Clonal hematopoiesis and risk of chronic liver disease

Supplementary Information

Supplementary Tables

Supplementary Table 1. Chronic liver disease cases and definitions in five samples.

Cohort	Cases	Controls	Definition	Analysis
Framingham Heart Study	46	4194	Prevalent cirrhosis or chronic liver disease, physician-diagnosed or ICD codes K70.2, K70.3, K70.4, K74.0, K74.1, K74.2, K74.6, or I85	Observational
Atherosclerosis Risk in Communities Study	33	7381	Prevalent cirrhosis or chronic liver disease, physician-diagnosed or ICD codes K70.2, K70.3, K70.4, K74.0, K74.1, K74.2, K74.6, or I85	Observational
UK Biobank WES	555	200,854	Prevalent chronic liver disease, hospitalization or death due to ICD codes K70.2, K70.3, K70.4, K74.0, K74.1, K74.2, K74.6, or I85	Observational
UK Biobank Array	825	238,491	Incident chronic liver disease, hospitalization or death due to ICD codes K70.2, K70.3, K70.4, K74.0, K74.1, K74.2, K74.6, or I85	Observational
MGB Biobank	114	1386	Biopsy-diagnosed non-alcoholic steatohepatitis	Observational
Multi-cohort GWAS[20]	5777	487780	Prevalent chronic liver disease, hospitalization or death due to cirrhosis	Mendelian randomization

WES, whole exome sequencing; MGB, Mass General Brigham; GWAS, genome-wide association study.

Supplementary Table 2. Association of CHIP with known risk factors across cohorts.

Risk Factor	FHS, n=4,240	ARIC, n=7,414	UK Biobank WES, n=201,409	UK Biobank Array, n=239,316
Age, year	OR 1.04 CI 1.03, 1.05, p<0.001	OR 1.08 CI 1.06, 1.10, p<0.001	OR 1.05 CI 1.04, 1.05, p<0.001	OR 1.04 CI 1.02, 1.06, p<0.001
Sex, female versus male	OR 1.24 CI 0.98, 1.56, p=0.07	OR 1.03 CI 0.85, 1.25, p=0.77	OR 1.06 CI 1.00, 1.11, p=0.04	OR 1.37 CI 1.02, 1.74, p=0.01
Current Smoking	OR 1.31 CI 0.98, 1.78, p=0.07	OR 1.25 CI 1.00, 1.55, p=0.05	OR 1.34 CI 1.21, 1.48, p<0.001	OR 1.13 CI 0.74, 1.74, p=0.57
Body mass index, kg/m^2	OR 0.96 CI 0.94, 0.99, p=0.002	OR 0.99 CI 0.97, 1.01, p=0.47	OR 1.00 CI 1.00, 1.01 p=0.27	OR 0.99 CI 0.97, 1.02 p=0.55
Type 2 Diabetes mellitus	OR 0.96 CI 0.55, 1.69, p=0.90	OR 0.96 CI 0.68, 1.35, p=0.81	OR 0.92 CI 0.83, 1.03, p=0.14	OR 0.89 CI 0.51, 1.54, p=0.67

Estimates were derived using multivariable logistic regression.

Supplementary Table 3. CHIP variants ascertained through genotyping in the UK Biobank.

Variant	Gene	Chr	Location	Reference Allele	Effect Allele	Consequence
rs373145711	*ASXL1*	20	31021211	C	T	Arg404Ter
rs373873045	*DNMT3A*	2	25459834	C	A	Glu817Ter
rs765045799	*DNMT3A*	2	25462086	T	C	Splice Acceptor
rs1190050788	*DNMT3A*	2	25466765	A	C	Splice Donor
rs568207978	*DNMT3A*	2	25467083	G	A	Arg598Ter
rs369109129	*DNMT3A*	2	25469922	G	A	Gln374Ter
rs776841024	*DNMT3A*	2	25470556	C	T	Trp306Ter
rs767439400	*DNMT3A*	2	25471030	GGGCT	G	SerPro243Fs
rs77375493	*JAK2*	9	5073770	G	T	Val617Phe
rs370735654	*TET2*	4	106196213	C	T	Arg1516Ter
rs757144251	*TET2*	4	106157271	TA	T	Lys725Fs

Chr, chromosome; Fs, frameshift

Supplementary Table 4. Association of $CHIP_{\geq 10\%}$ with prevalent and incident chronic liver disease in UK Biobank.

Analysis	Cases	Controls	OR	P-value
Prevalent CLD	247	199,881	1.16 CI 0.61, 2.20	0.63
Incident CLD	555	200,854	1.61 CI 1.07, 2.41	0.02

CLD, chronic liver disease

Supplementary Table 5. Association of CHIP and clinical risk factors with incident chronic liver disease.

Risk factor	Hazard Ratio for incident chronic liver disease	P-value
CHIP	1.54 CI 1.05, 2.28	0.02
Age, per 10 years	1.24 CI 1.09, 1.39	$5x10^{-4}$
BMI, per 5 kg/m^2	1.23 CI 1.14, 1.34	$5x10^{-7}$
Type 2 diabetes	6.21 CI 5.06, 7.63	$<2x10^{-16}$
Current smoking	1.94 CI 1.50, 2.51	$5x10^{-7}$

Hazard ratios for risk factors were derived in a Cox proportional hazard model with mutual adjustment for CHIP, age more than six years, body mass index > 30 kg/m^2, type 2 diabetes, current smoking, and sex. BMI, body mass index

Supplementary Table 6. Association of CHIP with ICD-coded chronic liver disease.

Outcome	Codes	Cases	Controls	Effect	P-value
Alcoholic liver disease	K70.2, K70.3, K70.4	535	199,593	OR 1.70 CI 0.98, 2.96	0.06
Non-alcoholic liver disease	K74.0, K74.1, K74.2, K74.6	707	199,421	OR 1.78 CI 1.23, 2.57	0.002
Fatty liver	K76.0	1,920	198,208	OR 0.96 CI 0.71, 1.32	0.80
Cirrhosis	K70.3, K74.6, I85	787	199,341	OR 1.64 CI 1.03, 2.61	0.04

Estimates were derived using logistic regression with adjustment for age, sex, type 2 diabetes and current smoking.

Supplementary Table 7. Baseline characteristics of MGB Biobank participants.

