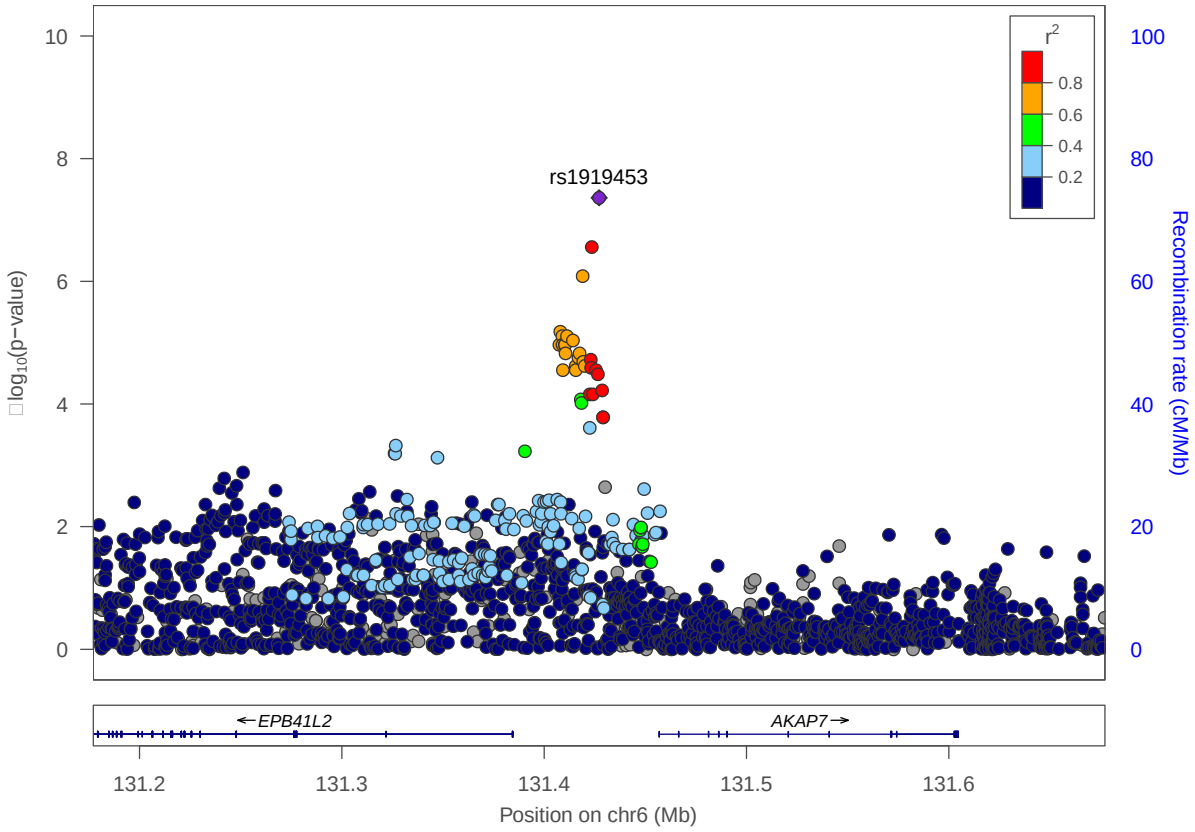
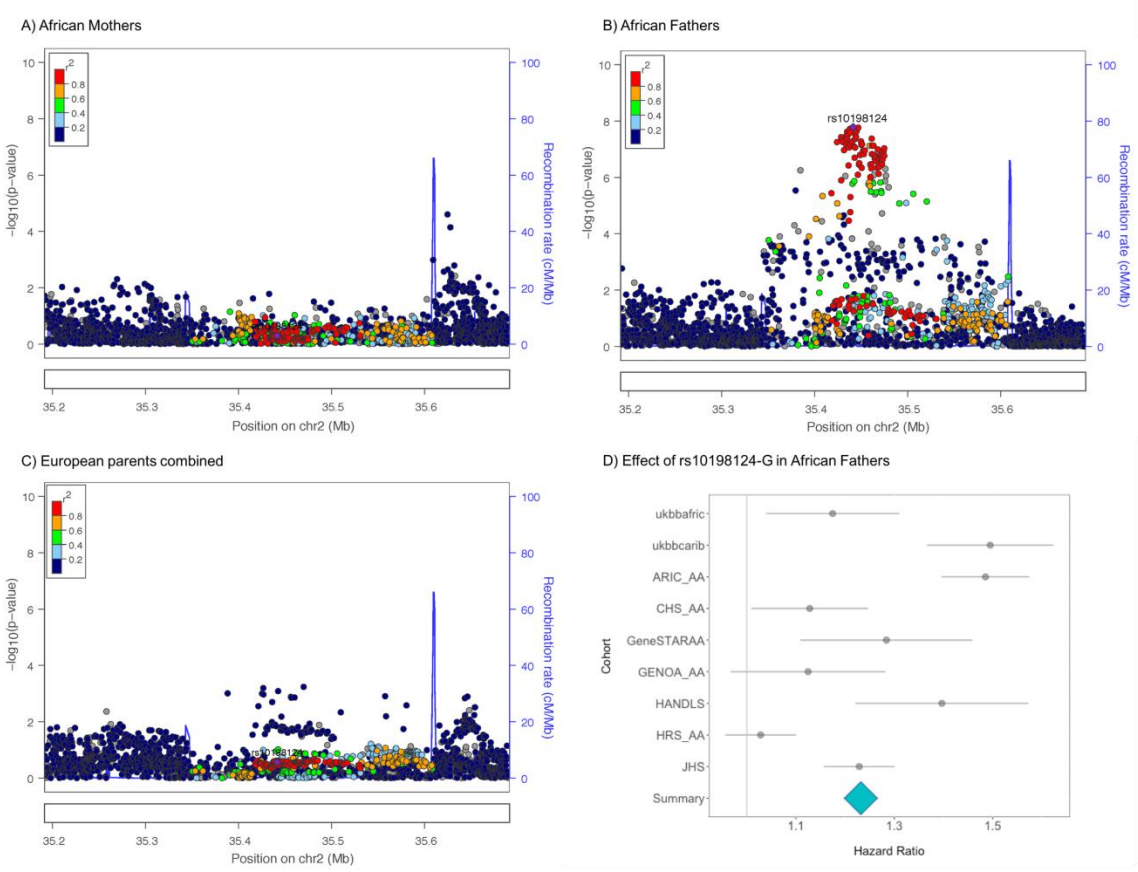
Supplementary Figure 1 | Locus zoom plot of the p-values of association for 1 further genome-wide significant association when meta-analysing CHAREG EU's longevity GWAMA and LifeGen across both parents in cohorts of European Ancestry. By combining our discovery association analysis with a long-livedness GWAS, we found an association with longevity for rs1919453, between genes AKAP7 and EBP41L2, but had no further data with which to seek replication. In the absence of replication, it is unclear if this SNP is reliably associated with lifespan.

