# Supplementary Text, Tables and Figures

COMPARISON OF FAMILIAL, POLYGENIC AND BIOCHEMICAL

PREDICTORS OF MORTALITY

Supplementary Text.

Estimation of Martingale residuals

The Martingale residual is a variable representing mortality/survival which can be estimated for each study participant based on their status at follow-up and their deviation from the expected survival curve for their sex.
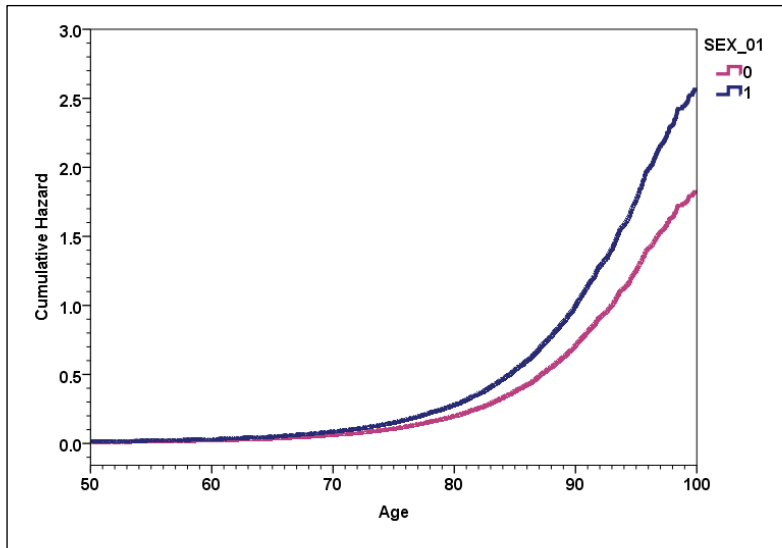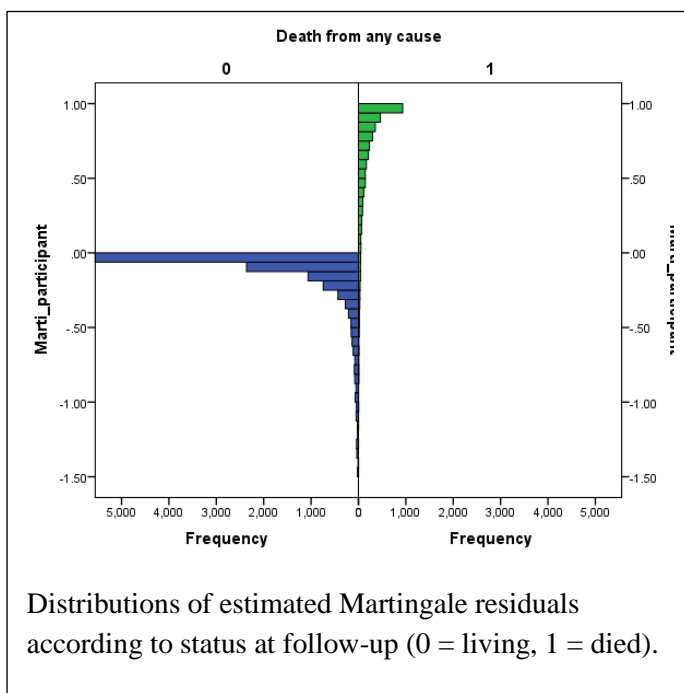
The Figure to the left plots the Hazard against age for men and women (SEX_01 = 1, blue line, for men or SEX_01 = 0, pink line, for women).

The Martingale residual for any person is defined as

$$marti = 1 - censor - HAZ$$

where censor = 1 if the person is living and 0 if dead, and HAZ is the hazard function (the survival probability, dependent on age).

Consider a woman who is alive (and therefore censored) at age 85. The Hazard for a woman aged 85 is approximately 0.35 so the Martingale residual is (1 – 1 - 0.35) = -0.65. Similarly for a man known to have died at age 70, the Hazard is approximately 0.06 so the Martingale residual is (1 – 0 – 0.06) = 0.94. The Martingale residuals can take values between +1 and -∞ but in practice nearly all are above -3.

As can be seen in the Figure to the left, comparing the frequency distributions of Martingale residuals in study participants who are alive or dead, if the person is living at last known date (censored) then the residual will always be negative but if they have died it will usually (but not always) be positive.

Distributions of estimated Martingale residuals according to status at follow-up (0 = living, 1 = died).

Genotyping, imputation and calculation of polygenic risk scores.

Genotyping was performed on DNA extracted from blood samples, using Illumina 317K, 370K, 610K, ('1st generation'), or Core Exome plus Omni-family ('2nd generation') arrays, and GenomeStudio software for genotype calling (Illumina Inc., 200 Lincoln Centre Dr, Foster City, CA 94404). This was followed by imputation from a common SNP set to the 1000 Genomes (Phase 3 Release 5) reference panel, a strategy that allows genotype data from different arrays to be combined.

Initial quality control procedures included exclusion of samples with <95% call rate, non-European ancestry (> 6 SD from the mean European-population cluster for PC1 and PC2) or with familial relationships incompatible with those reported by study participants. Observed genotypes were cleaned (by batch) for call rate ($\geq$95%); minor allele frequency ($\geq$ 1%); Hardy-Weinberg equilibrium ($p \geq 10^{-3}$), GenCall score (≥ 0.15 per genotype; mean ≥ 0.7) and standard Illumina filters, before integrating batches and re-running the quality control and Mendelian checks.

