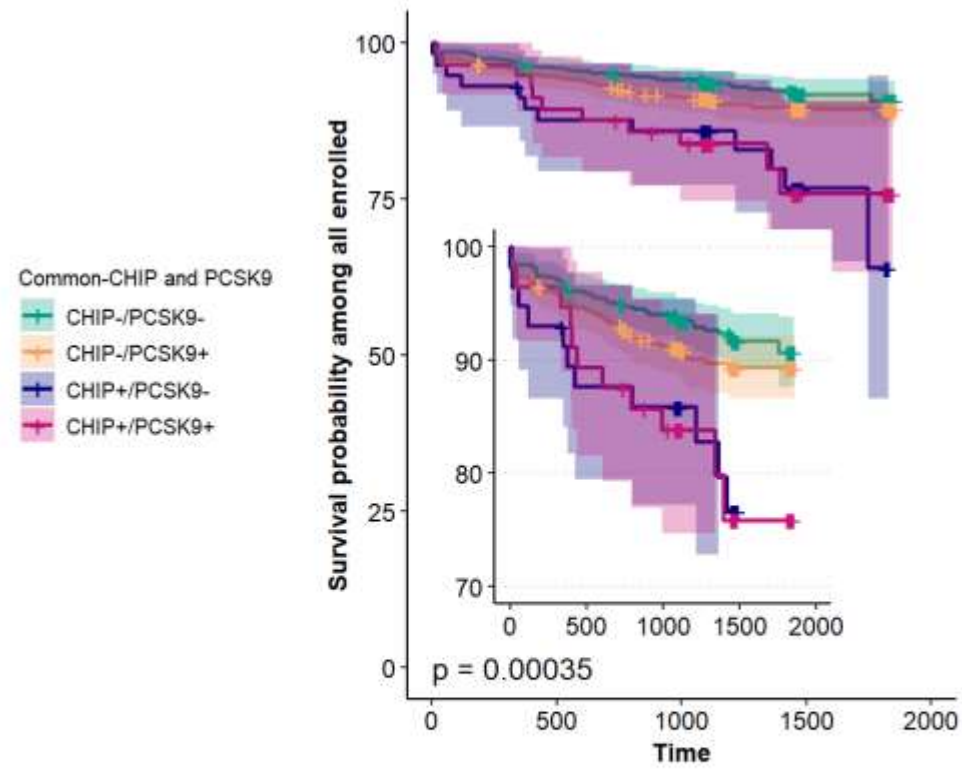
Supplemental Table 10. Mendelian randomization estimates of the effect of PCSK9 on CHIP mutation

ID.exposure	*ID. outcome*	*Outcome*	*Exposure*	*Method*	*SNP*	*B*	*SE*	*P value*	*Lower CI*	*Upper CI*	*OR*	*Lower CI 95%*	*Upper CI 95%*
Overall CHIP mutations													
0K69UK	tfg26S	GCST90102618	prot-c-5231_79_3	Inverse variance weighted	2	-0.00122	0.002614	0.640319	-0.00634	0.003902	0.998779	0.993675	1.00391
res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	mRsCPO	GCST90102618	res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	Inverse variance weighted	3	-0.00094	0.002834	0.739944	-0.00649	0.004614	0.99906	0.993526	1.004624
5231_79_PCSK9_PCSK9.txt	cpgVqd	GCST90102618	5231_79_PCSK9_PCSK9.txt	Inverse variance weighted	3	-0.00078	0.002599	0.765241	-0.00587	0.004317	0.999224	0.994148	1.004327
PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	7MgF2c	GCST90102618	PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	Inverse variance weighted	3	-0.00106	0.002185	0.6289	-0.00534	0.003226	0.998945	0.994677	1.003231
DNMT3A CHIP mutations													
0K69UK	ze3KJD	GCST90102619	prot-c-5231_79_3	Inverse variance weighted	2	0.000235	0.001948	0.904134	-0.00358	0.004053	1.000235	0.996422	1.004062
res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	UW45l0	GCST90102619	res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	Inverse variance weighted	3	-0.00199	0.002112	0.344903	-0.00613	0.002145	0.998007	0.993885	1.002147
5231_79_PCSK9_PCSK9.txt	unzRph	GCST90102619	5231_79_PCSK9_PCSK9.txt	Inverse variance weighted	3	-0.00155	0.001937	0.422568	-0.00535	0.002243	0.998448	0.994666	1.002245
PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	6f6Vjx	GCST90102619	PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	Inverse variance weighted	3	-0.00158	0.002005	0.431623	-0.00551	0.002353	0.998425	0.994509	1.002356
TET2 CHIP mutations													
0K69UK	XYbc1G	GCST90102620	prot-c-5231_79_3	Inverse variance weighted	2	-0.00207	0.001257	0.098896	-0.00454	0.000389	0.997928	0.995472	1.000389
res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	lhpaeW	GCST90102620	res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	Inverse variance weighted	3	0.000469	0.001574	0.765761	-0.00262	0.003554	1.000469	0.997388	1.00356
5231_79_PCSK9_PCSK9.txt	hCCu48	GCST90102620	5231_79_PCSK9_PCSK9.txt	Inverse variance weighted	3	0.0001	0.001498	0.946754	-0.00284	0.003036	1.0001	0.997168	1.003041
PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	qtaDge	GCST90102620	PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	Inverse variance weighted	3	0.000305	0.001238	0.805299	-0.00212	0.002732	1.000305	0.997881	1.002735
Small CHIP mutations													
0K69UK	7fxmTx	GCST90102621	prot-c-5231_79_3	Inverse variance weighted	2	-0.00285	0.001737	0.100557	-0.00626	0.000552	0.997152	0.993764	1.000552
res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	mvjVOQ	GCST90102621	res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	Inverse variance weighted	3	-0.00019	0.003011	0.948927	-0.00609	0.005708	0.999807	0.993925	1.005725
5231_79_PCSK9_PCSK9.txt	sZn4Ox	GCST90102621	5231_79_PCSK9_PCSK9.txt	Inverse variance weighted	3	0.00016	0.00279	0.954158	-0.00531	0.005629	1.00016	0.994706	1.005644

PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	V9yn8O	GCST90102621	PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	Inverse variance weighted	3	-0.00072	0.001519	0.633287	-0.0037	0.002252	0.999276	0.996305	1.002255
Large CHIP mutations													
0K69UK	n8Tyn6	GCST90102622	prot-c-5231_79_3	Inverse variance weighted	2	0.001542	0.002107	0.464283	-0.00259	0.005671	1.001543	0.997416	1.005687
res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	G8WSXZ	GCST90102622	res_invn_X5231_79_Fenland_MA_auto_chrX_filtered_1pc	Inverse variance weighted	3	-0.00082	0.002284	0.719246	-0.0053	0.003656	0.999179	0.994716	1.003662
5231_79_PCSK9_PCSK9.txt	FZHAzr	GCST90102622	5231_79_PCSK9_PCSK9.txt	Inverse variance weighted	3	-0.00099	0.002094	0.635679	-0.0051	0.003112	0.999008	0.994916	1.003117
PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	7ier2p	GCST90102622	PCSK9_Q8NBP7_OID20235_v1_Cardiometabolic_new	Inverse variance weighted	3	-0.00042	0.001761	0.813413	-0.0038	0.003035	0.999585	0.996141	1.00304

Abbreviations: *CRP, C-reaction protein; CHIP, clonal hematopoiesis of indeterminate potential; OR, odds ratio; CI, confidential interval; SNP, single nucleotide polymorphisms; MR，Mendelian randomization; *p＜0.05*

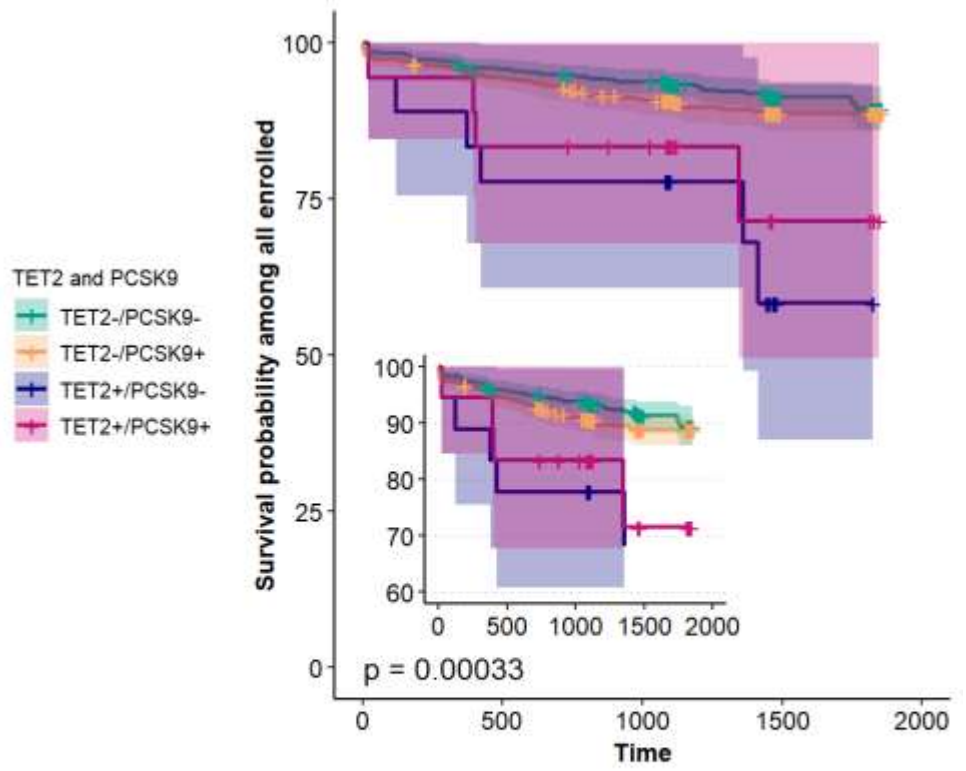
Supplemental Figure 1



Number at risk

CHIP-/PCSK9-	586	560	545	93	0
CHIP-/PCSK9+	587	552	526	95	0
CHIP+/PCSK9-	57	49	48	6	0
CHIP+/PCSK9+	56	50	45	9	0

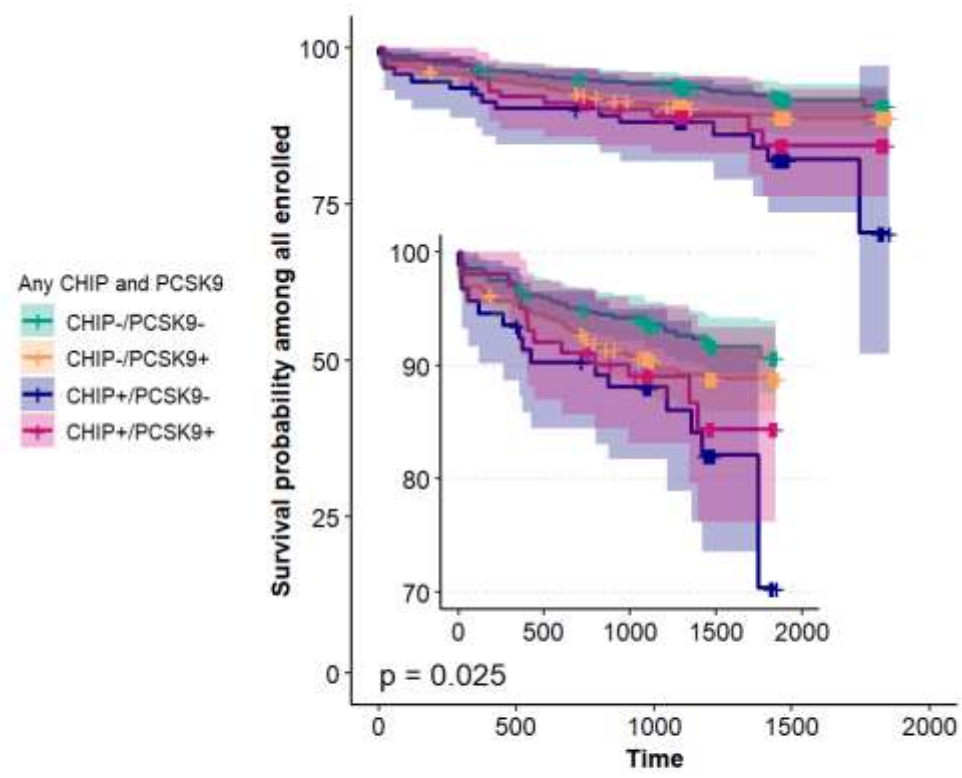
SFigure 1A 1
commomly CHIP and PCSK9 among all enrolled cohort