	Controls (n=1368)	**NASH on biopsy (n=114)**
Age, mean (SD) years	54 (12)	54 (12)
Female sex, n (%)	804 (59%)	67 (59%)
Body mass index, mean (SD) kg/m^2	31 (8)	31 (9)
Type 2 diabetes, n(%)	228 (17%)	19 (17%)
Weekly alcoholic drinks, mean (SD)	3 (7)	4 (8)

MGB, Mass General Brigham; NASH, nonalcoholic steatohepatitis; SD, standard deviation

Supplementary Table 8. Genetic variants used for Mendelian randomization analyses.

SNP	CHR	POS	Effect_allele	CHIP.Beta	CHIP.SE	Cirrhosis.Beta	Cirrhosis.SE	pval.het
rs7705526	chr5	1285859	A	0.26256577	0.02572599	-0.0238	0.0288	0.23183947
rs58322641	chr3	160497760	C	0.14209986	0.02334552	0.0142	0.0251	0.72615368
rs9520550	chr13	107684706	G	-0.2011417	0.03750183	-0.0299	0.05	0.65651629
rs13250317	chr8	135993012	G	0.13128256	0.02610216	0.0066	0.0274	0.95457943
rs7636946	chr3	166887539	C	-0.1506791	0.03094269	0.01	0.0303	0.60054582
rs112963793	chr14	55099311	C	0.54699644	0.11332264	-0.0475	0.1175	0.55815756
rs154978	chr6	32931519	T	-0.1109292	0.02315176	0.0278	0.025	0.19798189
rs28637066	chr17	76249356	C	0.11165055	0.02353426	-0.0342	0.025	0.12223427
rs2538478	chr7	148513385	T	0.1141746	0.02414857	0.0432	0.0278	0.16135139
rs71574228	chr6	107092319	A	-0.2048133	0.04335864	0.0096	0.0569	0.75821714
rs11648858	chr16	85798686	G	-0.2037944	0.04344019	0.0167	0.0559	0.65995317
rs6510126	chr19	58164549	T	-0.1403395	0.03040669	0.0322	0.0321	0.23983917
rs7949595	chr11	79935819	T	0.36800491	0.0800441	0.1413	0.0694	0.06548094
rs2388989	chr12	32337341	A	-0.1266603	0.02762878	0.0143	0.0304	0.52698971
rs1968864	chr15	93309389	A	0.1344106	0.02935602	-0.0161	0.0327	0.51412927
rs9499858	chr6	104406121	C	0.13170943	0.02877552	-0.019	0.0318	0.44777242
rs113554316	chr20	13589476	G	0.48295832	0.10562186	0.0957	0.2315	0.73877523
rs10994735	chr10	61354476	C	-0.1253714	0.02747721	-0.0103	0.0282	0.84532209
rs1963791	chr7	24546024	C	-0.1353832	0.02978164	-0.0391	0.0345	0.32444966
rs12897081	chr14	76845130	T	-0.1831918	0.0407624	-0.0266	0.043	0.64809448
rs17705912	chr3	8244077	G	0.20461226	0.04556538	0.0518	0.0555	0.42739561
rs592236	chr6	140855084	C	0.19457058	0.0433567	0.0495	0.0405	0.29736958
rs57538453	chr16	86960750	C	0.25814129	0.05774208	0.0728	0.0863	0.46549816
rs74055946	chr12	3641529	A	-0.1705324	0.03819864	-0.0032	0.0464	0.94221568

rs2585780	chr11	19954773	T	-0.113483	0.02547936	0.0147	0.0283	0.49928726
rs2618613	chr20	17815547	G	0.11489059	0.02584519	0.0174	0.0258	0.61346131
rs77331144	chr4	28536689	A	0.20125111	0.04533759	0.0162	0.0694	0.90277244
rs2967322	chr16	82268774	T	0.13622168	0.03070137	-0.0172	0.0337	0.50425557
rs72860429	chr11	15255188	C	0.31256012	0.07046951	0.0459	0.063	0.58893556
rs2079661	chr6	105447965	T	-0.1349513	0.03049917	-0.0323	0.0331	0.41125343
rs4241744	chr4	182236160	A	-0.1964009	0.04440433	9.00E-04	0.0572	0.88231159
rs4835780	chr5	138343624	C	0.10444837	0.02367116	0.0306	0.0258	0.30131111
rs1052432	chr5	177137188	A	0.14144794	0.03207036	-0.0093	0.0356	0.67800299
rs9954262	chr18	52296429	C	-0.1791186	0.04071978	0.0394	0.0413	0.26072508
rs143835086	chr15	101528199	T	0.7521186	0.17111201	-0.1932	0.1952	0.25385246
rs76964416	chr5	142146989	G	0.33922682	0.07719557	0.2532	0.0745	0.00121103
rs10044384	chr5	25481466	G	0.12244664	0.02792222	0.0155	0.0305	0.72261817
rs62353215	chr4	166856860	C	0.28071111	0.06428828	0.0136	0.0757	0.97030951
rs6064151	chr20	55018501	A	0.21150262	0.04845254	0.0608	0.0454	0.24405881
rs150778589	chr4	158933035	A	0.43262624	0.09912134	-7.00E-04	0.105	0.86849841
rs2363947	chr3	126568597	A	-0.1273962	0.02919676	-0.0049	0.0323	0.99991929
rs74255875	chr19	51404849	T	0.14871067	0.03417559	0.0306	0.0348	0.47305137
rs142644661	chr11	133736472	A	1.22382938	0.28144091	-0.2305	0.4102	0.49794145
rs146378626	chr5	39172625	A	1.61077172	0.37060471	0.2819	0.4023	0.58336465
rs2159912	chr14	90386317	C	0.14432608	0.03324981	0.0067	0.0396	0.97672344
rs8108135	chr19	53485191	T	0.10106876	0.02329939	-0.0155	0.0269	0.46996064
rs17865343	chr4	117351922	A	-0.173088	0.03991053	0.0135	0.0429	0.63749052
rs11064570	chr12	851177	G	-0.1486108	0.03427246	-0.0017	0.0332	0.90344866
rs75144663	chr2	215905462	T	0.3191598	0.07384028	-0.0153	0.0847	0.74416337
rs116482203	chr5	91033697	G	0.54407045	0.12589004	-0.0195	0.1278	0.75101673
rs57547130	chr2	189047645	G	-0.1406853	0.03263725	0.0123	0.0355	0.61687636