Phasing and imputation was carried out at the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!) using the 1000 Genomes Phase 3 Release 5 'mixed population' reference panel, with phasing by SHAPEIT followed by imputation using minimac 3.. '1st generation' and '2nd generation' data were imputed separately due to poor overlap between typed markers. Imputation was based on 277,690 ('1st generation') and 240,297 ('2nd generation') typed markers (passing QC in all relevant batches); and the two were combined after imputation to maximise sample size, using for each individual the '1st generation' imputation if available, otherwise using the '2nd generation' imputation. This resulted in 9,411,304 SNPs available for analysis, after quality control.

Polygenic risk scores for longevity were computed for each study participant using the clumping and thresholding method in PLINK 1.9. Coefficients (effect sizes) were taken from a meta-analysis of genome-wide association studies for longevity, as published (Joshi et al., 2017, reference 19 in this paper) but recalculated excluding data from our cohorts to avoid overlap with participants in this study. From our data, we excluded SNPs with low imputation quality ($r^2 < 0.6$) or minor allele frequency below 1%, and PRS were calculated from the imputed genotype dosages. SNPs in linkage disequilibrium (except for the most significant one at each locus) were excluded by linkage disequilibrium criteria, $r^2 < 0.1$ within windows of 10 MBp. p-value thresholds for inclusion of loci were 5 x 10^{-8}, 10^{-5}, 0.001, 0.01, 0.05, 0.1 , 0.5 and 1.0, giving eight PRS (PRS1 to PRS8) for each person.

Supplementary Table 1. Cox regression for all-cause mortality using either linear (sex-adjusted z-score only) or quadratic (z-score and z-score-squared) terms for test results, with familial clustering to adjust standard errors for relatedness. With additional covariates (BMI, smoking history, alcohol history) for comparison against results with sex as the only covariate in Table 2. p-values < 0.0021 (0.05/24) are shown in bold type.

	N Total	N Deaths	Beta	Linear SE	P		Beta	Quadratic SE	p
Creatinine	10554	1059	0.0338	0.0256	0.186	z	-0.0105	0.0316	0.739
						z-squared	0.0219	0.0094	0.020
Urea	10547	1056	0.0277	0.0239	0.247	z	-0.0144	0.0283	0.612
						z-squared	0.0200	0.0081	0.013
Uric acid	10616	1070	0.0624	0.0286	0.029	z	0.0241	0.0305	0.430
						z-squared	0.0390	0.0131	0.0030
Calcium	8859	841	-0.0621	0.0370	0.093	z	-0.0625	0.0389	0.108
						z-squared	-0.0004	0.0147	0.979
Total protein	10447	1056	-0.0025	0.0327	0.939	z	0.0138	0.0313	0.658
						z-squared	0.0351	0.0158	0.027
Albumin	10550	1066	-0.0543	0.0348	0.118	z	-0.0110	0.0330	0.740
						z-squared	0.0516	0.0206	0.012
Globulins	10437	1055	0.0294	0.0317	0.353	z	0.0222	0.0306	0.469
						z-squared	0.0327	0.0155	0.035
Bilirubin	10501	1055	-0.0229	0.0341	0.503	z	-0.0227	0.0323	0.483
						z-squared	0.0361	0.0216	0.095
ALP	8872	841	0.1157	0.0353	**0.0011**	z	0.0987	0.0313	**0.0016**

						z-squared	0.0446	0.0136	**0.0010**
AST	11100	1136	-0.0048	0.0306	0.876	z	-0.0050	0.0281	0.860
						z-squared	0.0124	0.0084	0.138
ALT	11099	1135	-0.0288	0.0341	0.397	z	-0.0271	0.0302	0.369
						z-squared	0.0293	0.0107	0.0060
AST/ALT ratio	11094	1134	0.0406	0.0275	0.140	z	0.0307	0.0382	0.422
						z-squared	0.0038	0.0089	0.664
GGT	11100	1136	0.1059	0.0328	**0.0012**	z	0.0546	0.0314	0.082
						z-squared	0.0550	0.0127	**1.63 x 10^{-5}**
BCHE	10292	1023	-0.0158	0.0332	0.634	z	-0.0224	0.0317	0.481
						z-squared	0.0278	0.0128	0.030
Total cholesterol	11386	1183	-0.0164	0.0302	0.586	z	-0.0287	0.0294	0.329
						z-squared	0.0299	0.0154	0.052
LDL-C	10977	1130	0.0020	0.0303	0.949	z	-0.0084	0.0309	0.785
						z-squared	0.0186	0.0149	0.212
HDL-C	11387	1184	0.0042	0.0297	0.887	z	-0.0074	0.0315	0.815
						z-squared	0.0169	0.0189	0.370
Triglycerides	11387	1184	-0.0421	0.0319	0.187	z	-0.0482	0.0318	0.129
						z-squared	0.0182	0.0181	0.315
Glucose	7109	594	0.1225	0.0325	**1.63 x 10^{-4}**	z	0.0633	0.0460	0.169
						z-squared	0.0218	0.0124	0.079
CRP	9574	924	0.0755	0.0440	0.086	z	0.0912	0.0372	0.014
						z-squared	0.0587	0.0143	**3.96 x 10^{-5}**