Number at risk

TET2-/PCSK9-	625	595	579	98	0
TET2-/PCSK9+	625	587	558	101	0
TET2+/PCSK9-	18	14	14	1	0
TET2+/PCSK9+	18	15	13	3	0

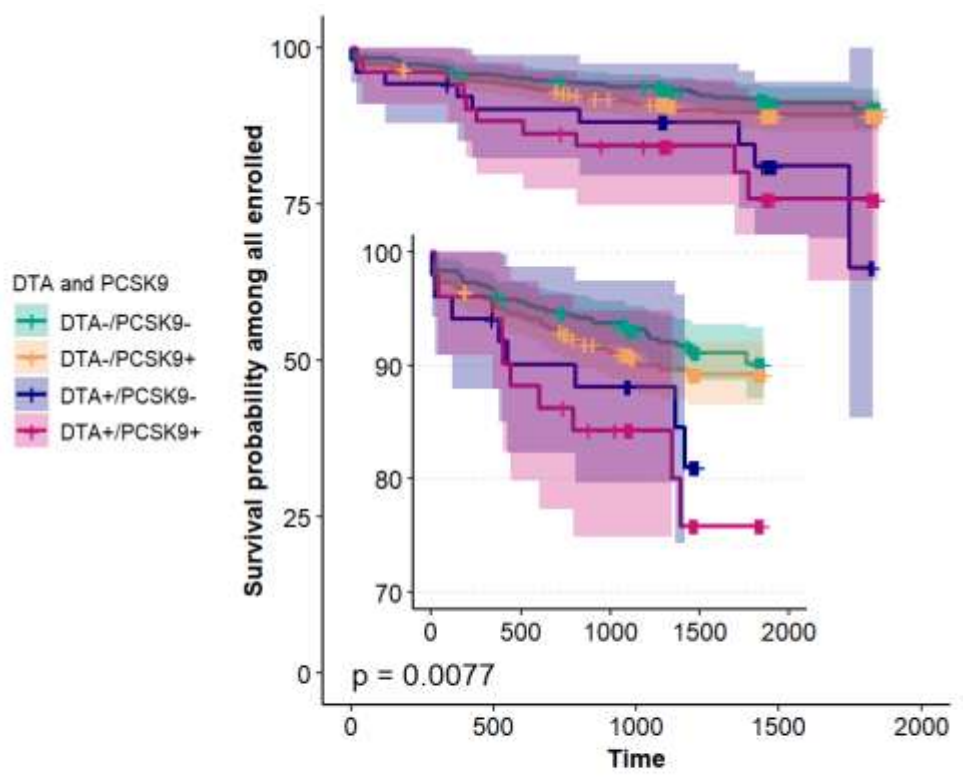
SFigure 1A 2
TET2 CHIP mutation and PCSK9 among all enrolled cohort



Number at risk

CHIP-/PCSK9-	550	526	513	92	0
CHIP-/PCSK9+	542	509	484	88	0
CHIP+/PCSK9-	93	83	80	7	0
CHIP+/PCSK9+	101	93	87	16	0

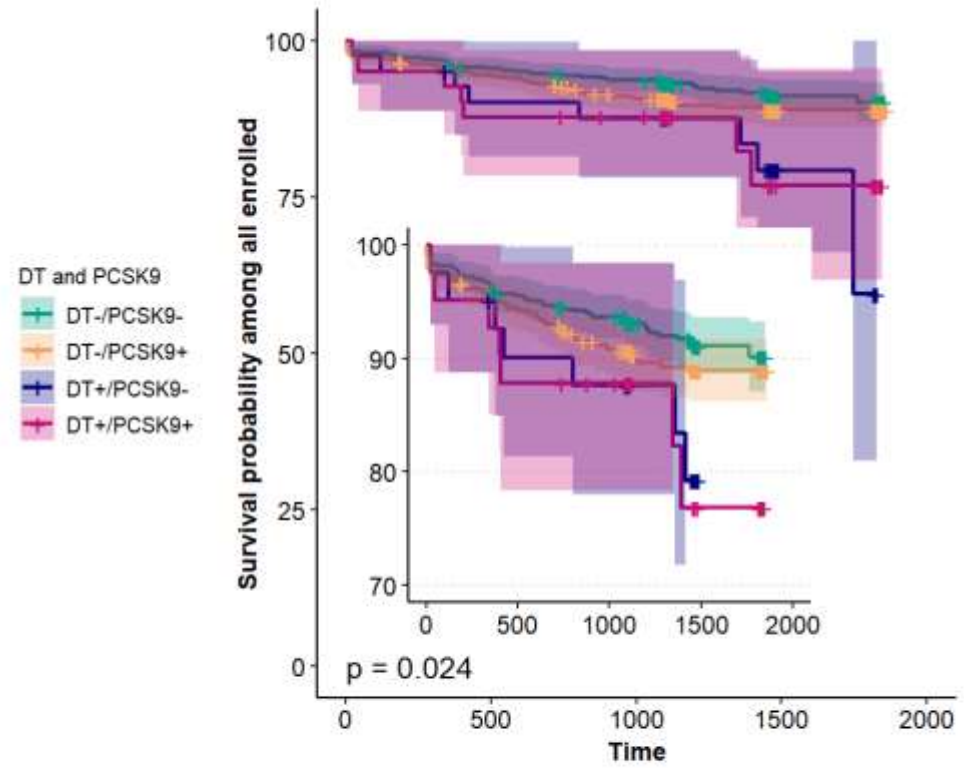
SFigure 1A 3
any CHIP and PCSK9 among all enrolled cohort



Number at risk

DTA-/PCSK9-	592	564	549	94	0
DTA-/PCSK9+	592	557	530	95	0
DTA+/PCSK9-	51	45	44	5	0
DTA+/PCSK9+	51	45	41	9	0

SFigure 1A 4
DNMAT3, TET2 and ASXL1 CHIP mutation and PCSK9 among all enrolled cohort