rs1011905	chr6	34241739	T	0.18821351	0.04369006	-6.00E-04	0.0518	0.87948706
rs56205841	chr4	55179348	T	0.22012098	0.05144805	0.0291	0.0562	0.71264334
rs117843939	chr7	15035342	G	0.33516226	0.07837845	0.0576	0.0803	0.57635966
rs4778799	chr15	80484358	A	0.11467422	0.02687444	-0.0422	0.0295	0.11309632
rs77068362	chr10	7999435	G	-0.2121526	0.04979263	-0.1601	0.1249	0.2235293
rs11127654	chr3	79663831	C	0.10845305	0.02549993	0.0358	0.0267	0.23468166
rs72873061	chr3	60994629	C	0.29194572	0.06864904	0.1081	0.1246	0.43638108
rs118083311	chr1	87128705	T	0.30956454	0.07281472	0.0308	0.0762	0.80349973
rs148795020	chr16	77329939	A	1.33020752	0.31313131	-0.128	0.4229	0.67130087
rs141473570	chr8	22763037	T	1.04299003	0.24610628	0.3676	0.226	0.14567061
rs4961467	chr9	16229249	T	0.10679923	0.02525512	0.0238	0.0257	0.44198901
rs140919813	chr11	127696291	T	0.43271319	0.10235938	0.2642	0.1099	0.02386761
rs151165594	chr10	3629297	G	0.31023936	0.07374134	-0.0298	0.0756	0.57980563
rs4814402	chr20	236640	A	0.10050288	0.02390093	0.0352	0.0253	0.21412458
rs6595950	chr5	130505172	G	-0.1980934	0.04711747	0.0926	0.0981	0.30662267
rs9900036	chr17	4835866	G	0.10128079	0.02413117	0.0145	0.0263	0.6858902
rs6983251	chr8	124020363	T	-0.0983436	0.02345442	0.0133	0.0267	0.5213026
rs11742154	chr5	168186539	G	-0.1096793	0.02615845	0.0314	0.0257	0.1643487
rs12497942	chr3	14344401	A	0.15642605	0.03732514	0.0016	0.0392	0.91010686
rs73762686	chr5	74300470	T	-0.1571639	0.03750286	-0.011	0.0428	0.9075251
rs12451733	chr17	974413	T	0.14560123	0.03478938	0.0187	0.0456	0.77341591
rs11822751	chr11	26573092	T	-0.2556086	0.06108122	0.2279	0.1222	0.05153757
rs76174129	chr16	79727458	G	-0.3856515	0.09248725	-0.0261	0.1146	0.92144772
rs1353341	chr1	4312932	A	0.17386636	0.04177042	0.0711	0.049	0.18758567
rs1077878	chr2	2718084	A	-0.1065204	0.02559181	0.0511	0.0286	0.05299995
rs2445304	chr11	5017286	G	0.09653849	0.02324722	-0.0159	0.025	0.43149655
rs6584278	chr10	99518342	T	0.09906691	0.02389262	-0.0234	0.0257	0.28839962

rs7555835	chr1	164668543	T	0.30988711	0.07474407	0.0631	0.0999	0.60772081
rs2281566	chr20	63261160	A	-0.1028816	0.02481862	-0.0204	0.0295	0.57632977
rs335407	chr6	155344307	T	-0.2510662	0.06063142	0.063	0.0737	0.32319531
rs78801578	chr17	2086134	C	0.18926252	0.04571514	0.0095	0.045	0.96042828
rs6869328	chr5	81085345	C	0.16815796	0.04062679	0.038	0.0461	0.49283589
rs10732707	chr10	132880491	A	-0.0969731	0.02343134	0.0193	0.0273	0.39783173
rs10118399	chr9	71481590	G	0.11461873	0.0277175	0.1073	0.0343	0.00264579
rs10095665	chr8	6333439	G	0.12843788	0.03106594	0.0246	0.0342	0.56429251
rs73594788	chr11	121386774	C	-0.1961537	0.04747648	-0.1297	0.0917	0.18242637
rs2661384	chr3	21331417	A	0.12153072	0.02943797	-0.0233	0.029	0.33318145
rs1441470	chr2	140665747	C	-0.1254065	0.03037792	0.0108	0.0378	0.67880692
rs17007563	chr2	71884812	T	-0.1909729	0.04635323	0.0117	0.0675	0.77755565
rs7795417	chr7	11831085	A	0.11140423	0.0271337	-0.0185	0.0275	0.40597101
rs9613021	chr22	25786592	T	-0.1016146	0.02477397	0.0017	0.0274	0.83747766
rs72858963	chr2	129709273	A	0.21997493	0.05366024	0.0684	0.0631	0.34100907
rs745098	chr5	68764409	C	0.14566353	0.03555132	0.0029	0.0444	0.95143166
rs61783495	chr1	99324370	A	0.11466031	0.02799376	0.0063	0.028	0.94593406
rs75584603	chr7	27225099	C	0.36347976	0.08875512	0.0849	0.0915	0.43687116
rs61183515	chr15	54883424	C	0.12364042	0.03019452	-0.0404	0.0321	0.15837635
rs116868446	chr11	114762354	C	0.24714239	0.06052222	0.0082	0.0628	0.98344331
rs17006345	chr1	219691632	G	0.23878031	0.05849909	-0.0932	0.0644	0.11097123
rs927330	chr6	135810618	T	0.10034721	0.02459353	0.0108	0.0273	0.79874761
rs138533438	chr12	15617615	T	0.87849461	0.21542652	-0.0349	0.5778	0.90535976
rs7184533	chr16	60712423	G	0.16327066	0.04003906	-5.00E-04	0.0742	0.92717534
rs74767296	chr3	156629610	A	0.29218115	0.07173552	0.1785	0.0681	0.01371008
rs12436948	chr14	22140460	C	0.11060075	0.02719819	0.0327	0.0296	0.33522646
rs4470166	chr16	62197815	T	-0.1065662	0.02621698	-0.0093	0.0281	0.85268415