Iron	9489	937	-0.0984	0.0391	0.012	z	-0.1073	0.0391	0.0061
						z-squared	0.0243	0.0200	0.225
Transferrin	11162	1160	0.0048	0.0335	0.887	z	-0.0244	0.0329	0.457
						z-squared	0.0564	0.0174	**0.0012**
Saturation	9483	936	-0.0737	0.0407	0.070	z	-0.0902	0.0402	0.025
						z-squared	0.0267	0.0207	0.198
Ferritin	11168	1160	-0.0155	0.0312	0.619	z	-0.0108	0.0321	0.737
						z-squared	0.0079	0.0200	0.694

Supplementary Table 2. Cox regression for all-cause mortality using either linear (sex-adjusted z-score only) or quadratic (z-score and z-score-squared) terms for test results, with familial clustering to adjust standard errors for relatedness. Excluding participants who died within two years of baseline blood collection (for comparison against results for all participants in Table 2). p-values < 0.0021 (0.05/24) are shown in bold type.

	N Total	N Deaths	Beta	Linear SE	P		Beta	Quadratic SE	p
Creatinine	11511	1279	0.0457	0.0233	0.050	z	0.0007	0.0279	0.980
						z-squared	0.0242	0.0082	0.0031
Urea	11501	1274	0.0211	0.0228	0.354	z	-0.0316	0.0259	0.223
						z-squared	0.0267	0.0068	**8.18 x 10^{-5}**
Urate	11570	1287	0.0857	0.0260	**0.0010**	z	0.0444	0.0272	0.102
						z-squared	0.0411	0.0123	**8.38 x 10^{-4}**
Calcium	9721	1048	-0.0216	0.0335	0.520	z	-0.0297	0.0356	0.405
						z-squared	-0.0094	0.0149	0.528
Total protein	11392	1271	0.0025	0.0300	0.934	z	0.0134	0.0282	0.634
						z-squared	0.0396	0.0138	0.0042
Albumin	11505	1283	-0.0827	0.0321	0.0100	z	-0.0440	0.0304	0.148
						z-squared	0.0546	0.0187	0.0035
Globulins	11383	1270	0.0475	0.0279	0.089	z	0.0353	0.0271	0.193
						z-squared	0.0360	0.0144	0.0130
Bilirubin	11449	1271	-0.0463	0.0308	0.133	z	-0.0480	0.0297	0.106
						z-squared	0.0238	0.0198	0.230
ALP	9735	1050	0.0902	0.0317	0.0045	z	0.0849	0.0310	0.0061

						z-squared	0.0138	0.0168	0.410
AST	12053	1352	0.0047	0.0295	0.873	z	0.0031	0.0279	0.912
						z-squared	0.0123	0.0081	0.130
ALT	12052	1351	-0.0121	0.0327	0.712	z	-0.0158	0.0293	0.589
						z-squared	0.0299	0.0114	0.0088
AST/ALT ratio	12046	1350	0.0320	0.0271	0.238	z	0.0150	0.0363	0.679
						z-squared	0.0068	0.0080	0.392
GGT	12053	1352	0.1335	0.0289	3.66×10^{-6}	z	0.1102	0.0301	2.52×10^{-4}
						z-squared	0.0216	0.0162	0.181
BCHE	11251	1242	0.0235	0.0291	0.420	z	0.0155	0.0272	0.570
						z-squared	0.0392	0.0121	0.0012
Total cholesterol	12336	1397	0.0208	0.0273	0.445	z	0.0103	0.0261	0.693
						z-squared	0.0304	0.0141	0.031
LDL-C	11890	1335	0.0233	0.0276	0.399	z	0.0120	0.0274	0.661
						z-squared	0.0227	0.0134	0.090
HDL-C	12337	1398	-0.0102	0.0278	0.715	z	-0.0422	0.0288	0.142
						z-squared	0.0460	0.0164	0.0050
Triglycerides	12337	1398	0.0092	0.0285	0.746	z	0.0008	0.0273	0.978
						z-squared	0.0240	0.0184	0.192
Glucose	7549	787	0.1286	0.0269	1.75×10^{-6}	z	0.1037	0.0414	0.012
						z-squared	0.0084	0.0121	0.490
CRP	10538	1147	0.1274	0.0379	7.79×10^{-4}	z	0.1301	0.0335	1.00×10^{-4}
						z-squared	0.0545	0.0157	5.01×10^{-4}

Iron	10351	1142	-0.0439	0.0341	0.198	z	-0.0532	0.0335	0.112
						z-squared	0.0255	0.0175	0.146
Transferrin	12115	1374	0.0039	0.0294	0.894	z	-0.0150	0.0308	0.626
						z-squared	0.0363	0.0181	0.045
Saturation	10345	1141	-0.0332	0.0344	0.334	z	-0.0512	0.0331	0.122
						z-squared	0.0295	0.0182	0.104
Ferritin	12121	1374	0.0362	0.0269	0.179	z	0.0367	0.0291	0.207
						z-squared	0.0009	0.0169	0.959

Supplementary Table 3. Associations between sex- and age-adjusted test result quintiles and all-cause mortality. Analysis was performed in Stata with family as a cluster variable to adjust for relatedness of study participants. Hazard Ratios (HR) for quintiles 2, 3, 4 and 5 are compared against the lowest quintile (Q1).