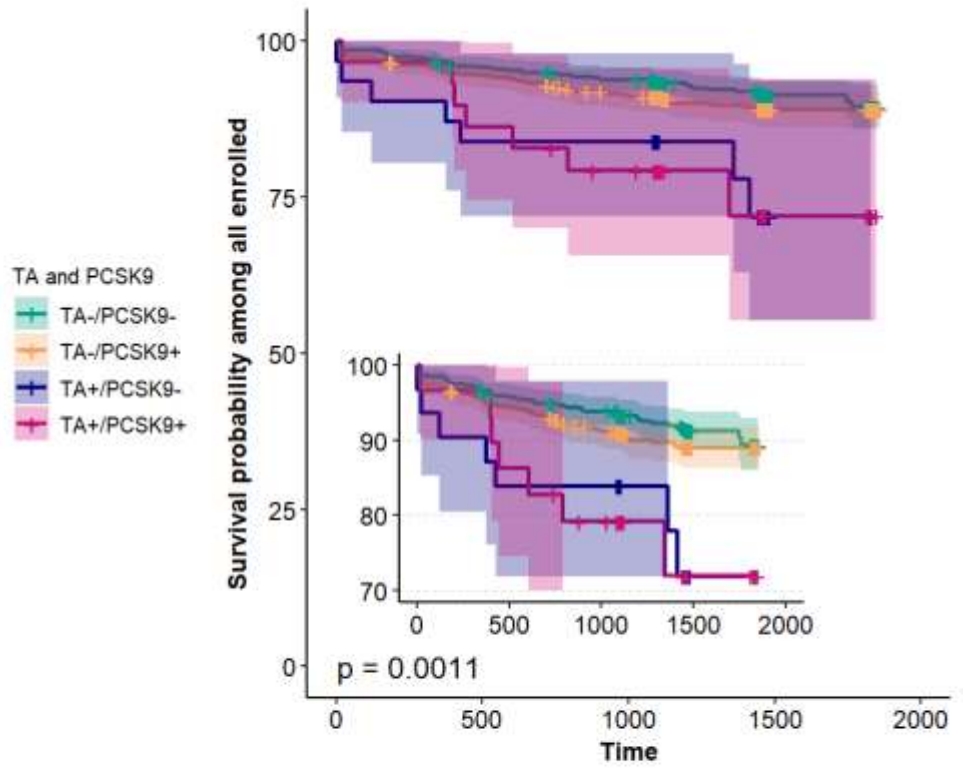


Number at risk

DT-/PCSK9-	602	573	558	95	0
DT-/PCSK9+	602	566	537	96	0
DT+/PCSK9-	41	36	35	4	0
DT+/PCSK9+	41	36	34	8	0

SFigure 1A 5

DNMAT3 and TET2 CHIP mutation and PCSK9 among all enrolled cohort

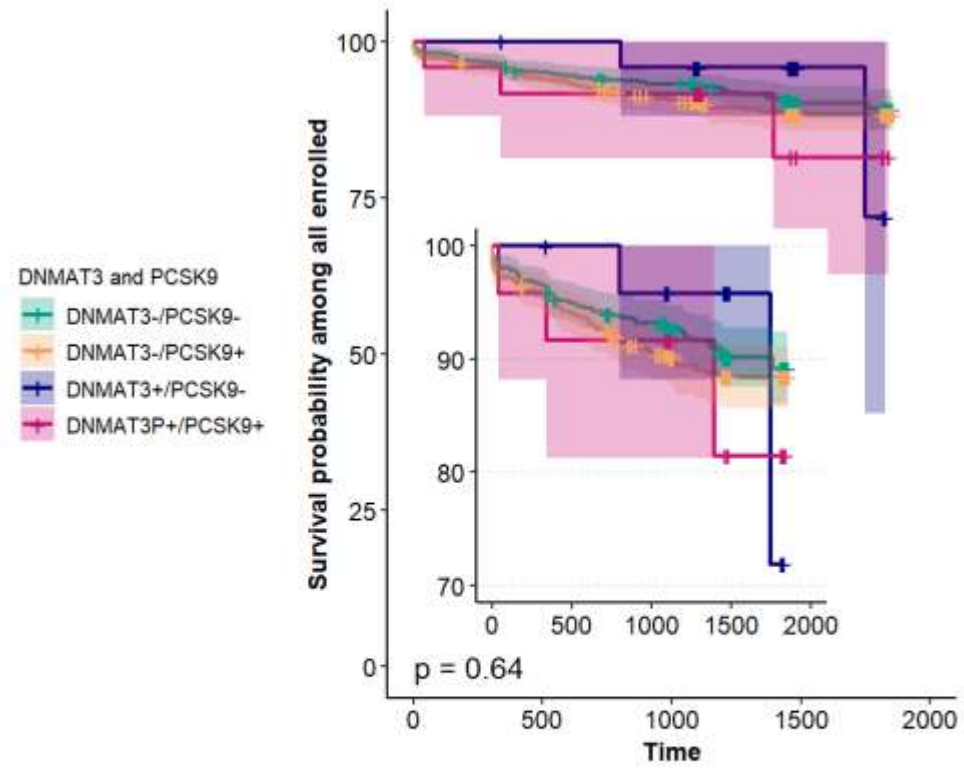


Number at risk

TA-/PCSK9-	612	583	567	97	0
TA-/PCSK9+	614	577	550	100	0
TA+/PCSK9-	31	26	26	2	0
TA+/PCSK9+	29	25	21	4	0

SFigure 1A 6

TET2 and ASXL1 CHIP mutation and PCSK9 among all enrolled cohort

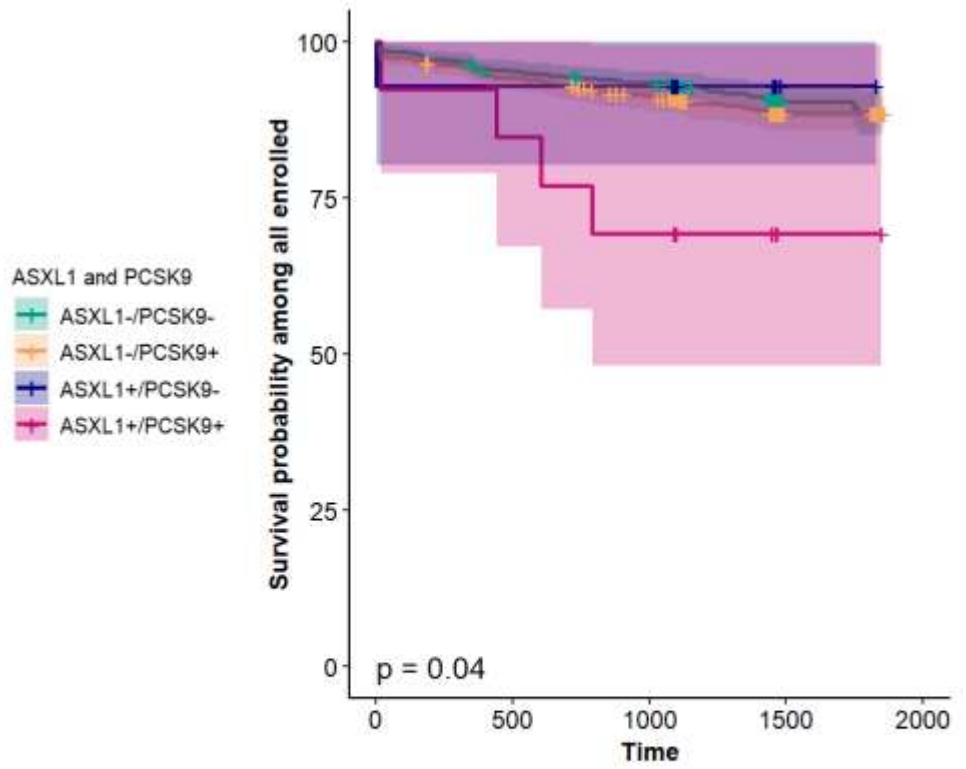


Number at risk

DNMAT3-/PCSK9-	618	585	570	95	0
DNMAT3-/PCSK9+	619	580	549	99	0
DNMAT3+/PCSK9-	25	24	23	4	0
DNMAT3P+/PCSK9+	24	22	22	5	0

SFigure 1A 7

DNMAT3 CHIP mutation and PCSK9 among all enrolled cohort

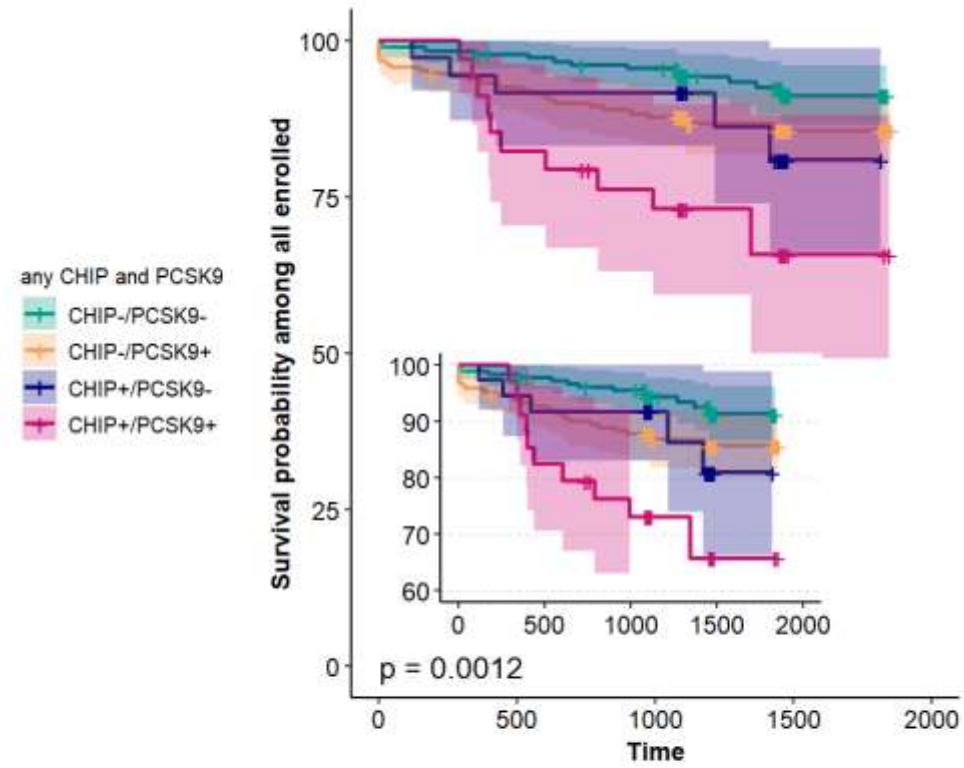


Number at risk

ASXL1-/PCSK9-	629	596	580	98	0
ASXL1-/PCSK9+	630	591	562	103	0
ASXL1+/PCSK9-	14	13	13	1	0
ASXL1+/PCSK9+	13	11	9	1	0

SFigure 1A 8

ASXL1 CHIP mutation and PCSK9 among all enrolled cohort

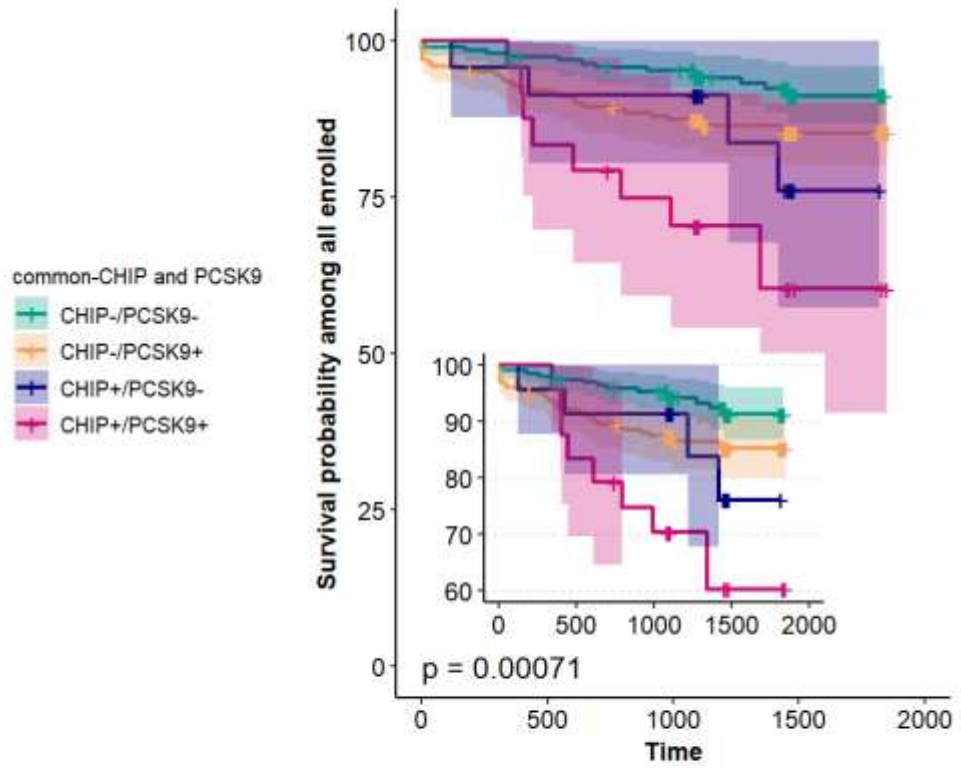


Number at risk

CHIP-/PCSK9-	178	172	167	24	0
CHIP-/PCSK9+	189	174	165	25	0
CHIP+/PCSK9-	36	33	33	1	0
CHIP+/PCSK9+	34	28	23	2	0

SFigure 1B 1

any CHIP and PCSK9 among DM cohort