rs56243125	chr12	30963552	T	0.14466982	0.0355951	-0.0051	0.0342	0.75445589
rs8108710	chr19	2745531	G	0.1061049	0.02614214	-0.0084	0.0314	0.69044186
rs11264048	chr1	37436514	G	0.09544665	0.02351665	-0.0288	0.0251	0.19459604
rs73239895	chr17	7050239	T	-0.264467	0.06516789	0.0658	0.1418	0.59190862
rs62167014	chr2	120690646	A	0.15984553	0.03940261	0.0066	0.0515	0.99292253
rs2049553	chr2	52460568	A	0.11179721	0.02756533	0.0197	0.0299	0.6055028
rs72912392	chr18	47879275	G	0.72398365	0.17859821	0.1743	0.1722	0.39341969
rs1925919	chr6	6878657	A	0.10259714	0.02533435	0.0044	0.0258	0.9858422
rs76566774	chr17	70966776	G	0.15514036	0.03831688	0.0282	0.0378	0.55509201
rs7011923	chr8	106201761	G	0.10499014	0.0259317	0.044	0.0286	0.16124072
rs1279331	chr14	33106688	T	0.09588521	0.02368546	-0.0252	0.0251	0.24850547
rs139897249	chr12	60096759	A	0.65867769	0.16283752	0.3217	0.1357	0.02824747
rs1050909	chr8	469368	T	-0.1021671	0.02526079	0.013	0.028	0.54447893
rs55746901	chr6	152198774	C	-0.1520812	0.03761363	0.006	0.0526	0.82154726
rs247829	chr16	84548514	C	0.1072712	0.0265419	0.0164	0.027	0.64835336
rs144565704	chr13	28862556	C	0.41042574	0.10157898	0.08	0.105	0.53959569
rs11611740	chr12	90923067	T	-0.1227043	0.03038545	-0.031	0.0291	0.36480415
rs10816846	chr9	109646263	C	0.14477809	0.0358563	0.0037	0.035	0.95737049
rs77519543	chr6	69830497	A	0.40655384	0.10069489	0.1766	0.0864	0.06135683
rs6100832	chr20	60250439	A	-0.2902106	0.07190905	-0.1525	0.1346	0.29324442
rs10969441	chr9	29900227	A	0.16522827	0.04097691	0.0722	0.0565	0.24306988
rs11659919	chr18	78156222	A	0.09435645	0.02342511	-0.0119	0.0253	0.53834528
rs11897424	chr2	11016153	C	-0.0951714	0.02363728	-0.0382	0.0254	0.17271931
rs78039770	chr12	109362380	T	0.45708991	0.11357504	0	0.1459	0.90397439
rs10179302	chr2	39354518	C	0.12679484	0.0315122	0.074	0.0404	0.08648758
rs10268214	chr7	46285920	C	0.12002075	0.02983476	-0.0106	0.0352	0.66491178
rs73016184	chr6	147737833	G	-0.1300987	0.03237578	-0.0157	0.0383	0.77950457

rs58028036	chr19	16034613	G	-0.2053458	0.0511444	-0.0417	0.09	0.70691513
rs11621256	chr14	98955293	T	0.10873479	0.02708657	-0.0204	0.0297	0.40671806
rs55774549	chr7	89231067	G	-0.1022214	0.02547321	-0.0159	0.0273	0.66018748
rs73244753	chr5	113220707	G	-0.1534509	0.0382476	-0.0269	0.0515	0.68291863
rs62079882	chr18	10130589	G	-0.1235745	0.03082083	0.0175	0.0309	0.47015114
rs150150078	chr2	46679261	C	0.3810169	0.09505278	0.0146	0.119	0.99969641
rs4971548	chr2	20697776	G	-0.1420598	0.0354449	0.0042	0.0412	0.81420835
rs61932730	chr12	74533902	C	0.13551742	0.03386732	-0.0525	0.0363	0.11094588
rs7104475	chr11	81781607	C	-0.0941108	0.02353658	-0.0228	0.025	0.44168136
rs2239206	chr12	120238287	A	0.09952729	0.0248933	-0.0147	0.025	0.45733753
rs3905902	chr3	11984305	A	0.13722115	0.03436621	0.0218	0.0495	0.73812765
rs4935413	chr10	53276387	C	0.2228026	0.05582528	-0.1144	0.0865	0.15464252
rs8001898	chr13	44032411	T	0.10057805	0.02522597	0.0173	0.0283	0.63419363
rs140481838	chr1	176898177	A	-0.3442444	0.0863649	-0.0903	0.0884	0.38195101
rs10997266	chr10	66626827	T	0.09402046	0.02359735	-9.00E-04	0.0256	0.85968763
rs111400910	chr1	157843742	A	0.558159	0.14010689	0.1688	0.1664	0.3748795
rs1144986	chr5	147883415	G	0.10897161	0.02736483	0.0416	0.0271	0.16614146
rs6569619	chr6	129676740	G	0.09337452	0.02346818	-0.0551	0.0252	0.01954545
rs11973042	chr7	13489838	A	-0.1215159	0.03055876	0.0111	0.0403	0.69505582
rs10144740	chr14	43794338	A	0.09376311	0.02359145	0.0304	0.0252	0.28637369
rs55823910	chr1	246683479	G	0.10841938	0.02728156	-0.009	0.0294	0.65341937
rs55641075	chr5	89781846	T	0.10959336	0.02757704	0.0075	0.0271	0.90314757
rs140804866	chr8	62039202	G	0.3899505	0.0981827	0.0072	0.099	0.93710994
rs10745289	chr10	48926221	T	-0.0958245	0.0241571	0.0494	0.0256	0.03761338
rs141515873	chr10	11142567	T	0.2171518	0.05475507	0.1011	0.0602	0.12245925
rs71632376	chr1	168699771	T	0.34264556	0.08641107	-0.0161	0.0739	0.6908591
rs2187416	chr18	54975128	A	-0.1120015	0.02826269	0.0308	0.028	0.20855944