	Q1	Q2			Q3			Q4			Q5		
	HR	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Creatinine	1.00	0.948	0.812 - 1.108	0.506	1.008	0.860 - 1.181	0.923	0.893	0.760 - 1.050	0.171	1.017	0.881 - 1.173	0.820
Urea	1.00	0.864	0.736 - 1.014	0.074	0.835	0.712 - 0.978	0.026	0.801	0.679 - 0.946	0.0088	0.976	0.852 - 1.118	0.728
Uric acid	1.00	0.825	0.699 - 0.973	0.022	0.894	0.761 - 1.050	0.174	0.930	0.797 - 1.086	0.361	1.117	0.966 - 1.292	0.134
Calcium	1.00	0.911	0.782 - 1.062	0.233	0.825	0.710 - 0.960	0.013	0.954	0.818 - 1.111	0.544	0.801	0.677 - 0.948	0.010
Total protein	1.00	0.852	0.728 - 0.997	0.046	0.917	0.788 - 1.066	0.259	0.937	0.802 - 1.096	0.418	0.917	0.780 - 1.078	0.294
Albumin	1.00	0.795	0.683 - 0.926	0.0032	0.724	0.622 - 0.844	3.47×10^{-5}	0.760	0.653 - 0.886	4.48×10^{-4}	0.803	0.683 - 0.944	0.0078
Globulins	1.00	0.907	0.774 - 1.064	0.233	0.917	0.784 - 1.073	0.279	0.953	0.816 - 1.113	0.544	1.013	0.870 - 1.178	0.872
Bilirubin	1.00	0.885	0.754 - 1.037	0.131	0.768	0.657 - 0.899	0.0010	0.860	0.746 - 0.990	0.036	0.853	0.727 - 1.000	0.050
ALP	1.00	0.857	0.731 - 1.005	0.058	0.961	0.829 - 1.114	0.594	0.949	0.811 - 1.111	0.516	1.145	0.978 - 1.341	0.092
AST	1.00	0.836	0.715 - 0.977	0.024	0.784	0.668 - 0.919	0.0027	0.769	0.659 - 0.896	8.08×10^{-4}	0.954	0.810 - 1.123	0.571
ALT	1.00	0.810	0.696 - 0.944	0.0072	0.793	0.678 - 0.927	0.0036	0.844	0.720 - 0.989	0.036	0.890	0.750 - 1.056	0.181
AST/ALT ratio	1.00	0.730	0.607 - 0.877	8.08×10^{-4}	0.765	0.647 - 0.904	0.0017	0.797	0.675 - 0.941	0.0076	0.909	0.777 - 1.064	0.236
GGT	1.00	0.954	0.824 - 1.105	0.532	1.092	0.931 - 1.279	0.280	1.035	0.880 - 1.218	0.678	1.368	1.170 - 1.601	9.23×10^{-5}
BCHE	1.00	0.809	0.692 - 0.946	0.0078	0.941	0.805 - 1.101	0.449	0.877	0.750 - 1.025	0.099	1.001	0.856 - 1.172	0.986
Total cholesterol	1.00	1.024	0.877 - 1.195	0.765	1.054	0.910 - 1.223	0.482	0.924	0.786 - 1.087	0.342	0.989	0.842 - 1.160	0.888
LDL-C	1.00	0.985	0.843 - 1.151	0.847	1.055	0.906 - 1.228	0.490	0.996	0.851 - 1.165	0.957	1.030	0.878 - 1.207	0.718
HDL-C	1.00	0.802	0.686 - 0.936	0.0053	0.934	0.795 - 1.097	0.406	0.903	0.770 - 1.060	0.212	0.847	0.725 - 0.989	0.036
Triglycerides	1.00	0.952	0.817 - 1.108	0.524	0.944	0.808 - 1.104	0.473	0.935	0.802 - 1.089	0.386	1.041	0.883 - 1.227	0.635
Glucose	1.00	0.844	0.711 - 1.003	0.054	0.974	0.808 - 1.173	0.781	1.046	0.871 - 1.256	0.629	0.998	0.859 - 1.159	0.979
CRP	1.00	0.811	0.695 - 0.946	0.0076	0.889	0.764 - 1.034	0.126	0.985	0.838 - 1.156	0.850	1.400	1.194 - 1.642	3.63×10^{-5}
Iron	1.00	0.903	0.780 - 1.046	0.174	0.849	0.732 - 0.984	0.030	0.771	0.661 - 0.898	8.38×10^{-4}	0.881	0.753 - 1.032	0.115
Transferrin	1.00	1.031	0.879 - 1.210	0.706	0.932	0.792 - 1.098	0.402	1.102	0.935 - 1.298	0.248	1.043	0.885 - 1.228	0.618
Saturation	1.00	0.813	0.700 - 0.945	0.0072	0.831	0.717 - 0.961	0.013	0.818	0.707 - 0.946	0.0067	0.849	0.726 - 0.994	0.042
Ferritin	1.00	1.048	0.898 - 1.222	0.551	1.121	0.953 - 1.318	0.169	1.010	0.856 - 1.191	0.908	1.077	0.923 - 1.258	0.346

Supplementary Table 4. Cox regression for mortality by major cause-of-death groups, using either linear (sex-adjusted z-score only) or quadratic (z-score and z-score-squared) terms for test results, with familial clustering to adjust standard errors for relatedness. p-values < 0.0021 (0.05/24) are shown in bold type.

