Supplementary Note

For conditional analysis and fine-mapping we used an LD reference panel consisting of 10,000 randomly selected individuals of European ancestry from UK Biobank. To check that this LD panel is suitable, we performed conditional analysis with GCTA on both the IGAP study (Kunkle et al. 2019) and on our meta-analysis (Kunkle et al. + UK Biobank GWAX). Because the Kunkle et al. study has lower power, we do not expect to detect as many independent signals as in the meta-analysis. The table below shows the independent signals detected with GCTA at a threshold of $p<10^{-5}$ in each dataset. Lines absent in the Kunkle-only dataset had no SNP with $p<10^{-5}$ in their discovery stage summary statistics.

		Kunkle + UKB meta				Kunkle	
Chr	**Lead SNP pos**	**Lead p**	**Indep SNPs**	**N snps**	**N snps**	**lead_p**	**SNPs**
1	161,155,392	4.30E-08	rs4575098	1			
1	207,750,568	1.40E-23	rs679515	1	1	1.72E-16	rs679515
2	65,608,363	1.54E-08	rs268134	1			
2	106,366,056	1.28E-12	rs143080277 rs116038905	2			
2	127,892,810	1.10E-54	rs7584040 rs6733839	2	2	4.11E-28	rs34745987 rs6733839
2	135,372,951	5.24E-08	rs35564151	1			
2	233,981,912	1.41E-10	rs10933431	1	1	2.47E-07	rs10933431
4	11,027,619	2.59E-11	rs4351014	1			
6	32,560,025	2.88E-15	rs36096565	1	2	3.98E-07	rs3132963 rs112742095
6	40,942,196	1.83E-23	rs187370608 rs114812713 rs3857580	3	3	2.91E-12	rs192675224 rs114812713 rs75932628
6	47,595,155	1.11E-11	rs1385742	1	1	2.41E-08	rs1385742
7	50,270,105	7.68E-08	rs2168589	1	1	3.34E-06	rs11423121
7	99,971,834	3.28E-18	rs1859788	1			
7	143,107,588	9.63E-12	rs12703526 rs10265814	2	1	1.62E-08	rs11767557
8	27,468,503	7.71E-26	rs73223431 rs867230	2	2	3.26E-17	rs73223431 rs867230
10	11,720,308	1.08E-11	rs7920721	1	1	3.40E-08	rs12416487
10	61,645,833	3.80E-08	rs1171814	1	1	8.67E-06	rs142366127
10	82,280,137	2.74E-09	rs1878036	1	1	6.97E-06	rs1870148
11	47,391,948	6.91E-11	rs10437655	1	1	8.41E-11	rs3740688
11	60,095,740	9.33E-20	rs72924626	1	1	1.36E-16	rs1582763
11	85,867,875	5.21E-26	rs10792832	1	1	5.75E-16	rs3851179
11	121,435,587	5.59E-14	rs11218343	1	1	2.64E-08	rs11218343
14	53,391,680	3.69E-10	rs17125924	1	1	6.78E-07	rs17125924
14	92,938,855	7.45E-14	rs12590654	1	1	7.89E-09	rs12590654

15	50,992,311	1.74E-09	rs12592778	1			
15	59,022,615	2.67E-11	rs4775044 rs442495	2	1	3.79E-06	rs383902
15	63,569,902	1.05E-08	rs117618017	1			
16	31,126,321	4.47E-09	rs2884738	1			
16	81,773,209	5.46E-08	rs12444183	1	1	2.06E-06	rs34971488
17	5,133,128	1.35E-09	rs61182333	1			
17	56,404,349	3.07E-07	rs2526378	1	1	3.61E-07	rs2632516
17	61,560,763	1.21E-08	rs3730025 rs4311	2	1	7.51E-06	rs138190086
19	1,050,874	2.41E-13	rs12151021 rs4147918	2	1	2.34E-10	rs12151021
19	51,727,962	1.29E-08	rs3865444	1	1	3.61E-07	rs3865444
20	54,998,544	1.07E-10	rs6014724	1	1	3.53E-07	rs6014724
21	28,148,191	3.09E-08	rs4817090 rs2830489	2	1	2.38E-07	rs2830489

For most loci, the same number of independent signals is detected, but in a few cases there are more signals discovered in the meta-analysis, as might be expected based on increased study power. Notably, although UK Biobank is not a perfect match with the Kunkle et al. study, we did not see evidence of spurious independent signals.

To investigate fine-mapping, we applied FINEMAP to summary statistics from Kunkle et al. as well as to our meta-analysis. For each locus we specified the maximum number of causal variants as the number determined by GCTA for the meta-analysis, under the assumption that there are likely to be at least this many causal variants. We compared overlap between the 95% credible sets determined by FINEMAP. In general, fine-mapped credible sets based on the meta-analysis were considerably smaller, as expected. In most cases >90% of the SNP probability was in variants that overlapped with the credible set determined from fine-mapping Kunkle et al.