rs61957178	chr13	73421057	T	-0.1196143	0.03018385	-0.0151	0.0337	0.75474927
rs1023780	chr15	98289869	T	-0.1317882	0.03327313	0.0047	0.0358	0.78448571
rs116993813	chr14	80680034	A	0.39817787	0.10063233	-0.1509	0.1131	0.14075843
rs145475731	chr4	8074008	T	-0.2311921	0.05857881	0.0352	0.0584	0.44896839
rs1294715	chr20	5828048	G	-0.1166582	0.02956472	0.0255	0.0315	0.33991386
rs7801635	chr7	57537269	G	0.12537764	0.03180371	-0.0093	0.0308	0.64562534
rs7420256	chr2	240228496	G	-0.1017626	0.02582147	0.0033	0.0292	0.80449553
rs72679932	chr1	110535007	G	0.14306241	0.03632385	-0.0136	0.0389	0.62255897
rs878035	chr13	106426937	A	0.21888415	0.05558832	-0.0047	0.054	0.80754718
rs4725269	chr7	10320787	T	-0.0927101	0.0235648	0.0244	0.025	0.26209989
rs2696141	chr9	130878712	A	0.13318501	0.03387357	-0.0681	0.0418	0.07925806
rs12293674	chr11	130834614	C	-0.2121921	0.05398677	0.0245	0.0719	0.64915804
rs3058639	chr20	19486199	C	0.10337832	0.02630492	-0.0263	0.0282	0.28181481
rs17736652	chr2	146260968	G	-0.1213052	0.03087225	-0.0648	0.0321	0.06031481
rs60256580	chr12	92447211	C	-0.1631152	0.0415454	-0.1192	0.0579	0.05077788
rs10842580	chr12	25560368	A	-0.1214582	0.03094027	-0.056	0.1113	0.64458149
rs7032591	chr9	78318642	C	-0.0958795	0.0244386	-0.0083	0.0252	0.85431019
rs12757342	chr1	3292266	G	-0.2093941	0.05340236	0.0282	0.0546	0.50558103
rs6935498	chr6	115404482	G	-0.1856988	0.04736146	0.1059	0.0625	0.07004635
rs28856324	chr1	81247214	C	-0.1751792	0.04469831	0.07	0.0532	0.14837249
rs2328868	chr6	25212672	T	-0.190212	0.04853889	0.0309	0.116	0.7417223
rs11041877	chr11	8318306	A	-0.0912097	0.02327609	-0.0187	0.0251	0.54394876
rs499827	chr20	3623800	G	-0.1164606	0.0297258	0.0777	0.0298	0.00568278
rs77825133	chr5	94705888	C	0.42631139	0.10885621	-0.1997	0.1218	0.07537035
rs744877	chr1	145720709	A	-0.0917231	0.02342217	-0.011	0.0253	0.7671047

Supplementary Table 9. Mendelian randomization analyses of CHIP associations with chronic liver disease.

Mendelian randomization analysis	P-value threshold to select variants	Number of Variants	OR (95% CI)	p-value	P-heterogeneity
Observational	NA	NA	2.59 (1.65, 4.05)	$3x10^{-5}$	NA
MR-RAPS, primary analysis	p<0.0001	184	2.37 (1.57, 3.6)	$4x10^{-5}$	0.37
MR-RAPS	p<0.001	824	2.05 (1.44, 2.91)	$6x10^{-5}$	0.83
MR-RAPS	p<0.00005	90	2.34 (0.97, 5.67)	0.06	0.87
MR-RAPS excluding pleiotropic SNPs	p<0.00005	63	4.2 (1.14, 15.4)	0.03	0.56
IVW	p<0.0001	184	2.44 (1.29, 4.61)	0.007	0.44
MR-Egger	p<0.0001	184	20.4 (4.04, 103)	0.0004	0.008
MR-PRESSO	p<0.0001	184	2.45 (1.3, 4.59)	0.006	0.49
Multivariate IVW	p<0.0001	184	2.56 (1.41, 4.63)	0.002	0.08
IVW	p<0.00005	90	2.25 (0.985, 5.14)	0.06	0.45
MR-Egger	p<0.00005	90	11.2 (1.38, 91.4)	0.02	0.11
MR-PRESSO	p<0.00005	90	2.25 (0.996, 5.08)	0.05	0.631
Median regression MR	p<0.0001	184	1.79 (0.89, 3.61)	0.1	0.52

Number of variants refers to the number of SNPs used in the Mendelian randomization score. IVW, inverse variance weighted regression; MR, Mendelian randomization; MR-RAPS, Mendelian randomization with adjusted profile score; MR-PRESSO, Mendelian randomization Pleiotropy RESidual Sum and Outlier

Supplementary Table 10. Phenome-wide Mendelian randomization analysis of CHIP with potential confounding risk factors.

Outcome	N	Effect (CI), SD	P-value
Type 2 diabetes	62,892 cases, 596,424 controls	-0.09 (-0.46 , 0.29)	0.66
Glycated hemoglobin	146806	0.07 (0.02 , 0.12)	0.004
Total cholesterol	187365	-0.08 (-0.34 , 0.17)	0.54
HDL cholesterol	403943	-0.06 (-0.17 , 0.05)	0.28
LDL cholesterol	440546	-0.02 (-0.11 , 0.07)	0.69
Triglycerides	441016	-0.03 (-0.11 , 0.05)	0.45
C-Reactive protein	204402	-0.05 (-0.21 , 0.12)	0.57
Systolic blood pressure	757601	-0.03 (-1.64 , 1.58)	0.47
Diastolic blood pressure	757601	-0.03 (-0.97 , 0.91)	0.53
Body mass index	681275	0.06 (-0.09 , 0.21)	0.42
Current tobacco smoking, categorical	337030	0.03 (-0.02 , 0.08)	0.20
Current alcohol use	23807 cases, 360726 controls	1.01 (0.98 , 1.03)	0.61

MR analysis was performed using MR Base platform. Estimates were derived using inverse variance weighted meta-analysis using 90 independent variants associated with CHIP with $p<5x10^{-5}$.

Supplementary Table 11. Histologic grading criteria for steatohepatitis in mice.

Steatosis	
Grade 0	Absent
Grade 1	< 33% of hepatocytes
Grade 2	33-66% of hepatocytes
Grade 3	> 66% of hepatocytes
Inflammation	
Grade 0	Absent
Grade 1	< 100 inflammatory cells per focus or < 3 inflammatory foci per 20x field
Grade 2	100-500 inflammatory cells per focus or 3 - 4 inflammatory foci per 20x field
Grade 3	> 500 inflammatory cells per focus or > 5 inflammatory foci per 20x field
Hepatocyte Injury/Ballooning	
Grade 0	Absent
Grade 1	Rare balloon cells
Grade 2	Widespread hepatocyte ballooning and apoptosis
Modified NASH activity score (NAS)	
Grade 1	0-2 points
Grade 2	3-4 points
Grade 3	> 5 points

Modified from NASH Clinical Research Network scoring system for NAFLD[35].

Supplementary Table 12. CHIP variants ascertained through whole-exome sequencing.