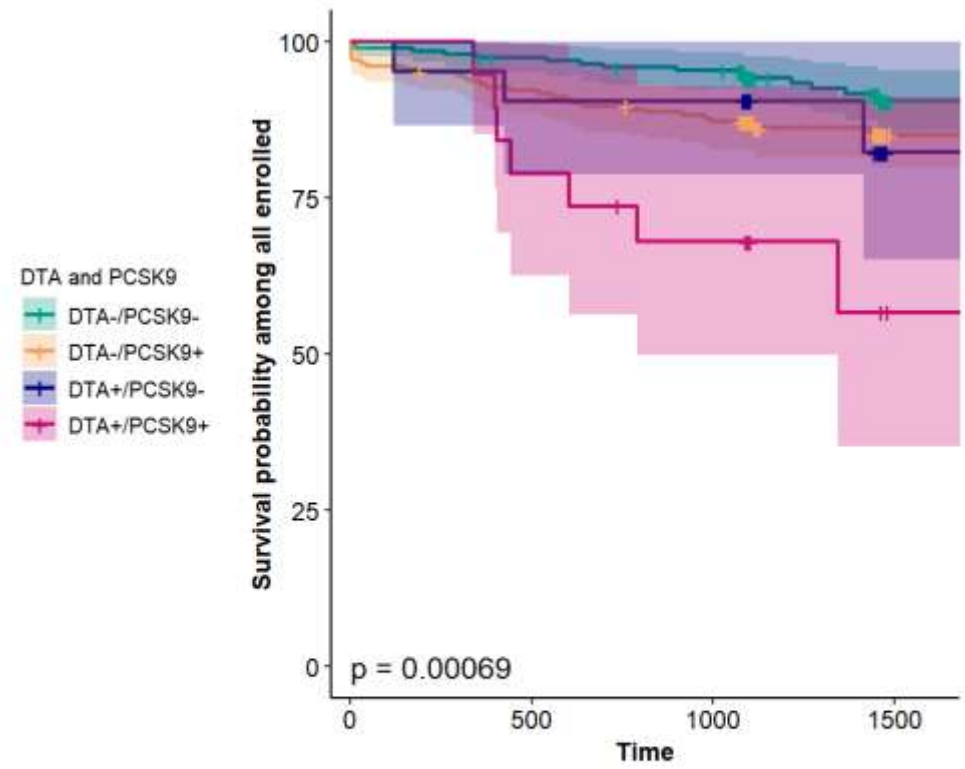


Number at risk

CHIP-/PCSK9-	191	184	179	24	0
CHIP-/PCSK9+	199	182	172	25	0
CHIP+/PCSK9-	23	21	21	1	0
CHIP+/PCSK9+	24	20	16	2	0

SFigure 1B 2

commomly CHIP and PCSK9 among DM cohort among DM cohort

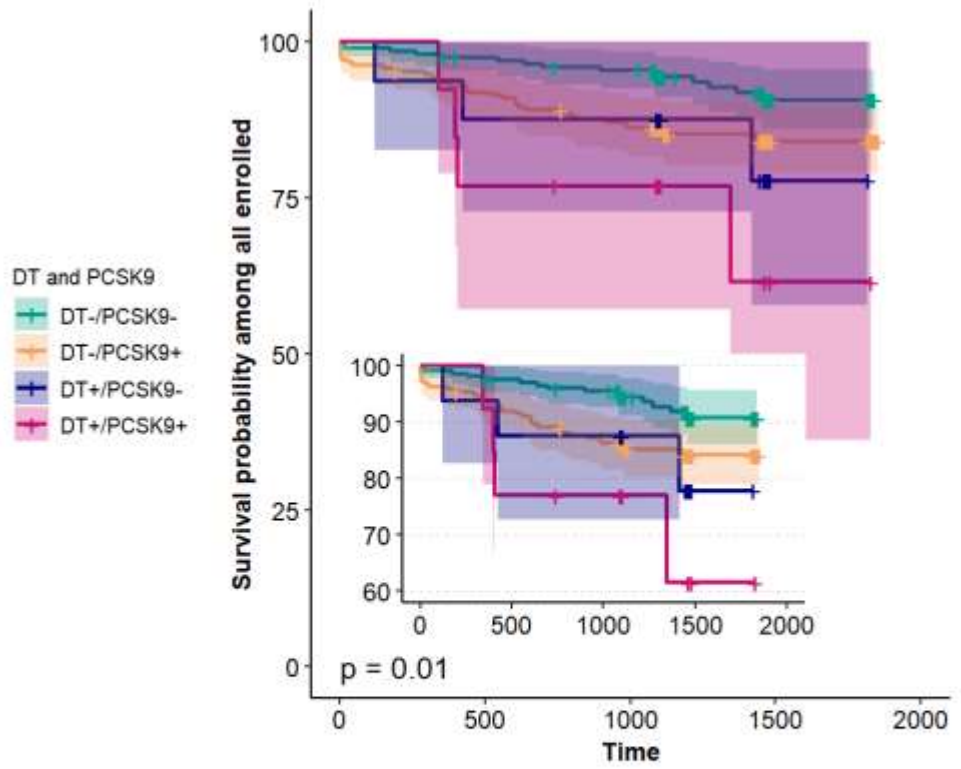


Number at risk

DTA-/PCSK9-	193	186	181	24
DTA-/PCSK9+	204	187	176	25
DTA+/PCSK9-	21	19	19	1
DTA+/PCSK9+	19	15	12	2

SFigure 1B 3

DNMAT3, TET2 and ASXL1 CHIP mutation and PCSK9 among DM cohort

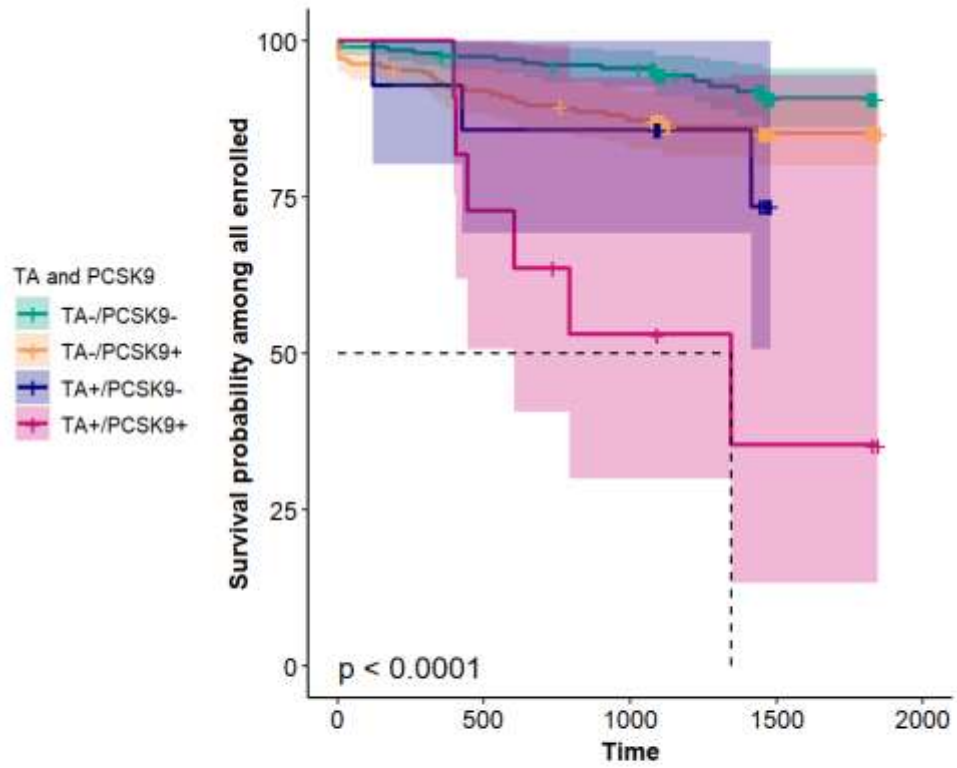


Number at risk

DT-/PCSK9-	198	191	186	24	0
DT-/PCSK9+	210	192	179	26	0
DT+/PCSK9-	16	14	14	1	0
DT+/PCSK9+	13	10	9	1	0

SFigure 1B 4

DNMAT3 and TET2 CHIP mutation and PCSK9 among DM cohort

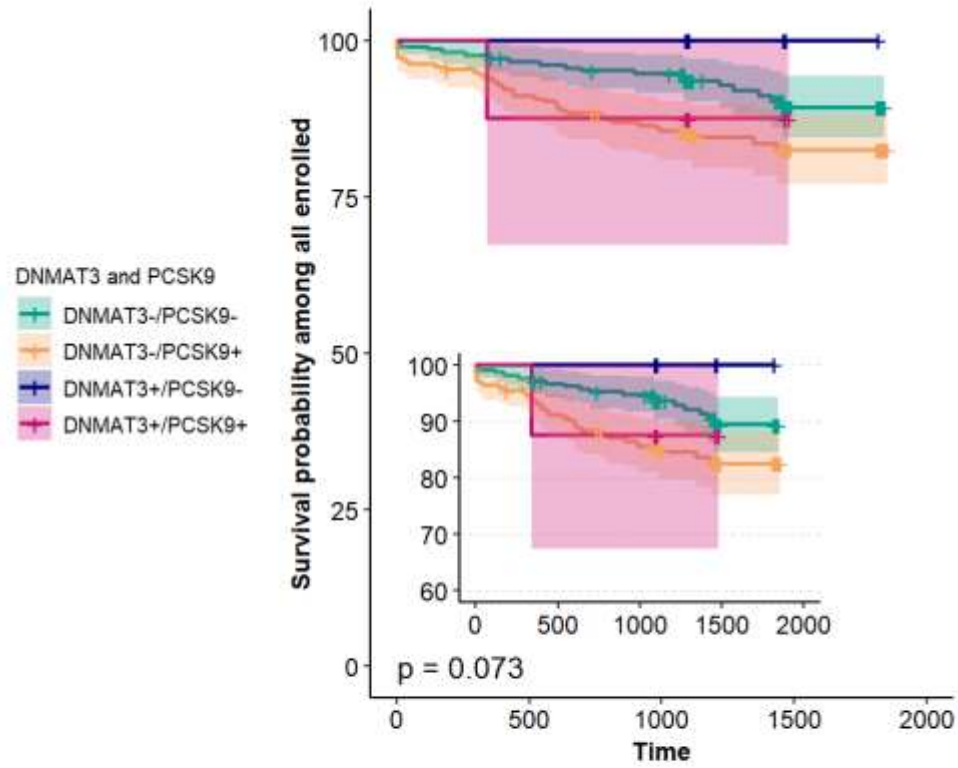


Number at risk

TA-/PCSK9-	200	193	188	25	0
TA-/PCSK9+	212	194	183	25	0
TA+/PCSK9-	14	12	12	0	0
TA+/PCSK9+	11	8	5	2	0

SFigure 1B 5

TET2 and ASXL1 CHIP mutation and PCSK9 among DM cohort

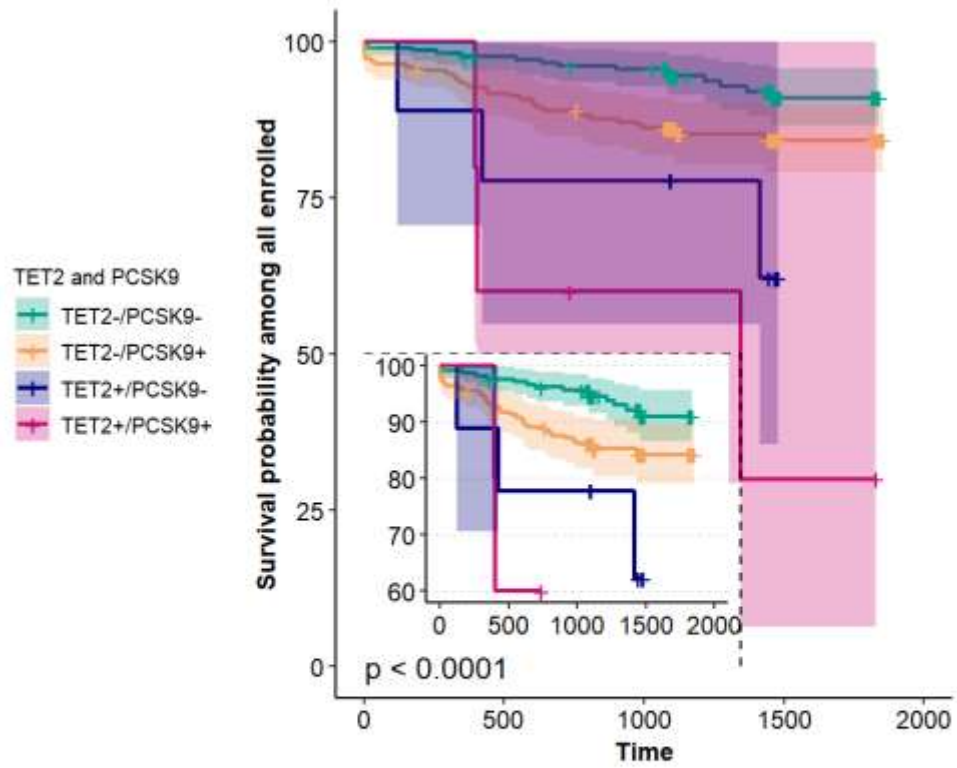


Number at risk

DNMAT3-/PCSK9-	207	198	193	24	0
DNMAT3-/PCSK9+	215	195	181	27	0
DNMAT3+/PCSK9-	7	7	7	1	0
DNMAT3+/PCSK9+	8	7	7	0	0

SFigure 1B 6

DNMAT3 CHIP mutation and PCSK9 among DM cohort

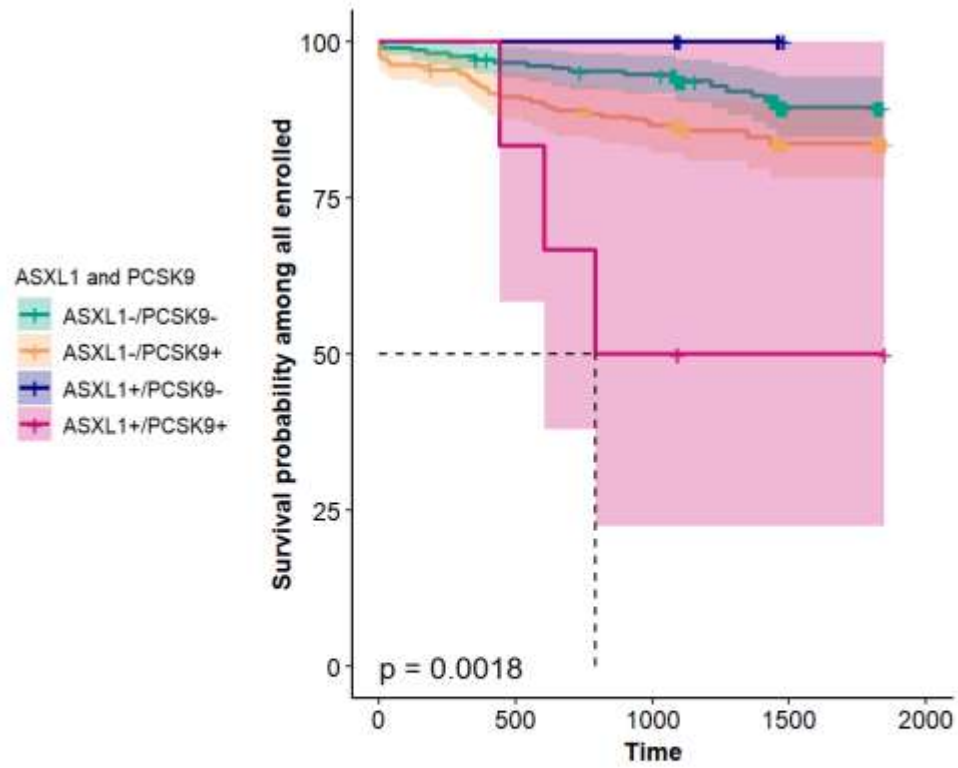


Number at risk