Cancer deaths

	N Total	N Deaths	Beta	Linear SE	P		Beta	Quadratic SE	p
Creatinine	12230	399	-0.0091	0.0447	0.838	z	-0.0376	0.0511	0.462
						z-squared	0.0186	0.0194	0.338
Urea	12220	397	0.0053	0.0404	0.896	z	0.0101	0.0484	0.834
						z-squared	-0.0033	0.0185	0.858
Uric acid	12292	402	0.0426	0.0455	0.349	z	0.0359	0.0495	0.468
						z-squared	0.0085	0.0245	0.727
Calcium	10416	320	-0.0650	0.0554	0.240	z	-0.0732	0.0655	0.264
						z-squared	-0.0092	0.0224	0.682
Total protein	12110	398	-0.1301	0.0548	0.018	z	-0.0900	0.0488	0.065
						z-squared	0.0618	0.0234	0.0083
Albumin	12225	400	-0.1073	0.0592	0.070	z	-0.0515	0.0508	0.311
						z-squared	0.0760	0.0236	**0.0013**
Globulins	12099	397	-0.0809	0.0507	0.110	z	-0.0836	0.0458	0.068
						z-squared	0.0419	0.0252	0.096
Bilirubin	12166	399	-0.0665	0.0575	0.247	z	-0.0687	0.0489	0.160
						z-squared	0.0682	0.0286	0.017
ALP	10432	320	0.0607	0.0569	0.286	z	0.0514	0.0513	0.317
						z-squared	0.0317	0.0222	0.153

AST	12776	417	0.0175	0.0536	0.744	z	0.0060	0.0452	0.894
						z-squared	0.0188	0.0096	0.050
ALT	12775	416	0.0564	0.0575	0.326	z	0.0411	0.0529	0.438
						z-squared	0.0247	0.0148	0.095
AST/ALT ratio	12769	415	-0.0406	0.0513	0.429	z	-0.0547	0.0642	0.394
						z-squared	0.0071	0.0131	0.59
GGT	12776	417	0.0926	0.0473	0.051	z	0.0640	0.0511	0.210
						z-squared	0.0285	0.0241	0.237
BCHE	11968	383	0.0177	0.0533	0.739	z	0.0067	0.0484	0.890
						z-squared	0.0409	0.0226	0.071
Total cholesterol	13062	432	0.0167	0.0492	0.734	z	0.0014	0.0465	0.976
						z-squared	0.0371	0.0232	0.109
LDL-C	12587	415	0.0239	0.0485	0.623	z	0.0168	0.0487	0.730
						z-squared	0.0139	0.0299	0.643
HDL-C	13063	432	-0.0933	0.0483	0.054	z	-0.0892	0.0532	0.094
						z-squared	-0.0089	0.0350	0.798
Triglycerides	13063	432	0.0314	0.0509	0.537	z	0.0257	0.0499	0.607
						z-squared	0.0173	0.0335	0.606
Glucose	8158	238	0.1263	0.0431	0.0034	z	0.1673	0.0785	0.033
						z-squared	-0.0142	0.0218	0.514
CRP	11248	353	0.1501	0.0713	0.035	z	0.1726	0.0500	**5.61E-04**
						z-squared	0.0881	0.0196	**6.80E-06**

	N Total	N Deaths	Beta	SE	P		Beta	SE	p
Iron	11051	343	-0.1635	0.0644	0.011	z	-0.1683	0.0596	0.0048
						z-squared	0.0328	0.0308	0.286
Transferrin	12838	422	-0.0094	0.0544	0.863	z	-0.0334	0.0509	0.511
						z-squared	0.0439	0.0287	0.126
Saturation	11045	343	-0.1428	0.0650	0.028	z	-0.1632	0.0561	0.0036
						z-squared	0.0495	0.0289	0.087
Ferritin	12844	422	0.0099	0.0467	0.832	z	-0.0009	0.0540	0.987
						z-squared	-0.0182	0.0290	0.531

CVD deaths

	N Total	N Deaths	**Linear** Beta	SE	P		**Quadratic** Beta	SE	p
Creatinine	12230	272	0.1478	0.0478	**0.0020**	z	0.0526	0.0568	0.354
						z-squared	0.0376	0.0127	0.0030
Urea	12220	270	0.0718	0.0501	0.152	z	-0.0156	0.0574	0.786
						z-squared	0.0356	0.0129	0.0058
Uric acid	12292	275	0.0723	0.0630	0.251	z	-0.0246	0.0564	0.662
						z-squared	0.0890	0.0235	**1.57×10^{-4}**
Calcium	10416	217	-0.0347	0.0675	0.607	z	-0.0438	0.0837	0.601
						z-squared	-0.0095	0.0287	0.741
Total protein	12110	274	0.0867	0.0661	0.189	z	0.0981	0.0538	0.068
						z-squared	0.0709	0.0182	**9.62×10^{-5}**
Albumin	12225	274	-0.1152	0.0743	0.121	z	-0.0478	0.0698	0.493
						z-squared	0.0711	0.0226	**0.0016**