Gene name	Reported mutations used for variant calling	Accession
ASXL1	Frameshift/nonsense/splice-site in exon 11-12	NM_015338
ASXL2	Frameshift/nonsense/splice-site in exon 11-12	NM_018263
BCOR	Frameshift/nonsense/splice-site	NM_001123385
BCORL1	Frameshift/nonsense/splice-site	NM_021946
BRAF	G464E, G464V, G466E, G466V, G469R, G469E, G469A, G469V, V471F, V472S, L485W, N581S, I582M, I592M, I592V, D594N, D594G, D594V, D594E, F595L, F595S, G596R, L597V, L597S, L597Q, L597R, A598V, V600M, V600L, V600K, V600R, V600E, V600A, V600G, V600D, K601E, K601N, R603*, W604R, W604G, S605G, S605F, S605N, G606E, G606A, G606V, H608R, H608L, G615R, S616P, S616F, L618S, L618W	NM_004333
BRCC3	Frameshift/nonsense/splice-site	NM_024332
CBL	RING finger missense p.381-421	NM_005188
CBLB	RING finger missense p.372-412	NM_170662
CEBPA	Frameshift/nonsense/splice-site	NM_004364
CREBBP	Frameshift/nonsense/splice-site, D1435E, R1446L, R1446H, R1446C, Y1450C, P1476R, Y1482H, H1487Y, W1502C, Y1503D, Y1503H, Y1503F, S1680del	NM_004380
CSF1R	L301F, L301S, Y969C, Y969N, Y969F, Y969H, Y969D	NM_005211
CSF3R	T615A, T618I, truncating c.741-791	NM_000760
CTCF	Frameshift/nonsense, R377C, R377H, P378A, P378L	NM_006565
CUX1	Frameshift/nonsense	NM_181552
DNMT3A	Frameshift/nonsense/splice-site, F290I, F290C, V296M, P307S, P307R, R326H, R326L, R326C, R326S, G332R, G332E, V339A, V339M, V339G, L344Q, L344P, R366P, R366H, R366G, A368T, A368V, R379H, R379C, I407T, I407N, I407S, F414L,	NM_022552

	F414S, F414C, A462V, K468R, C497G, C497Y, Q527H, Q527P, Y533C, S535F, C537G, C537R, G543A, G543S, G543C, L547H, L547P, L547F, M548I, M548K, G550R, W581R, W581G, W581C, R604Q, R604W, R635W, R635Q, S638F, G646V, G646E, L653W, L653F, I655N, V657A, V657M, R659H, Y660C, V665G, V665L, M674V, R676W, R676Q, G685R, G685E, G685A, D686Y, D686G, R688H, G699R, G699S, G699D, P700L, P700S, P700R, P700Q, P700T, P700A, D702N, D702Y, V704M, V704G, I705F, I705T, I705S, I705N, G707D, G707V, C710S, C710Y, S714C, V716D, V716F, V716I, N717S, N717I, P718L, R720H, R720G, K721R, K721T, Y724C, R729Q, R729W, R729G, F731C, F731L, F731Y, F731I, F732del, F732C, F732S, F732L, E733G, E733A, F734L, F734C, Y735C, Y735N, Y735S, R736H, R736C, R736P, L737H, L737V, L737F, L737R, A741V, P742P, P743R, P743L, R749C, R749L, R749H, R749G, F751L, F751C, F752del, F752C, F752L, F752I, F752V, W753G, W753C, W753R, L754P, L754R, L754H, F755S, F755I, F755L, M761I, M761V, G762C, V763I, S770L, S770W, S770P, R771Q, F772I, F772V, L773R, L773V, E774K, E774D, E774G, I780T, D781G, R792H, W795C, W795L, G796D, G796V, N797Y, N797H, N797S, P799S, P799R, P799H, R803S, R803W, P804L, P804S, K826R, S828N, K829R, T835M, N838D, K841Q, Q842E, P849L, D857N, W860R, E863D, F868S, G869S, G869V, M880V, S881R, S881I, R882H, R882P, R882C, R882G, A884P, A884V, Q886R, L889P, L889R, G890D, G890R, G890S, V895M, P896L, V897G, V897D, R899L, R899H, R899C, L901R, L901H, P904L, F909C, P904Q, A910P, C911R, C911Y	
EED	Frameshift/nonsense/splice-site, L240Q, I363M	NM_003797
EP300	Frameshift/nonsense/splice_site, VF1148_1149del, D1399N, D1399Y, P1452L, Y1467N, Y1467H, Y1467C, R1627W, A1629V	NM_001429
ETNK1	N244S, N244T, N244K	NM_018638
ETV6	Frameshift/nonsense/splice-site	NM_001987

EZH2	Frameshift/nonsense/splice-site, Q62R, N102S, F145S, F145C, F145Y, F145L, G159R, E164D, R202Q, K238E, E244K, R283Q, H292R, P488S, R497Q, R561H, T568I, K629E, Y641N, Y641H, Y641S, Y641C, Y641F, D659Y, D659G, V674M, A677G, A677V, R679C, R679H, R685C, R685H, A687V, N688I, N688K, H689Y, S690P, I708V, I708T, I708M, E720K, E740K	NM_001203247
FLT3	V579A, V592A, V592I, F594L, FY590-591GD, D835Y, D835H, D835E, del835	NM_004119
GATA1	Frameshift/nonsense/splice-site	NM_002049
GATA2	Frameshift/nonsense/splice-site, R293Q, N317H, A318T, A318V, A318G, G320D, L321P, L321F, L321V, Q328P, R330Q, R361L, L359V, A372T, R384G, R384K	NM_001145661
GATA3	Frameshift/nonsense/splice-site ZNF domain, R276W, R276Q, N286T, L348V,	NM_001002295
GNA13	I34T, G57S, S62F, M68K, Q134R, Y145F, L152F, E167D, Q169H, R264H, E273K, V322G, V362G, L371F	NM_006572
GNAS	R201S, R201C, R201H, R201L, Q227K, Q227R, Q227L, Q227H, R374C	NM_000516
GNB1	K57N, K57M, K57E, K57T, I80T, I80N	NM_002074
IDH1	R132C, R132G, R132H, R132L, R132P, R132V, V178I	NM_005896
IDH2	R140W, R140Q, R140L, R140G, R172W, R172G, R172K, R172T, R172M, R172N, R172S	NM_002168
IKZF1	Frameshift/nonsense	NM_006060
IKZF2	Frameshift/nonsense	NM_016260
IKZF3	Frameshift/nonsense	NM_012481
JAK1	T478A, T478S, V623A, A634D, L653F, R724H, R724Q, R724P, T782M, L783F	NM_002227
JAK2	N533D, N533Y, N533S, H538R, K539E, K539L, I540T, I540V, V617F, R683S, R683G, del/ins537-539L,	NM_004972