TET2-/PCSK9-	205	198	193	25	0
TET2-/PCSK9+	218	199	186	26	0
TET2+/PCSK9-	9	7	7	0	0
TET2+/PCSK9+	5	3	2	1	0

SFigure 1B 7

TET2 CHIP mutation and PCSK9 among DM cohort



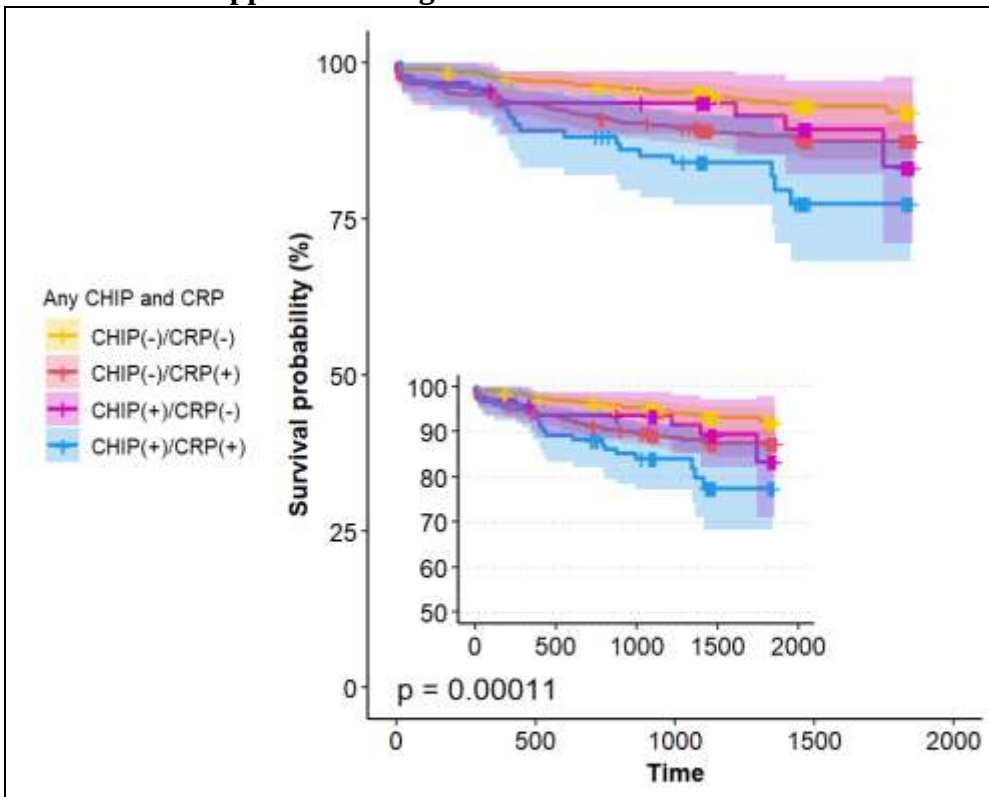
Number at risk

ASXL1-/PCSK9-	208	199	194	25	0
ASXL1-/PCSK9+	217	197	185	26	0
ASXL1+/PCSK9-	6	6	6	0	0
ASXL1+/PCSK9+	6	5	3	1	0

SFigure 1B 8

ASXL1 CHIP mutation and PCSK9 among DM cohort

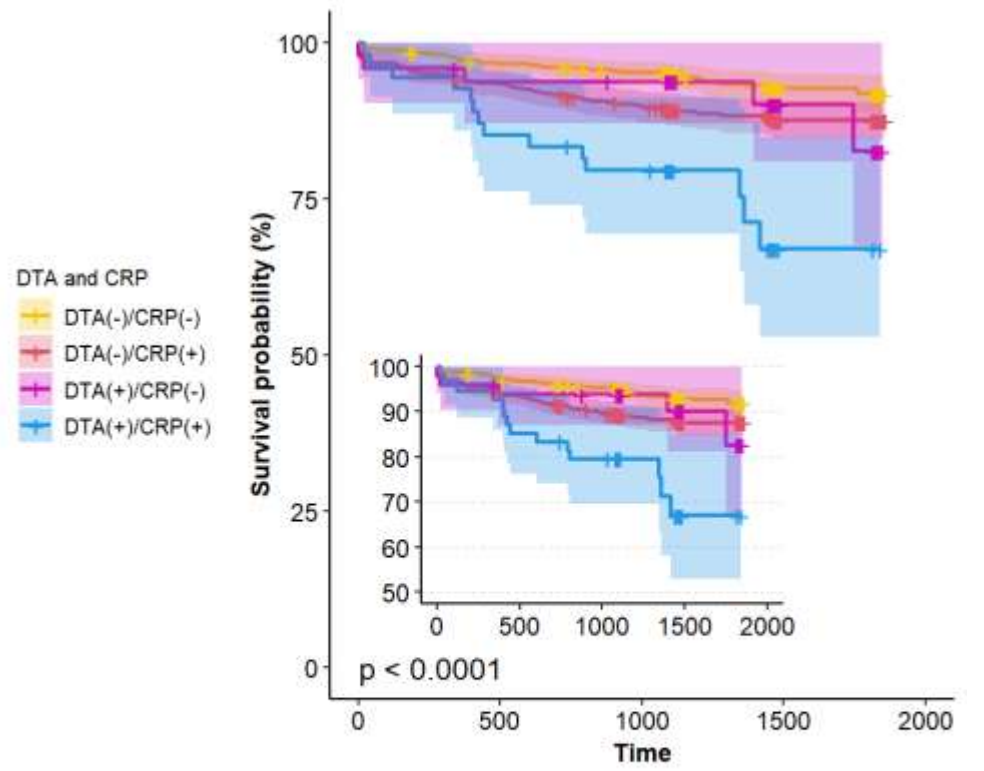
Supplemental Figure 2



Number at risk

CHIP(-)/CRP(-)	554	534	518	94	0
CHIP(-)/CRP(+)	538	501	479	86	0
CHIP(+)/CRP(-)	93	86	85	15	0
CHIP(+)/CRP(+)	101	90	82	8	0

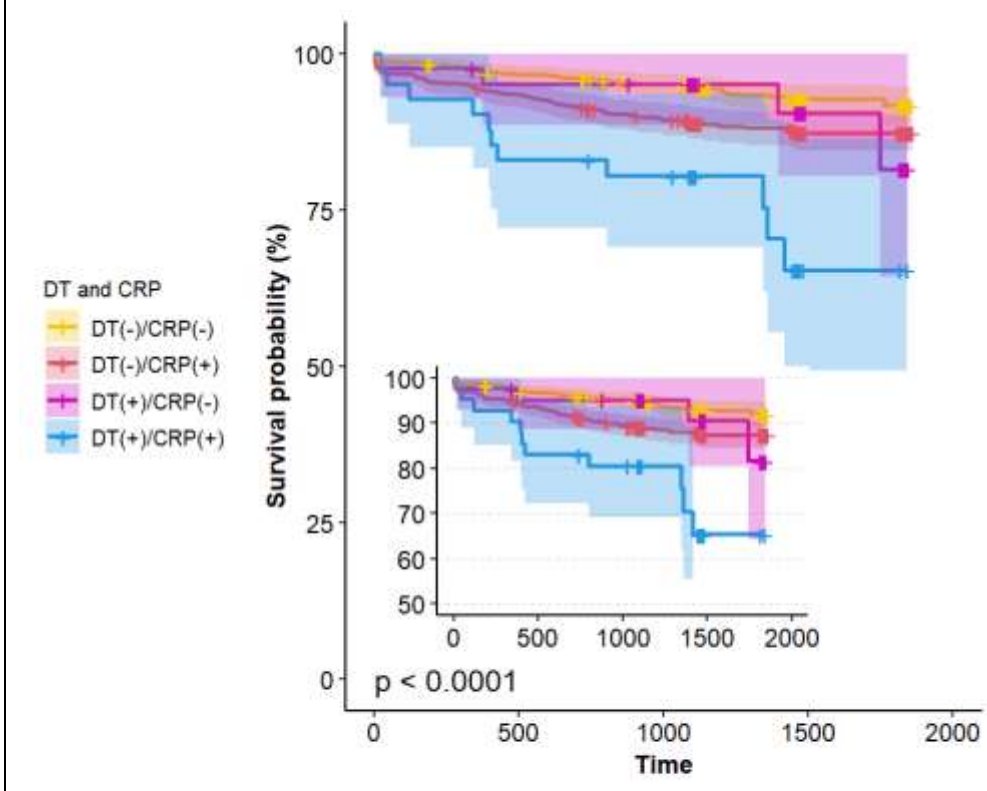
SFigure 2A 1
any CHIP and CRP among all enrolled cohort



Number at risk

DTA(-)/CRP(-)	599	576	560	97	0
DTA(-)/CRP(+)	585	545	519	92	0
DTA(+)/CRP(-)	48	44	43	12	0
DTA(+)/CRP(+)	54	46	42	2	0

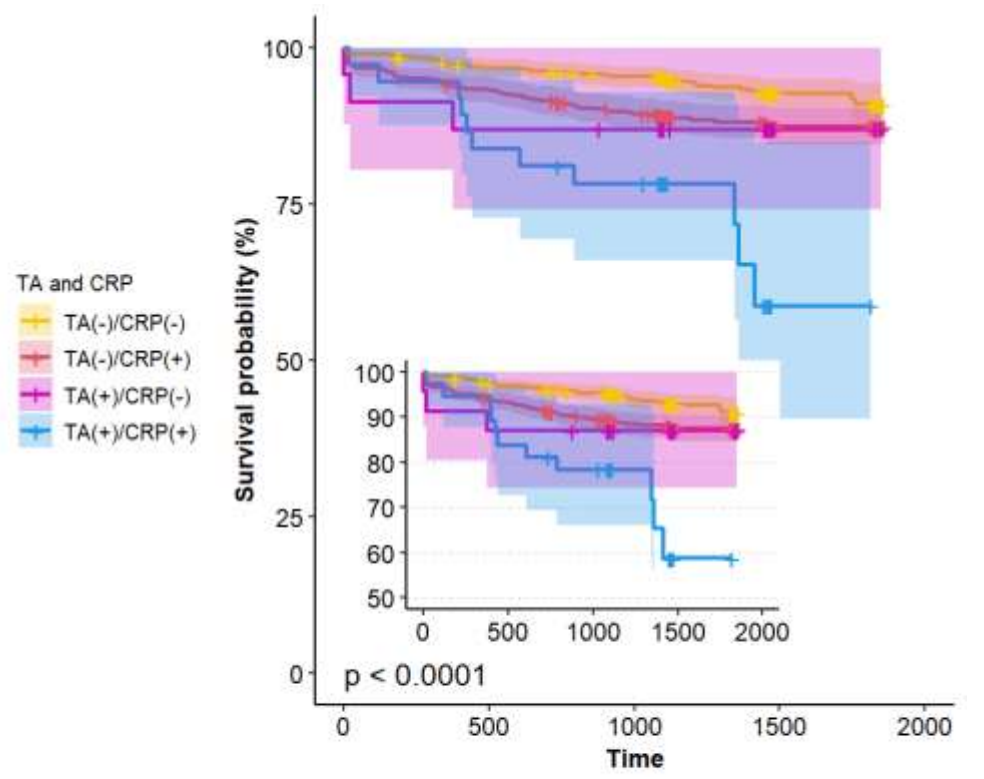
SFigure 2A 2
DNMAT3, TET2 and ASXL1 CHIP mutation and CRP among all enrolled cohort



Number at risk

DT(-)/CRP(-)	606	582	566	99	0
DT(-)/CRP(+)	598	557	529	92	0
DT(+)/CRP(-)	41	38	37	10	0
DT(+)/CRP(+)	41	34	32	2	0

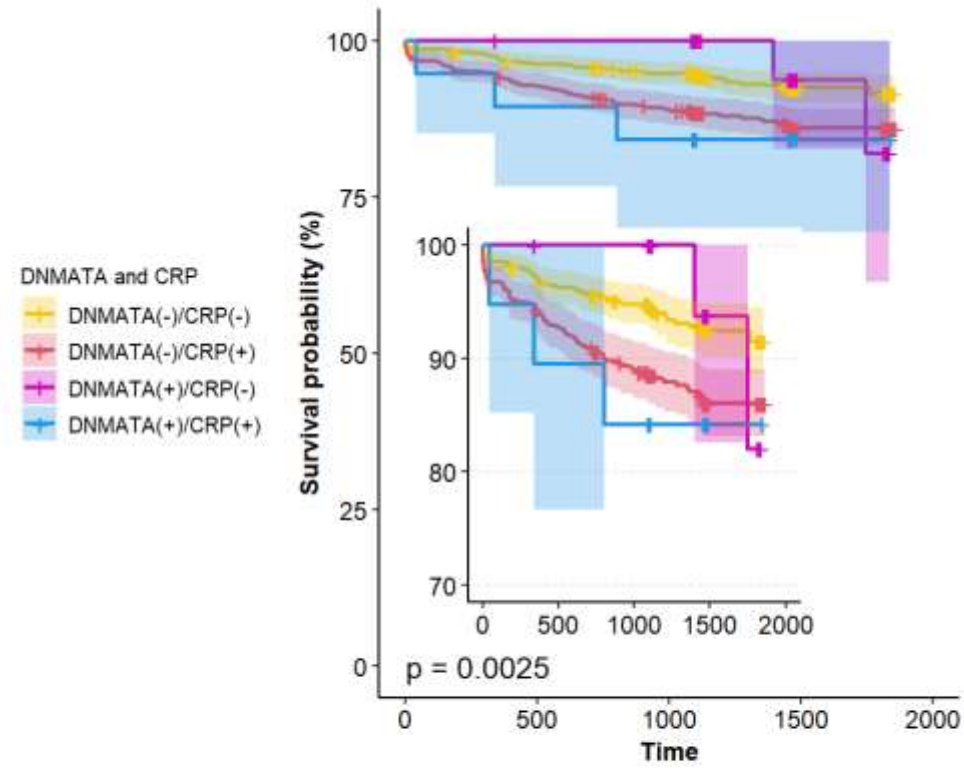
SFigure 2A 3
DNMAT3 and TET2 CHIP mutation and CRP among all enrolled cohort