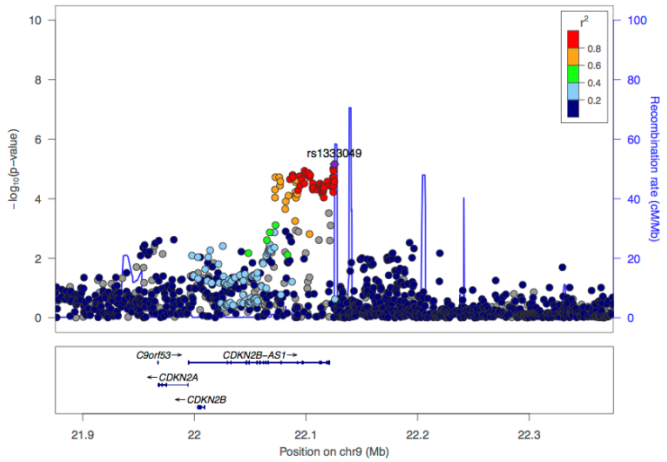


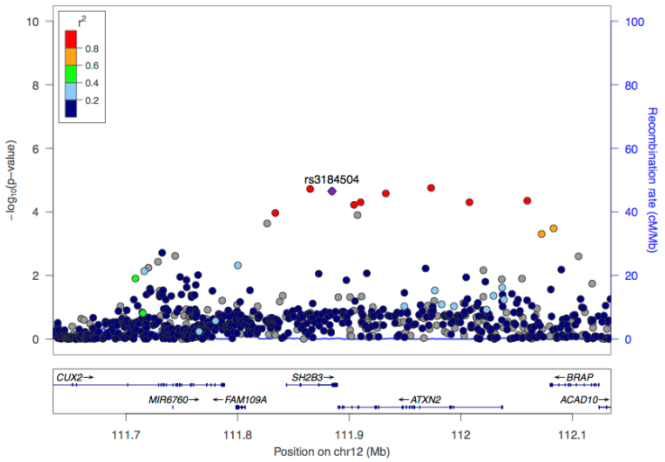
<u>Supplementary Figure 2 | Locus zoom plots for chromosome 2 region.</u> African mothers (**A**), African fathers (**B**), and Europeans with both parents combined (**C**). rs10198124 shows consistent association with lifespan in African fathers across cohorts, but no evidence in African mothers or Europeans of both ancestries. (**D**) The forest plot shows estimates of the hazard ratio for carrying 1 copy of the risk allele +/- 2 SE, for each cohort, i.e. observed father-child effect sizes were doubled. The apparent association with lifespan, in African fathers may be due to chance, as there are not even suggestive associations in African mothers or either European parent.

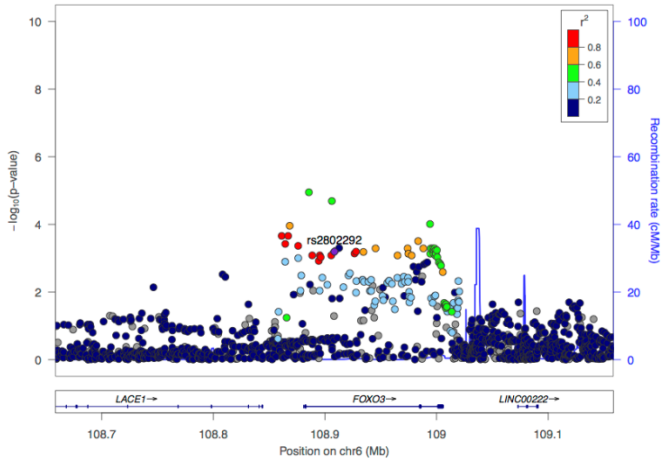


Supplementary Figure 3 | Locus Zoom plots of the Validated Candidate Loci.