		Meta-analysis			**Kunkle only**	
Locus	**credset size**	**credset overlap with Kunkle**	**snp prob overlap with Kunkle**	**credset size**	**credset overlap with Meta**	**snp prob overlap with Meta**
ADAMTS4	37	37	0.954	2645	37	0.051
CR1	10	10	0.965	17	10	0.749
SPRED2	4	4	0.962	2365	4	0.189
NCK2	1	1	1.000	3131	1	0.331
BIN1	150	11	1.270	11	11	1.964
TMEM163	104	104	0.952	920	104	0.053
INPP5D	6	6	0.957	19	6	0.804
CLNK	16	16	0.966	600	16	0.477
HLA	102	0	0.000	371	0	0.000
TREM2	10	4	2.537	7	4	1.068
CD2AP	66	66	0.951	82	66	0.809

IKZF1	14	0	0.000	19	0	0.000
PILRA	6	6	0.968	241	6	0.364
EPHA1	33	0	0.000	7	0	0.000
PTK2B-CLU	15	14	1.922	48	14	1.526
ECHDC3	6	1	0.457	6	1	0.057
CCDC6	33	33	0.952	2626	33	0.232
TSPAN14	16	16	0.958	384	16	0.636
SPI1	26	8	0.538	13	8	0.912
MS4A4A	65	50	0.560	79	50	0.698
PICALM	3	3	0.964	11	3	0.640
SORL1	1	1	1.000	1	1	0.965
FERMT2	74	70	0.935	105	70	0.886
SLC24A4	1	1	0.968	35	1	0.519
SPPL2A	46	46	0.951	352	46	0.473
ADAM10	56	26	1.417	127	26	0.668
APH1B	3	3	0.992	2251	3	0.052
VKORC1	48	48	0.951	1133	48	0.066
PLCG2	6	6	0.962	1246	6	0.015
SCIMP	105	104	0.949	493	104	0.595
TSPOAP1	3	3	0.976	9	3	0.913
ACE	95	95	1.904	251	95	0.855
ABCA7	11	0	0.000	2	0	0.000
CD33	8	7	0.948	7	7	0.951
CASS4	11	11	0.952	17	11	0.850
APP-ADAMTS1	34	4	0.953	8	4	0.908

The column “snp prob overlap with Kunkle” shows the total probability of SNPs in the 95% credible set for the meta-analysis which are also in the 95% credible set for Kunkle et al. The column “snp prob overlap with Meta” shows the inverse (Kunkle credible set SNPs that are also in the meta-analysis credible set). Note that in this table, the SNP probability overlap can be larger than 1 for loci with multiple causal variants, since secondary signals are included.

In Supplementary Figure 2, we plotted SNP probabilities determined for the two datasets against each other for each locus.

Based on the above tables, and Supplementary Figure 2, we observe the following:

- At the *BIN1* locus (chr2:127,892,810), two signals are detected in both datasets, with the same lead SNP but different secondary SNPs, which are in LD with each other (r^2 = 0.60 - 0.75 in 1000 genomes EUR populations for rs7584040 and rs34745987).
- At the *PTK2B-CLU* locus (chr:27,468,503), two signals are detected in both datasets, with the same lead SNPs.
- At the *APH1B* locus (chr15:63,569,902), fine-mapping in our meta-analysis strongly prioritises missense SNP rs117618017, whereas Kunkle et al. has low power an prioritises rs12913805. Notably, the FinnGen and Gr@ace studies further support rs117618017 and not rs12913805.

- At the *ABCA7* locus (chr19:1,050,874), fine-mapped SNPs do not overlap. Candidate causal missense SNP rs4147918 (~4% frequency) is prioritised in the meta-analysis, but not in Kunkle et al.
- At the *ECHDC3* locus (chr10:11,720,308), fine-mapped SNPs show some degree of correlation, but a handful of SNPs have strong association in Kunkle et al. and only weak association in UK Biobank.
- At the *HLA* locus (chr6:32,560,025), a single signal is detected in the meta-analysis, but two in the Kunkle-only dataset, with different lead SNPs and inconsistent fine-mapping results. We note that the HLA locus is challenging to fine-map due to its extreme population variability, and in general requires custom imputation and analysis methods to handle.
- At the *EPHA1* locus (chr7:143,107,588), the association pattern (SNP p-values) differs significantly between Kunkle et al. and UK Biobank, and this is reflected in divergent SNP fine-mapping probabilities.

A number of loci are poorly powered in the Kunkle et al. stage 1 summary statistics (e.g. absent or not genome-wide significant in the GCTA table above). Although in most cases fine-mapping results are consistent between the two datasets for these loci, we think that the comparison is less meaningful, and the fine-mapping results from our meta-analysis are likely to be more accurate.