Globulins	12099	174	0.1530	0.0561	0.0063	z	0.1434	0.0572	0.012
						z-squared	0.0158	0.0347	0.648
Bilirubin	12166	273	-0.0584	0.0627	0.352	z	-0.0558	0.0712	0.433
						z-squared	-0.0714	0.0545	0.190
ALP	10432	217	0.2297	0.0655	4.48×10^{-4}	z	0.2378	0.0764	**0.0019**
						z-squared	-0.0098	0.0448	0.826
AST	12776	297	-0.0122	0.0597	0.838	z	-0.0110	0.0551	0.842
						z-squared	0.0085	0.0117	0.470
ALT	12775	297	-0.0888	0.0663	0.180	z	-0.0820	0.0617	0.184
						z-squared	0.0193	0.0211	0.360
AST/ALT ratio	12769	297	0.0870	0.0504	0.085	z	0.1220	0.0794	0.124
						z-squared	-0.0139	0.0186	0.457
GGT	12776	297	0.2151	0.0549	8.85×10^{-5}	z	0.2062	0.0627	**0.0010**
						z-squared	0.0067	0.0281	0.812
BCHE	11968	277	0.0893	0.0647	0.167	z	0.0586	0.0541	0.278
						z-squared	0.0667	0.0161	**3.47×10^{-5}**
Total cholesterol	13062	304	-0.0463	0.0570	0.417	z	-0.0503	0.0528	0.340
						z-squared	0.0332	0.0259	0.201
LDL-C	12587	293	0.0098	0.0568	0.863	z	-0.0021	0.0546	0.969
						z-squared	0.0273	0.0220	0.215
HDL-C	13063	305	-0.1215	0.0647	0.060	z	-0.1645	0.0580	0.0045
						z-squared	0.0838	0.0292	0.0041

	N Total	N Deaths	Beta	SE	P		Beta	SE	p
Triglycerides	13063	305	0.0064	0.0576	0.912	z	0.0116	0.0606	0.848
						z-squared	-0.0205	0.0374	0.583
Glucose	8158	168	0.1190	0.0633	0.060	z	-0.0099	0.0811	0.903
						z-squared	0.0423	0.0206	0.040
CRP	11248	259	0.1218	0.0863	0.158	z	0.1301	0.0622	0.036
						z-squared	0.0750	0.0309	0.015
Iron	11051	246	-0.0047	0.0701	0.947	z	0.0114	0.0786	0.885
						z-squared	-0.0512	0.0455	0.261
Transferrin	12838	303	0.0062	0.0615	0.920	z	0.0070	0.0716	0.922
						z-squared	-0.0017	0.0491	0.972
Saturation	11045	246	-0.0166	0.0687	0.809	z	-0.0065	0.0735	0.929
						z-squared	-0.0195	0.0386	0.614
Ferritin	12844	303	-0.0428	0.0534	0.423	z	-0.0677	0.0628	0.280
						z-squared	-0.0342	0.0404	0.397

Other-cause deaths

	N Total	N Deaths	Beta	Linear SE	P		Beta	Quadratic SE	p
Creatinine	12230	469	0.0522	0.0390	0.181	z	-0.0022	0.0460	0.961
						z-squared	0.0281	0.0123	0.022
Urea	12220	469	0.0106	0.0423	0.803	z	-0.1076	0.0435	0.013
						z-squared	0.0526	0.0085	**5.65×10^{-10}**
Urate	12292	474	0.1185	0.0435	0.0065	z	0.0313	0.0422	0.459
						z-squared	0.0736	0.0154	**1.67×10^{-6}**

Calcium	10416	393	-0.0151	0.0533	0.777	z	-0.0059	0.0549	0.915
						z-squared	0.0096	0.0204	0.639
Total protein	12110	466	0.0252	0.0468	0.589	z	0.0262	0.0466	0.573
						z-squared	0.0075	0.0246	0.762
Albumin	12225	473	-0.1274	0.0531	0.017	z	-0.0838	0.0506	0.098
						z-squared	0.0503	0.0250	0.045
Globulins	12099	466	0.0889	0.0469	0.058	z	0.0623	0.0431	0.149
						z-squared	0.0558	0.0237	0.019
Bilirubin	12166	465	-0.0699	0.0513	0.173	z	-0.0706	0.0492	0.151
						z-squared	0.0226	0.0318	0.478
ALP	10432	393	0.0789	0.0518	0.128	z	0.0618	0.0454	0.174
						z-squared	0.0429	0.0213	0.044
AST	12776	495	-0.0162	0.0517	0.754	z	-0.0121	0.0447	0.786
						z-squared	0.0172	0.0097	0.075
ALT	12775	495	-0.1151	0.0569	0.043	z	-0.1004	0.0473	0.034
						z-squared	0.0390	0.0133	0.0033
AST/ALT ratio	12769	495	0.1208	0.0396	0.0023	z	0.1445	0.0599	0.016
						z-squared	-0.0083	0.0142	0.560
GGT	12776	495	0.1326	0.0456	0.0036	z	0.0913	0.0429	0.033
						z-squared	0.0373	0.0212	0.078
BCHE	11968	449	-0.1111	0.0497	0.025	z	-0.1062	0.0465	0.022
						z-squared	0.0230	0.0264	0.383