Number at risk

TA(-)/CRP(-)	624	600	584	104	0
TA(-)/CRP(+)	602	560	533	93	0
TA(+)/CRP(-)	23	20	19	5	0
TA(+)/CRP(+)	37	31	28	1	0

SFigure 2A 4
TET2 and ASXL1 CHIP mutation and CRP among all enrolled cohort

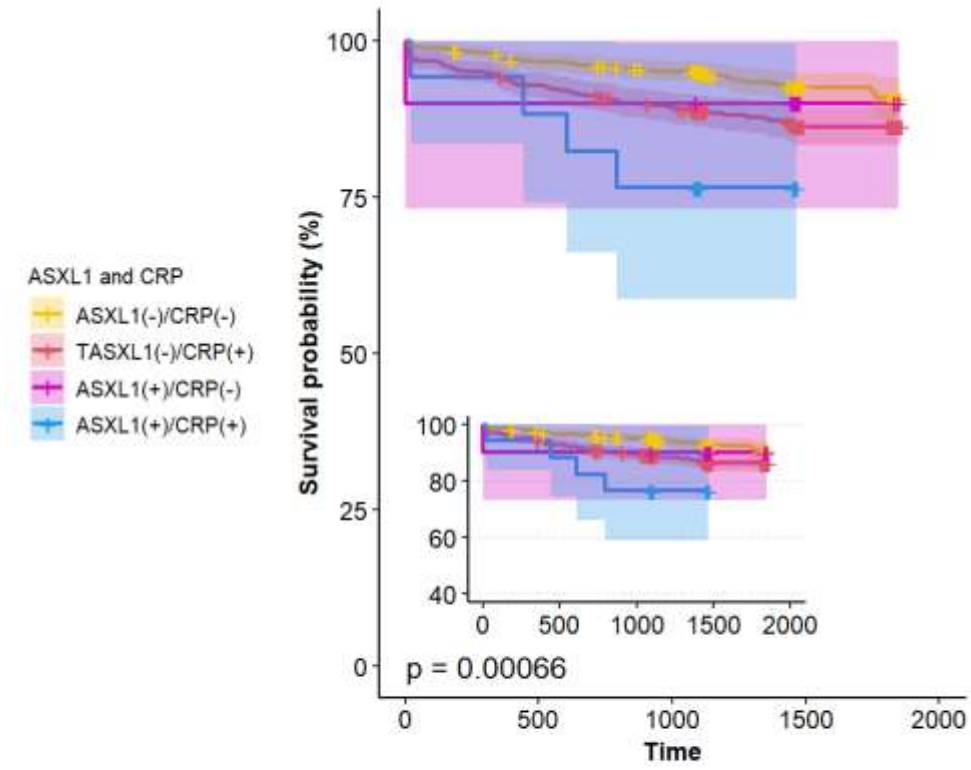


Number at risk

DNMATA(-)/CRP(-)	617	591	574	101	0
DNMATA(-)/CRP(+)	620	574	545	93	0
DNMATA(+)/CRP(-)	30	29	29	8	0
DNMATA(+)/CRP(+)	19	17	16	1	0

SFigure 2A 5

DNMAT3 CHIP mutation and CRP among all enrolled cohort

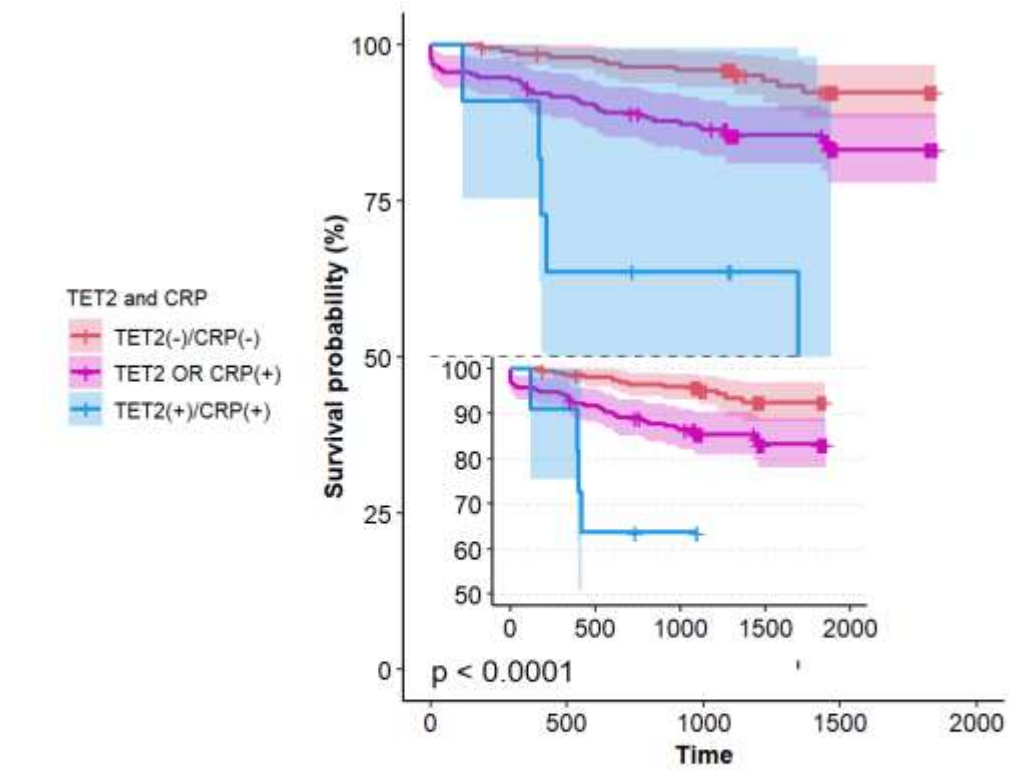


Number at risk

ASXL1(-)/CRP(-)	637	611	594	107	0
TASXL1(-)/CRP(+)	622	576	548	94	0
ASXL1(+)/CRP(-)	10	9	9	2	0
ASXL1(+)/CRP(+)	17	15	13	0	0