	del/ins538-539L, del/ins540-543MK, del/ins540-544MK, del/ins541-543K, del542-543, del543-544, ins11546-547	
JAK3	M511T, M511I, A572V, A572T, A573V, R657Q, V715I, V715A	NM_000215
KDM6A	Frameshift/nonsense/splice-site, del419	NM_021140
KIT	ins503, V559A, V559D, V559G, V559I, V560D, V560A, V560G, V560E, del560, E561K, del579, P627L, P627T, R634W, K642E, K642Q, V654A, V654E, H697Y, H697D, E761D, K807R, D816H, D816Y, D816F, D816I, D816V, D816H, del551-559	NM_000222
KRAS	G12D, G12A, G12E, G12V, G13D, G13C, G13Y, G13F, G13R, G13A, G13V, G13E, V14I, T58I, G60D, G60A, G60V, Q61K, Q61E, Q61P, Q61R, Q61L, Q61H, K117E, K117N, A146T, A146P, A146V	NM_033360
LUC7L2	Frameshift/nonsense/splice-site	NM_016019
MLL	Frameshift/nonsense	NM_005933
MLL2	Frameshift/nonsense	NM_003482
MPL	S505G, S505N, S505C, L510P, del513, W515A, W515R, W515K, W515S, W515L, A519T, A519V, Y591D, W515-518KT	NM_005373
NF1	Frameshift/nonsense	NM_000267
NPM1	Frameshift p.W288fs (insertion at c.859_860, 860_861, 862_863, 863_864)	NM_002520
NRAS	G12S, G12R, G12C, G12N, G12P, G12Y, G12D, G12A, G12V, G12E, G13S, G13R, G13C, G13N, G13P, G13Y, G13D, G13A, G13V, G13E, G60E, G60R, Q61R, Q61L, Q61K, Q61P, Q61H, Q61Q	NM_002524
PDS5B	Frameshift/nonsense/splice-site, R1292Q	NM_015032
PDSS2	Frameshift/nonsense	NM_020381
PHF6	Frameshift/nonsense/splice-site, A40D, M125I, S246Y, F263L, R274Q, C297Y, H302Y, H329L	NM_001015877

PHIP	Frameshift/nonsense/splice-site	NM_017934
PPM1D	Frameshift/nonsense, exon 5 or 6	NM_003620
PRPF40B	Frameshift/nonsense/splice-site, P15H, M58I, P405L, P562S,	NM_001031698
PRPF8	M1307I, C1594W, D1598Y, D1598N, D1598V	NM_006445
PTEN	Frameshift/nonsense/splice-site, D24G, R47G, F56V, L57W, H61R, K66N, Y68H, C71Y, F81C, Y88C, D92G, D92V, D92E, H93Y, H93D, H93Q, N94I, P95L, I101T, C105F, C105S, D107Y, L112V, H123Y, C124R, C124S, K125E, A126D, K128N, R130G, R130Q, R130L, G132D, I135V, I135K, C136R, C136F, K144Q, A151T, D153Y, D153N, Y155H, Y155C, R159K, R159S, R161K, R161I, G165R, G165E, S170N, S170I, R173C, Y174D, Y177C, H196Y, R234W, G251C, D252Y, F271S, D326G	NM_000314
PTPN11	G60V, G60R, G60A, D61Y, D61V, D61G, Y63C, E69K, E69G, E69D, E69Q, F71L, F71K, A72T, A72V, A72D, T73I, E76K, E76Q, E76M, E76A, E76G, E139G, E139D, N308D, N308T, N339S, P491L, S502P, S502A, S502L, G503V, G503G, G503A, G503E, Q506P, T507A, T507K	NM_002834
RAD21	Frameshift/nonsense/splice-site, R65Q, H208R, Q474R	NM_006265
RUNX1	Frameshift/nonsense/splice-site, S73F, H78Q, H78L, R80C, R80P, R80H, L85Q, P86L, P86H, S114L, D133Y, L134P, R135G, R135K, R135S, R139Q, R142S, A165V, R174Q, R177L, R177Q, A224T, D171G, D171V, D171N, R205W, R223C	NM_001001890
SETBP1	D868N, D868T, S869N, G870S, I871T, D880N, D880Q	NM_015559
SETD2	Frameshift/nonsense, V1190M	NM_014159
SETDB1	Frameshift/nonsense, K715E	NM_001145415
SF1	Frameshift/nonsense/splice-site, T454M, Y476C, A508G	NM_004630
SF3A1	Frameshift/nonsense/splice-site, A57S, M117I, K166T, Y271C	NM_005877

SF3B1	G347V, R387W, R387Q, E592K, E622D, Y623C, R625L, R625C, R625G, H662Q, H662D, T663I, K666N, K666T, K666E, K666R, K700E, V701F, A708T, G740R, G740E, A744P, D781G, E783K, R831Q, L833F, E862K, R957Q	NM_012433
SRSF2	Y44H, P95H, P95L, P95T, P95R, P95A, P107H, P95fs	NM_003016
SMC1A	K190T, R586W, M689V, R807H, R1090H, R1090C	NM_006306
SMC3	Frameshift/nonsense, R155I, Q367E, D392V, K571R, R661P, G662C	NM_005445
STAG1	Frameshift/nonsense/splice-site, H1085Y	NM_005862
STAG2	Frameshift/nonsense/splice-site	NM_006603
SUZ12	Frameshift/nonsense	NM_015355
TET2	Frameshift/nonsense/splice-site, missense mutations in catalytic domains (p.1104-1481 and 1843-2002)	NM_001127208
TP53	Frameshift/nonsense/splice-site, S46F, G105C, G105R, G105D, G108S, G108C, R110L, R110C, T118A, T118R, T118I, S127F, S127Y, L130V, L130F, K132Q, K132E, K132W, K132R, K132M, K132N, F134V. F134L, F134S, C135W, C135S, C135F, C135G, C135Y, Q136K, Q136E, Q136P, Q136R, Q136L, Q136H, A138P, A138V, A138A, A138T, T140I, C141R, C141G, C141A, C141Y, C141S, C141F, C141W, V143M, V143A, V143E, L145Q, W146C, W146L, L145R, V147G, P151T, P151A, P151S, P151H, P151R, P152S, P152R, P152L, T155P, T155A, V157F, R158H, R158L, A159V, A159P, A159S, A159D, A161T, A161D, Y163N, Y163H, Y163D, Y163S, Y163C, K164E, K164M, K164N, K164P, H168Y, H168P, H168R, H168L, H168Q, M169I, M169T, M169V, E171K, E171Q, E171G, E171A, E171V, E171D, V172D, V173M, V173L, V173G, R174W, R175G, R175C, R175H, C176R, C176G, C176Y, C176F, C176S, P177R, P177R, P177L, H178D, H178P, H178Q, H179Y, H179R, H179Q, R181C, R181Y, D186G, G187S, P190L, P190T, H193N, H193P, H193L, H193R, L194F, L194R, I195F, I195N, I195T, R196P, V197L, G199V, Y205N, Y205C, Y205H,	NM_001126112