Total cholesterol	13062	513	-0.0241	0.0449	0.591	z	-0.0278	0.0428	0.516
						z-squared	0.0211	0.0255	0.408
LDL-C	12587	484	-0.0286	0.0460	0.534	z	-0.0320	0.0456	0.483
						z-squared	0.0118	0.0253	0.639
HDL-C	13063	513	0.0416	0.0483	0.389	z	-0.0219	0.0477	0.646
						z-squared	0.0735	0.0256	0.0041
Triglycerides	13063	513	-0.0310	0.0465	0.505	z	-0.0445	0.0411	0.278
						z-squared	0.0516	0.0216	0.017
Glucose	8158	294	0.1749	0.0397	**1.08×10^{-5}**	z	0.1500	0.0687	0.029
						z-squared	0.0078	0.0177	0.658
CRP	11248	412	0.2078	0.0557	**1.91×10^{-4}**	z	0.2052	0.0546	**1.70×10^{-4}**
						z-squared	0.0078	0.0264	0.767
Iron	11051	424	-0.0539	0.0617	0.382	z	-0.0914	0.0542	0.092
						z-squared	0.0684	0.0197	**5.40×10^{-4}**
Transferrin	12838	503	-0.0363	0.0503	0.471	z	-0.0542	0.0487	0.266
						z-squared	0.0408	0.0284	0.151
Saturation	11045	424	-0.0151	0.0592	0.799	z	-0.0609	0.0539	0.259
						z-squared	0.0563	0.0229	0.014
Ferritin	12844	503	0.0760	0.0458	0.097	z	0.0879	0.0471	0.062
						z-squared	0.0228	0.0268	0.396

Supplementary Table 5. Analysis of associations with all-cause mortality, as for Tables 3 and 4 but restricted to participants who have biochemical data. In this Table, total N = 11,729 with 1323 deaths for PRS, and total N = 11,098 with 988 deaths for parental data (which only includes participants with data for both parents).

Z-transformed Polygenic Risk Scores

	Beta	Robust SE	p-value	HR	95% CI for HR
PRS1	0.079	0.027	0.0035	1.082	1.026 to 1.141
PRS2	0.066	0.028	0.019	1.069	1.011 to 1.129
PRS3	0.059	0.031	0.053	1.061	0.999 to 1.127
PRS4	0.062	0.031	0.044	1.064	1.002 to 1.129
PRS5	0.048	0.030	0.113	1.049	0.989 to 1.113
PRS6	0.056	0.030	0.062	1.057	0.997 to 1.121
PRS7	0.049	0.030	0.105	1.050	0.990 to 1.114
PRS8	0.051	0.030	0.091	1.052	0.992 to 1.116

Family History; Z-transformed Martingale Residuals

	Beta	Robust SE	p-value	HR	95% CI for HR
Mother	0.060	0.022	0.0054	1.062	1.018 to 1.108
Father	0.036	0.026	0.163	1.036	0.986 to 1.089
Mid-parent	0.061	0.024	0.0093	1.063	1.015 to 1.114

Supplementary Table 6. Associations between polygenic risk scores (PRS) and deaths from cancers, cardiovascular diseases and other causes. The total number of participants with PRS was 14,169 and the numbers of deaths in each group are shown below.

Cancer deaths (N = 466)

	HR	95% CI	p
PRS1, $p > 5 \times 10^{-8}$	1.062	0.972 - 1.161	0.180
PRS2, $p < 10^{-5}$	1.068	0.971 - 1.173	0.174
PRS3, $p < 0.001$	1.035	0.939 - 1.142	0.489
PRS4, $p < 0.01$	1.027	0.931 - 1.132	0.598
PRS5, $p < 0.05$	0.958	0.864 - 1.061	0.411
PRS6, $p < 0.1$	0.945	0.852 - 1.048	0.283
PRS7, $p < 0.5$	0.920	0.829 - 1.020	0.112
PRS8, $p \leq 1.0$	0.923	0.832 - 1.024	0.132

Cardiovascular deaths (N = 339)

	HR	95% CI	p
PRS1, $p > 5 \times 10^{-8}$	1.017	0.917 - 1.129	0.745
PRS2, $p < 10^{-5}$	1.068	0.961 - 1.187	0.224
PRS3, $p < 0.001$	1.057	0.937 - 1.193	0.367
PRS4, $p < 0.01$	1.113	0.994 - 1.247	0.064
PRS5, $p < 0.05$	1.112	0.995 - 1.242	0.062
PRS6, $p < 0.1$	1.149	1.025 - 1.287	0.017
PRS7, $p < 0.5$	1.124	0.995 - 1.270	0.060
PRS8, $p \leq 1.0$	1.135	1.005 - 1.281	0.041

Deaths from other causes (N = 579)

	HR	95% CI	p
PRS1, $p > 5 \times 10^{-8}$	1.180	1.082 - 1.286	1.77×10^{-4}
PRS2, $p < 10^{-5}$	1.100	1.005 - 1.205	0.039
PRS3, $p < 0.001$	1.040	0.949 - 1.140	0.400
PRS4, $p < 0.01$	1.109	1.014- 1.213	0.024

PRS5, p < 0.05	1.122	1.026 - 1.227	0.012
PRS6, p < 0.1	1.142	1.046 - 1.247	0.0031
PRS7, p < 0.5	1.164	1.066 - 1.272	7.25×10^{-4}
PRS8, p ≤ 1.0	1.163	1.065 - 1.269	7.52×10^{-4}

Supplementary Table 7. Associations between parental standardised Martingale residuals and deaths from cancers, cardiovascular diseases and other causes. Restricted to participants with data on both mother's and father's survival.