SFigure 2A 6

ASXL1 CHIP mutation and CRP among all enrolled cohort

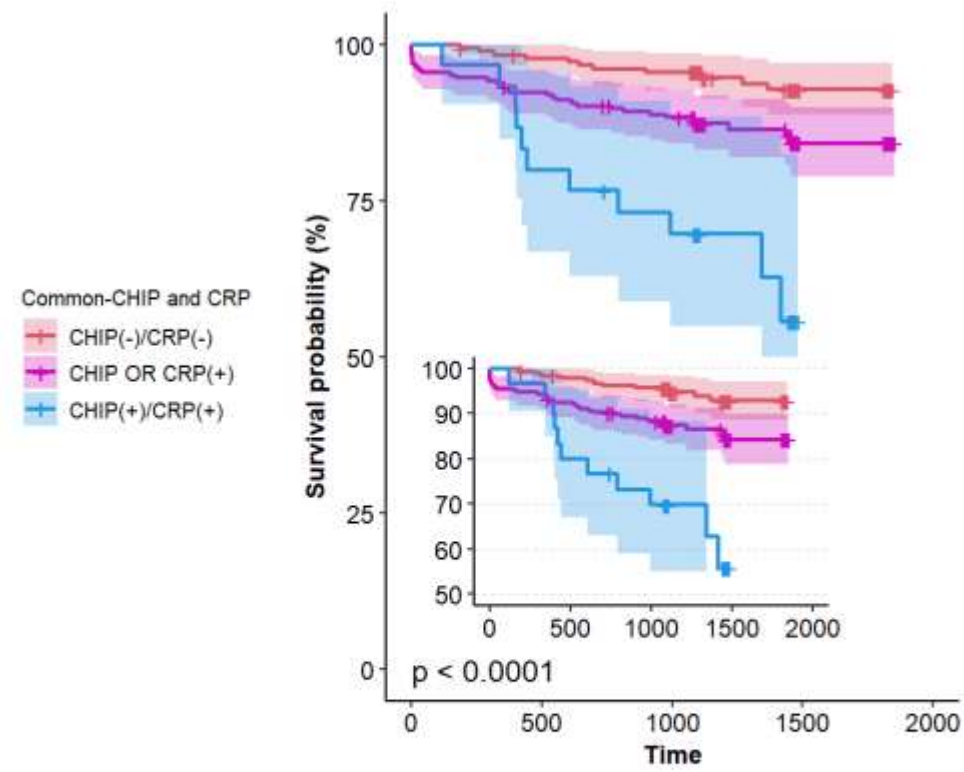


Number at risk

TET2(-)/CRP(-)	197	191	187	29	0
TET2 OR CRP(+)	229	209	195	23	0
TET2(+)/CRP(+)	11	7	6	0	0

SFigure 2B1

TET2 CHIP mutation and CRP among DM cohort

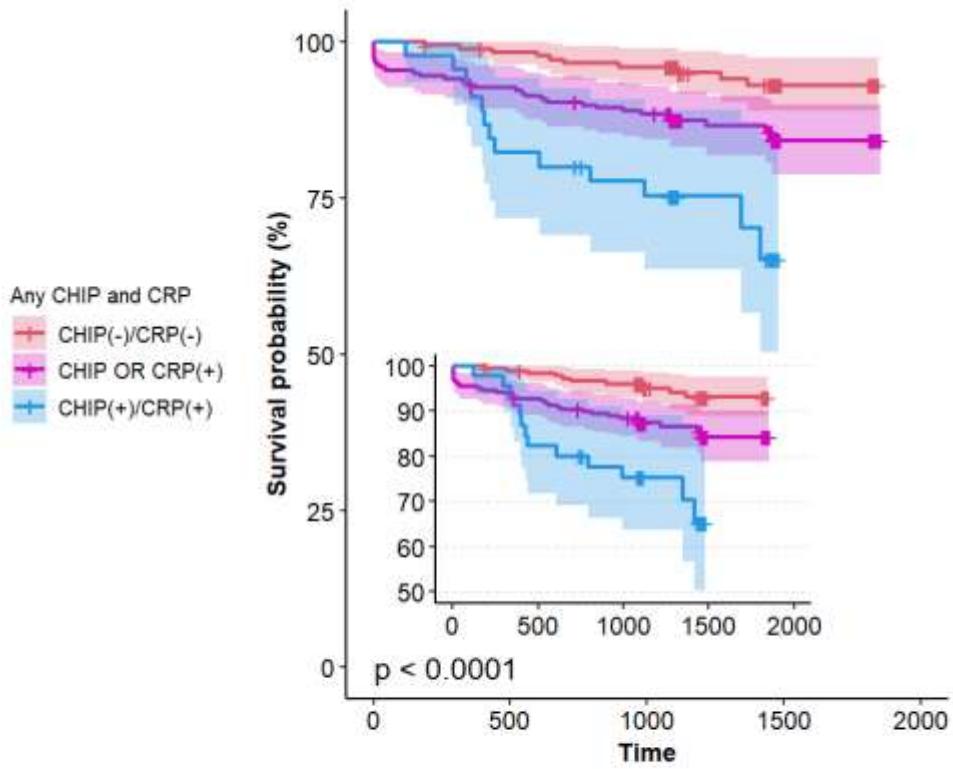


Number at risk

CHIP(-)/CRP(-)	183	177	173	27	0
CHIP OR CRP(+)	224	206	195	25	0
CHIP(+)/CRP(+)	30	24	20	0	0

SFigure 2B2

commomly CHIP and CRP among DM cohort

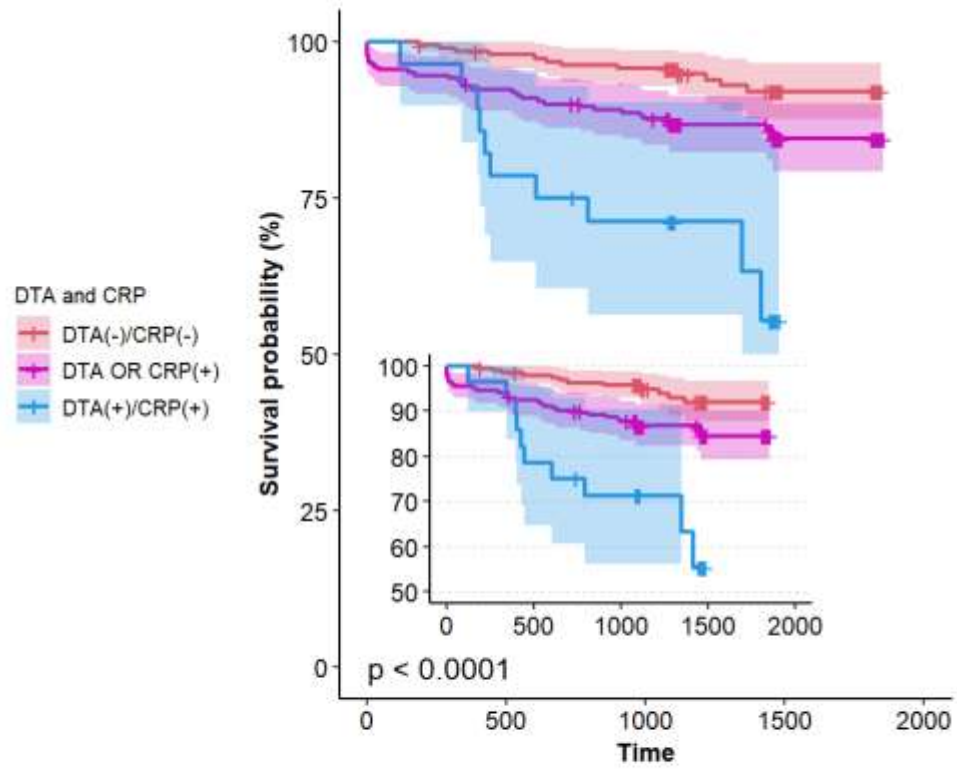


Number at risk

CHIP(-)/CRP(-)	175	170	166	27	0
CHIP OR CRP(+)	217	200	190	25	0
CHIP(+)/CRP(+)	45	37	32	0	0

SFigure 2B 3

any CHIP and CRP among DM cohort

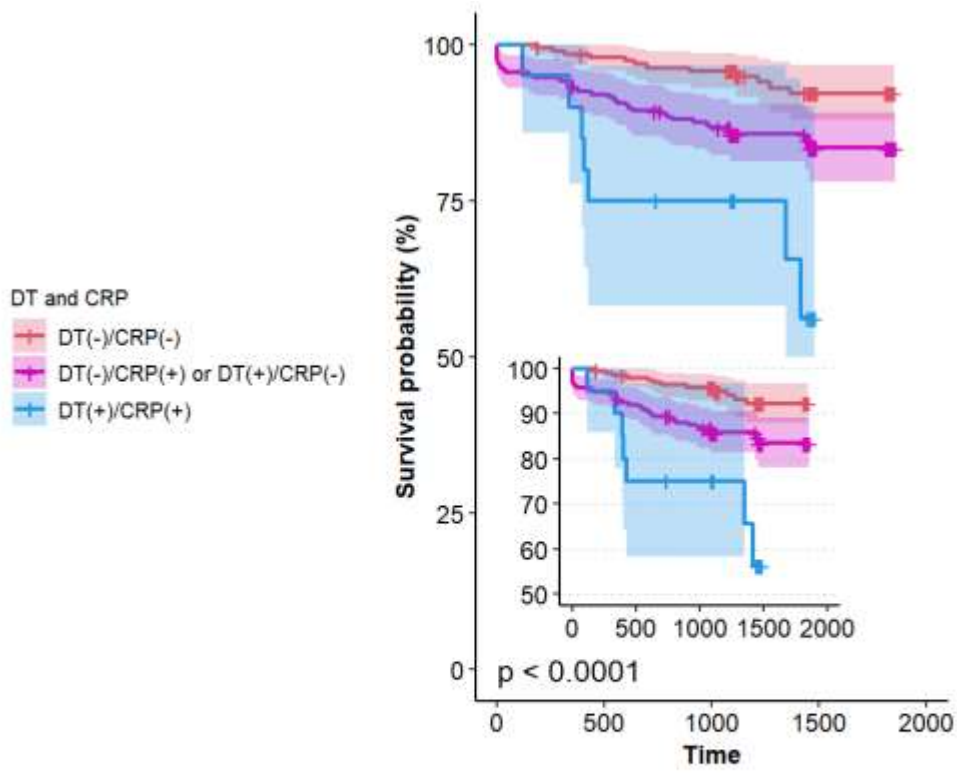


Number at risk

DTA(-)/CRP(-)	188	182	178	27	0
DTA OR CRP(+)	221	203	191	25	0
DTA(+)/CRP(+)	28	22	19	0	0

SFigure 2B 4

DNMAT3, TET2 and ASXL1 CHIP mutation and CRP among DM cohort

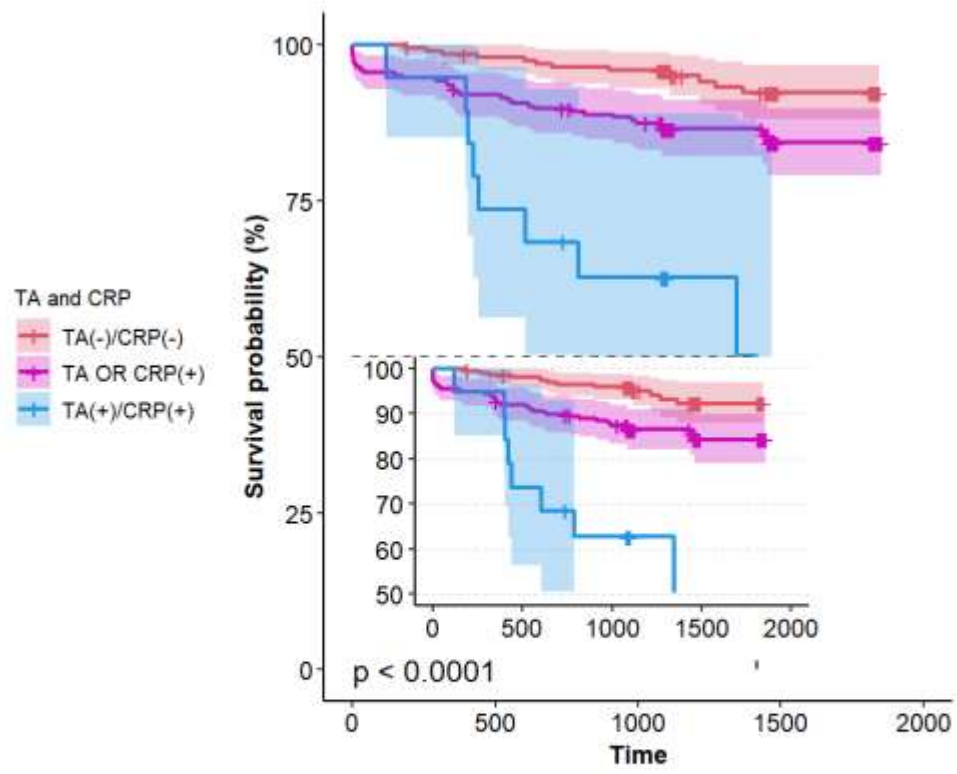


Number at risk

DT(-)/CRP(-)	191	185	181	28	0
DT(-)/CRP(+) or DT(+)/CRP(-)	226	207	193	24	0
DT(+)/CRP(+)	20	15	14	0	0

SFigure 2B 5

DNMAT3 and TET2 CHIP mutation and CRP among DM cohort