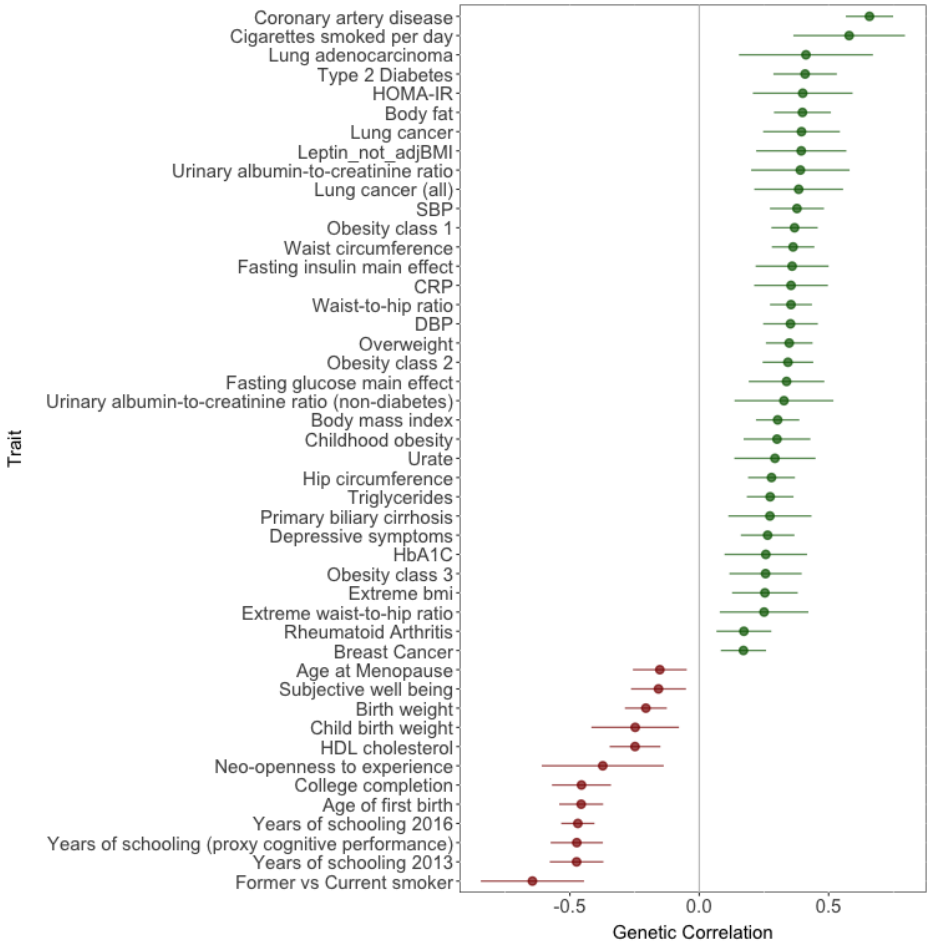
GWAMA and LifeGen across both parents in cohorts of European Ancestry.







Supplementary Figure 4 | Meaningful genetic correlations (r_g) between and mortality and trait. Traits which genetically correlate with increased mortality are shown in red and those correlating with increased longevity are in green. 113 traits were tested but only statistically significant correlations (FDR < 5%) with $|r_g| > 0.15$ are shown. Traits that are similar are all shown, for completeness and to avoid selection bias. The remaining traits and the studies from which the displayed genetic correlations were sourced can be found in Supplementary Table 3. HOMA-IR; homeostatic model assessment of insulin resistance, SBP; systolic blood pressure, CRP; C-reactive protein, DBP; diastolic blood pressure, HbA1c; glycated haemoglobin A1, HDL; heavy density lipoprotein.



Supplementary Table 1 | Genetic correlations and partial correlations of twelve trait clusters with mortality. The genetic correlation (rg) between the trait and lifespan was calculated from summary statistics using LD Score regression. The partial correlations (Partial rg), were derived from the genetic correlations using the matrix-inversion method. The lifespan trait is the LifeGen GWAMA for Europeans, both parents combined. CAD; coronary artery disease, T2D; type 2 diabetes, DL/WHR; dyslipidaemia/waist-hip-ratio, BP; blood pressure, Kidney; kidney function, BC; breast cancer, RA; rheumatoid arthritis, AM; age of menarche.

	rg	Partial rg
Smoking	0.68	0.61
CAD	0.66	0.62
T2D	0.48	0.33
DL/WHR	0.41	-0.19
BP	0.39	0.16
Obesity	0.37	0.24
Kidney	0.33	0.34
BC	0.17	0.23
RA	0.17	0.09
AM	-0.15	-0.01
Happiness	-0.24	-0.19
Edu	-0.5	-0.18

Supplementary Table 2 | Results from the discovery step MR for the 28 traits that were significant, prior to removal of trait overlap.