	D208V, R213Q, R213P, R213L, R213Q, H214D, H214R, S215G, S215I, S215R, V216M, V217G, Y220N, Y220H, Y220S, Y220C, E224D, I232F, I232N, I232T, I232S, Y234N, Y234H, Y234S, Y234C, Y236N, Y236H, Y236C, M237V, M237K, M237I, C238R, C238G, C238Y, C238W, N239T, N239S, S241Y, S241C, S241F, C242G, C242Y, C242S, C242F, G244S, G244C, G244D, G245S, G245R, G245C, G245D, G245A, G245V, G245S, M246V, M246K, M246R, M246I, N247I, R248W, R248G, R248Q, R249G, R249W, R249T, R249M, P250L, I251N, L252P, I254S, I255F, I255N, I255S, L257Q, L257P, E258K, E258Q, D259Y, S261T, G262D, G262V, L265P, G266R, G266E, G266V, R267W, R267Q, R267P, E271K, V272M, V272L, R273S, R273G, R273C, R273H, R273P, R273L, V274F, V274D, V274A, V274G, V274L, C275Y, C275S, C275F, A276P, C277F, C277Y, P278T, P278A, P278S, P278H, P278R, P278L, G279E, R280G, R280K, R280T, R280I, R280S, D281N, D281H, D281Y, D281G, D281E, R282G, R282W, R282Q, R282P, E285K, E285V, E286G, E286V, E286K, K320N, L330R, G334V, R337C, R337L, A347T, L348F, T377P	
U2AF1	D14G, S34F, S34Y, R35L, R156H, R156Q, Q157R, Q157P	NM_006758
U2AF2	R18W, Q143L, M144I, L187V, Q190L	NM_007279
WT1	Frameshift/nonsense/splice-site	NM_024426
ZRSR2	Frameshift/nonsense, R126P, E133G, C181F, H191Y, I202N, F239V, F239Y, N261Y, C280R, C302R, C326R, H330R, N382K	NM_005089

Supplementary Table 13. STROBE-MR guidelines checklist.

Item No.	Section	Checklist item	Page No.	Comment
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	**3**	**As MR is one of several analyses in the study, we have not included it in the study title. However, it is described in the abstract.**
	INTRODUCTION			
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question	**4**	
3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	**26**	
	METHODS			
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:	**Table 1**	
	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	**Table 1**	
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis	**Table 1**	
	c)	Describe measurement, quality control and selection of genetic variants	**26**	
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	**22-23, Supp Table 1,3**	
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	**24**	
5	**Assumptions**	Explicitly state the three core IV assumptions for the main analysis (relevance, independence	**26**	

		and exclusion restriction) as well assumptions for any additional or sensitivity analysis		
6	**Statistical methods: main analysis**	Describe statistical methods and statistics used	**26**	
	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	**7**	
	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	**7**	
	c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	**7**	
	d)	Explain how missing data were addressed	**7**	
	e)	If applicable, indicate how multiple testing was addressed	**NA**	
7	**Assessment of assumptions**	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	**7**	
8	**Sensitivity analyses and additional analyses**	Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	**7**	
9	**Software and pre-registration**			
	a)	Name statistical software and package(s), including version and settings used	**27**	
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	**NA**	
	RESULTS			
10	**Descriptive data**			
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	**Table 1**	
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	**Table 1**	

	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	**NA**	
	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	**27**	
11	**Main results**			
	a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	**Supp Table 6**	
	b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	**7**	
	c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**Extended Fig 2**	
	d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	**Extended Fig 4A**	
12	**Assessment of assumptions**			
	a)	Report the assessment of the validity of the assumptions	**7**	
	b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	**7**	
13	**Sensitivity analyses and additional analyses**			
	a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	**7**	
	b)	Report results from other sensitivity analyses or additional analyses	**7**	
	c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	**7**	

	d)	When relevant, report and compare with estimates from non-MR analyses	**7**	
	e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	**7**	
	DISCUSSION			
14	**Key results**	Summarize key results with reference to study objectives	**10**	
15	**Limitations**	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	**10**	
16	**Interpretation**			
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	**10**	
	b)	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	**10**	
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	**10**	
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	**10**	
	OTHER			
18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	**28**	
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	**28**	
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	**29**	

Supplementary Table 14. TOPMed Omics Support Table.

TOPMed Accession	TOPMed Project	Parent Study	TOPMed Phase	Omics Center	Omics Support	Omics Type
phs000974	AFGen	FHS AFGen	1	Broad Genomics	3R01HL092577-06S1	WGS
phs000974	FHS	FHS	pilot; 4.5	NWGC	HHSN268201600032I	RNASeq
phs000974	FHS	FHS	5	NWGC	HHSN268201600032I	RNASeq
phs000974	FHS	FHS	pilot; 4.5	Broad BIDMC Proteomics	HHSN268201600034I	Proteomics
phs000974	FHS	FHS	5	Broad Metabolomics	HHSN268201600034I	Metabolomics
phs000974	FHS	FHS	5	Keck MGC	HHSN268201600038I	Methylomics
phs000974	FHS	FHS	1	Broad Genomics	3U54HG003067-12S2	WGS