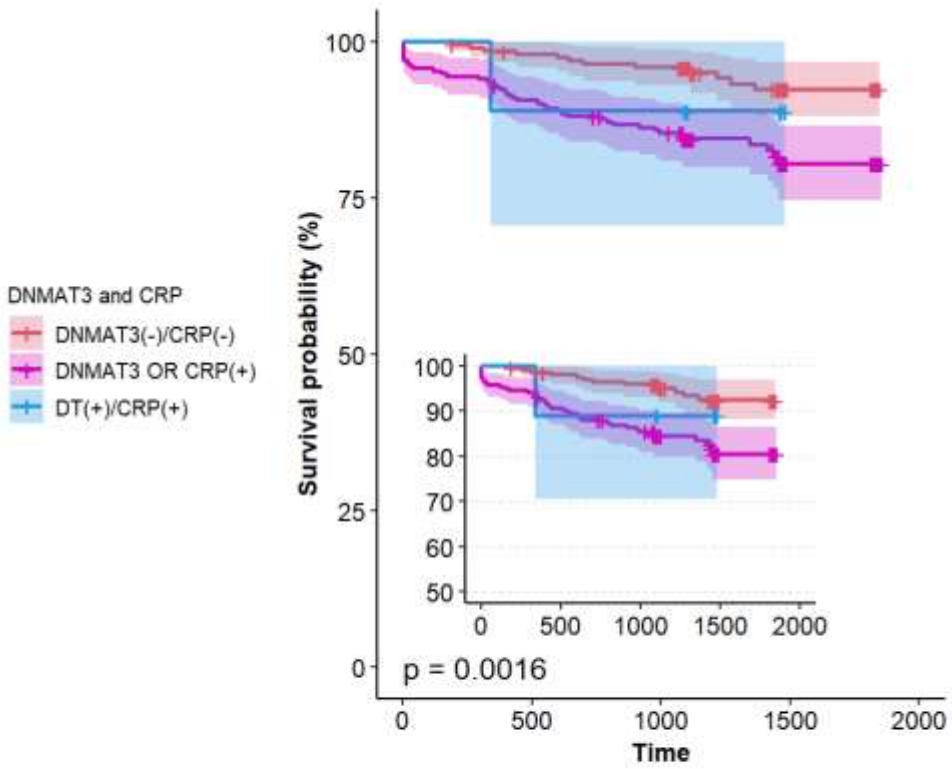


Number at risk

TA(-)/CRP(-)	194	188	184	28	0
TA OR CRP(+)	224	205	193	24	0
TA(+)/CRP(+)	19	14	11	0	0

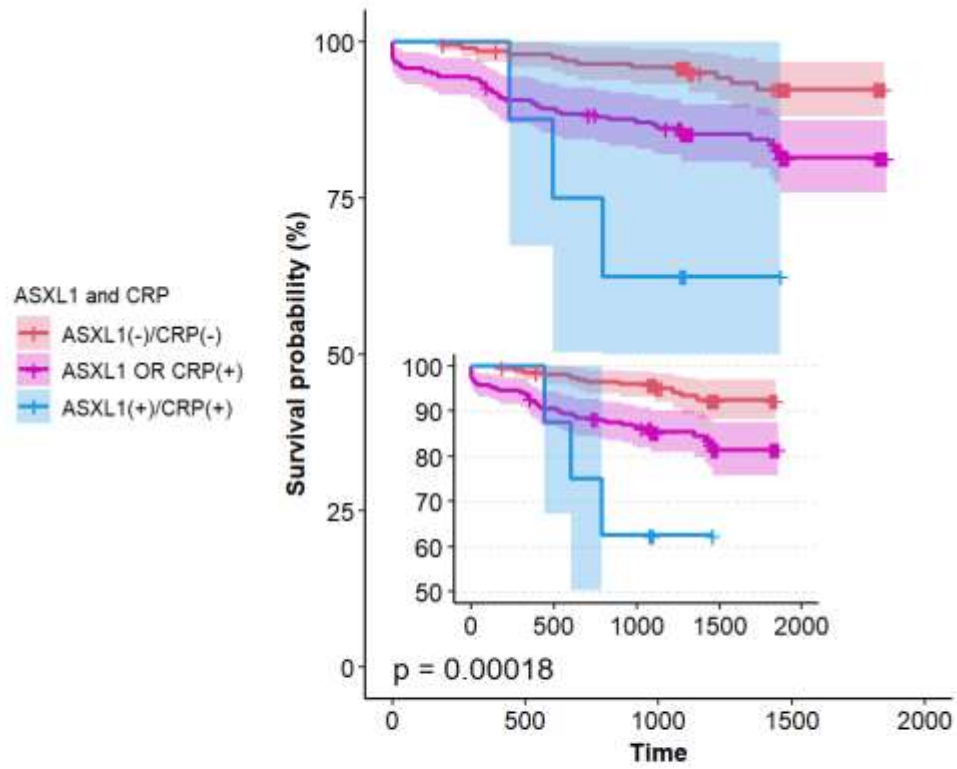
SFigure 2B 6

TET2 and ASXL1 CHIP mutation and CRP among DM cohort



SFigure 2B 7

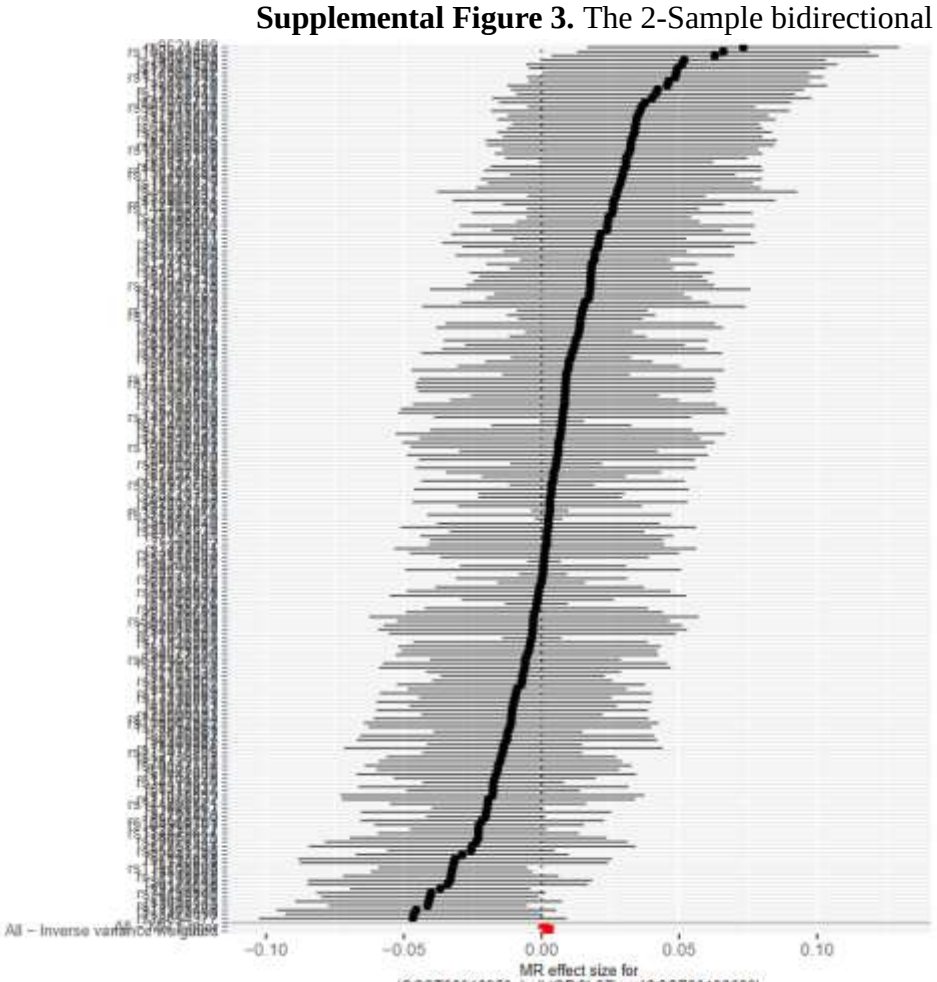
DNMAT3 CHIP mutation and CRP among DM cohort



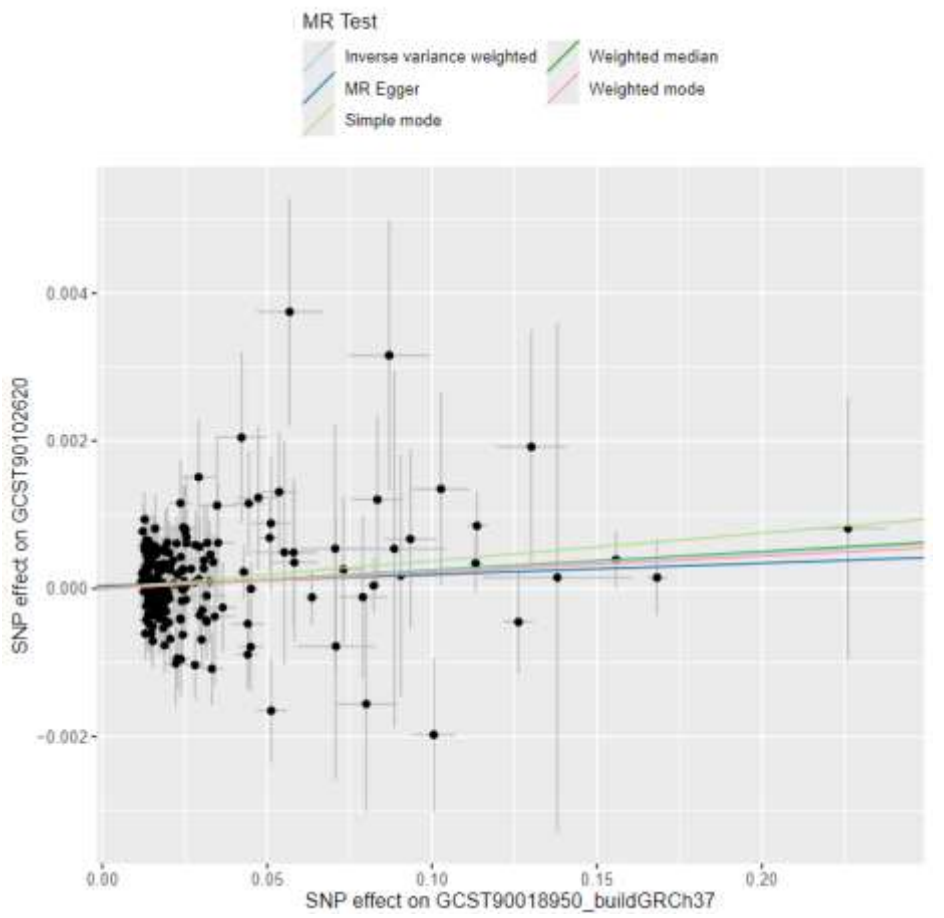
SFigure 2B 8

ASXL1 CHIP mutation and CRP among DM cohort

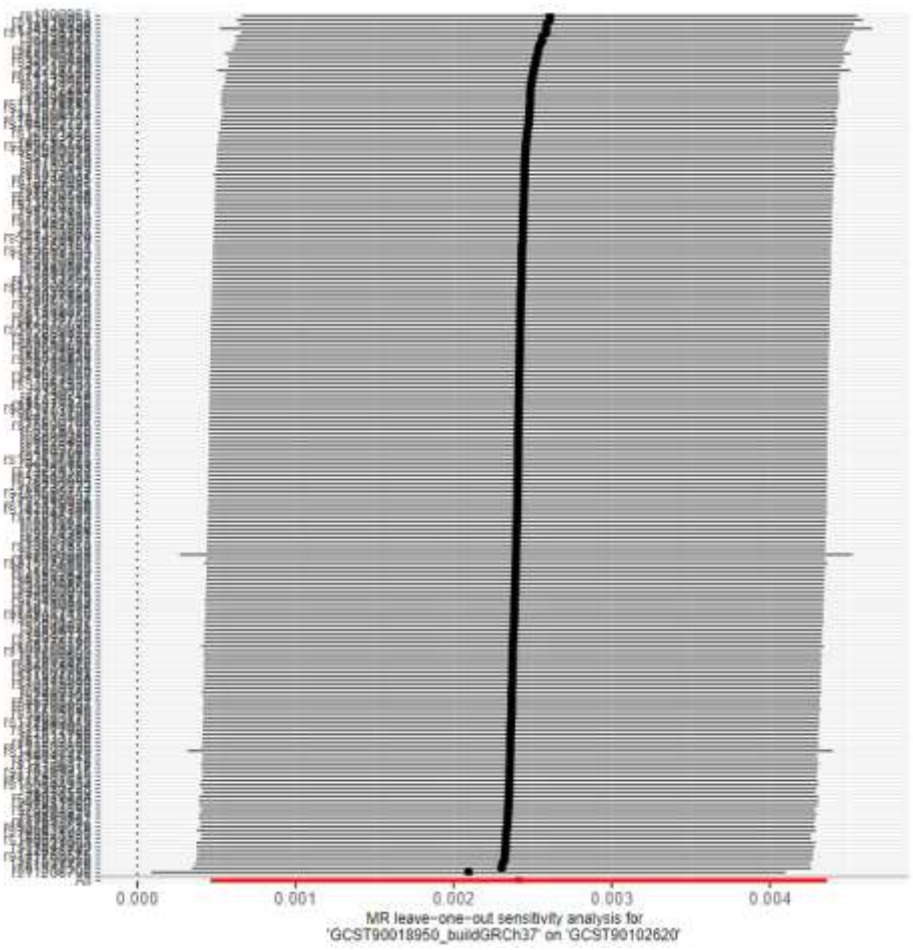
Supplemental Figure 3. The 2-Sample bidirectional Mendelian randomization of CRP on TET2-CHIP mutations



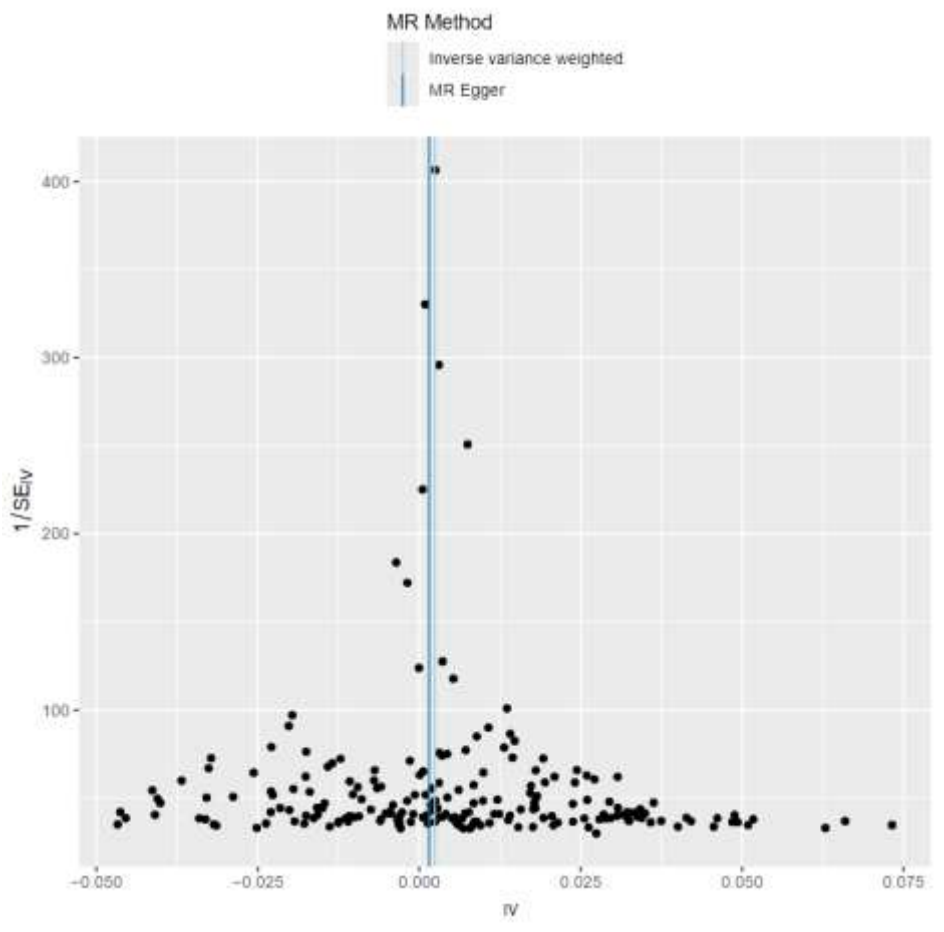
SFigure 3A. Forest plots for the causal association between hs-CRP and TET2-CHIP mutations



SFigure 3B. Scatter plots for the causal association between hs-CRP and TET2-CHIP mutations.



SFigure 3C. Leave-one-out plots for the causal association between hs-CRP and TET2-CHIP mutations.



SFigure 3 D. Funnel plots for the causal association between hs-CRP and TET2-CHIP mutations.

Abbreviations: *hs-CRP, high sensitive C reaction protion; CHIP, clonal hematopoiesis of indeterminate potential*