Exposure	# snps	b	se	pval	pleio_p	qvalue	het_p
Omega-6 fatty acids	13	0.0334	0.0135	1.32E-02	0.0203	3.80E-02	5.49E-03
LDL cholesterol	78	0.0543	0.0091	2.80E-09	0.8981	3.73E-08	1.13E-08
Obesity class 1	18	0.0435	0.0066	4.76E-11	0.2723	9.52E-10	4.95E-01
Alzheimer's disease	20	0.0181	0.0064	4.59E-03	0.725	1.53E-02	3.33E-01
HDL cholesterol	85	-0.0448	0.0127	4.07E-04	0.1318	1.55E-03	3.56E-14
Total cholesterol	85	0.0554	0.0096	9.41E-09	0.386	9.06E-08	2.75E-09
Coronary heart disease	39	0.0806	0.0109	1.67E-13	0.926	1.34E-11	6.10E-12
Extreme body mass index	7	0.0257	0.0063	4.08E-05	0.882	1.92E-04	2.92E-01
Myocardial infarction	25	0.0643	0.011	5.80E-09	0.1206	6.63E-08	1.16E-05
Omega-3 fatty acids	6	0.0302	0.0122	1.33E-02	0.5887	3.80E-02	5.28E-01
Years of schooling	69	-0.1774	0.0266	2.69E-11	0.0139	7.18E-10	1.37E-03
DBP	9	0.0144	0.0028	3.94E-07	0.1805	2.87E-06	1.99E-01
Hip circumference	52	0.0976	0.0218	7.86E-06	0.7006	4.49E-05	3.41E-07
Type 2 diabetes	25	0.0175	0.0069	1.15E-02	0.178	3.64E-02	2.20E-01
CRP	48	-0.041	0.0109	1.67E-04	0.9083	7.03E-04	3.31E-15
Obesity class 3	2	0.0237	0.0065	2.58E-04	NA	1.03E-03	1.00E+00
Apolipoprotein B	19	0.0535	0.0093	1.02E-08	0.5418	9.06E-08	3.57E-02
Body mass index	78	0.1226	0.0173	1.26E-12	0.3865	5.03E-11	1.01E-05
Triglycerides	54	0.0326	0.0129	1.18E-02	0.2659	3.64E-02	3.66E-06
Fasting insulin	14	0.1619	0.0501	1.23E-03	0.6666	4.29E-03	8.65E-01
SBP	8	0.0088	0.002	1.12E-05	0.0341	5.98E-05	2.16E-01
Obesity class 2	11	0.0335	0.0059	1.68E-08	0.9266	1.35E-07	3.67E-01
Childhood obesity	10	0.036	0.0109	1.00E-03	0.0475	3.64E-03	2.93E-05
Squamous cell lung cancer	3	0.0494	0.0098	4.86E-07	0.3085	3.24E-06	4.06E-01
Breast Cancer	111	0.0155	0.0039	6.65E-05	0.5674	2.95E-04	3.45E-02
Overweight	14	0.0592	0.0125	2.25E-06	0.3002	1.38E-05	1.45E-01
Cigarettes smoked per day	rs12914385	0.0169	0.0027	6.47E-10	NA	1.03E-08	NA
Ischaemic stroke	rs4984814	0.0058	0.0013	1.39E-05	NA	6.97E-05	NA

Supplementary Table 3 | Number of SNPs which composed the Instrumental Variables before and after pruning

Trait	Initial N SNPs	LD pruned SNPs
Alzheimer's disease	20	18
Apolipoprotein B	21	3
Breast Cancer	134	131
Body mass index SD (kg/m^2)	79	66
Cigarettes smoked per day	1	1
Coronary heart disease	41	28
CRP	53	44
DBP	9	3
Fasting insulin log pmol/L	14	6
HDL cholesterol SD (mg/dL)	89	40
Ischaemic stroke	1	1
LDL cholesterol SD (mg/dL)	80	17
Omega-3 fatty acids SD	6	1
SBP	11	4
Squamous cell lung cancer	4	3
Total cholesterol SD (mg/dL)	88	12
Triglycerides SD (mg/dL)	54	18
Type 2 diabetes	34	29
Years of schooling SD (years)	73	67

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