Cancer deaths (N = 1177)

	HR	95% CI	p
Mother	1.035	0.992 - 1.079	0.110
Father	1.044	0.994 - 1.096	0.082
Mid-parent	1.065	1.017 - 1.116	0.0076

Cardiovascular deaths (N = 844)

	HR	95% CI	p
Mother	1.140	1.081 - 1.202	1.51×10^{-6}
Father	1.166	1.094 - 1.242	1.94×10^{-6}
Mid-parent	1.213	1.138 - 1.294	4.36×10^{-9}

Deaths from other causes (N = 1275)

	HR	95% CI	p
Mother	1.030	0.991 - 1.071	0.138
Father	1.030	0.984 - 1.079	0.202
Mid-parent	1.039	0.995 - 1.086	0.085

Supplementary Table 8. Correlations between Polygenic Risk Score 1 (PRS1) and mid-parent Martingale residuals, and sex-adjusted biomarker Z-scores, with familial clustering to adjust p-values for inclusion of related subjects.

	PRS1 (Loci with $p < 5 \times 10^{-8}$)			Mid-parent Martingale residual		
	R	N	p	R	N	p
Creatinine	-0.003	11032	0.933	0.010	10524	0.491
Urea	-0.013	11023	0.215	0.016	10520	0.206
Uric acid	0.005	11092	0.550	0.069	10569	1.06×10^{-6}
Calcium	0.011	9577	0.302	0.008	8806	0.357
Total Protein	-0.022	10926	0.036	0.000	10420	0.925
Albumin	-0.007	11027	0.654	-0.037	10520	0.0016
Globulins	-0.020	10917	0.054	0.028	10411	0.015
Bilirubin (log)	0.007	10978	0.454	-0.040	10470	0.0017
ALP (log)	0.002	9589	0.830	0.028	8820	0.067
AST (log)	0.001	11544	0.828	0.000	11001	0.786
ALT (log)	0.007	11543	0.444	0.009	11000	0.498
AST/ALT Ratio	-0.007	11537	0.442	-0.004	10995	0.667
GGT (log)	0.015	11544	0.169	0.033	11001	0.0044
BCHE	0.029	10757	0.015	0.021	10297	0.087
Cholesterol (log)	0.042	11802	7.03×10^{-5}	0.018	11265	0.028
LDL-C (log)	0.048	11380	9.70×10^{-6}	0.029	10852	0.0029
HDL-C	-0.033	11803	0.0042	-0.066	11266	3.26×10^{-8}
Triglyceride (log)	0.019	11803	0.076	0.047	11266	5.28×10^{-5}
Glucose	0.004	7434	0.687	0.025	7048	0.080
CRP (log)	-0.061	10051	2.33×10^{-8}	0.044	9637	4.23×10^{-5}
Iron	0.022	10154	0.043	-0.020	9390	0.104
Transferrin	-0.021	11584	0.055	0.010	11087	0.574
Saturation	0.027	10148	0.015	-0.023	9385	0.094
Ferritin (log)	0.021	11590	0.048	0.012	11092	0.231

Supplementary Figure 1. Dates of blood collection (upper panel) and years of follow-up to death or until 21st October 2017 (lower panel).
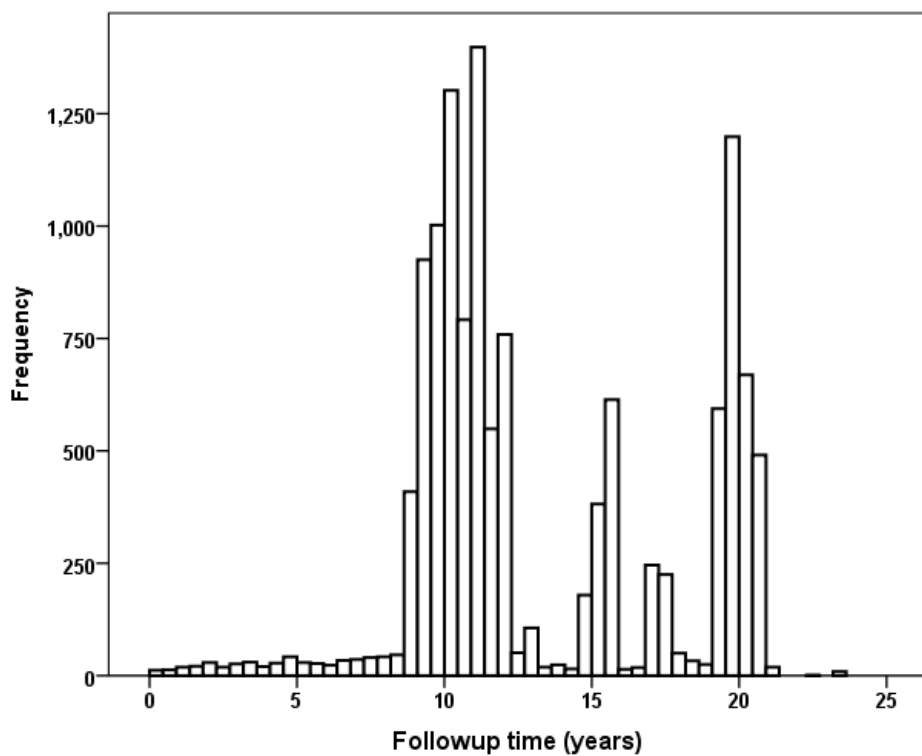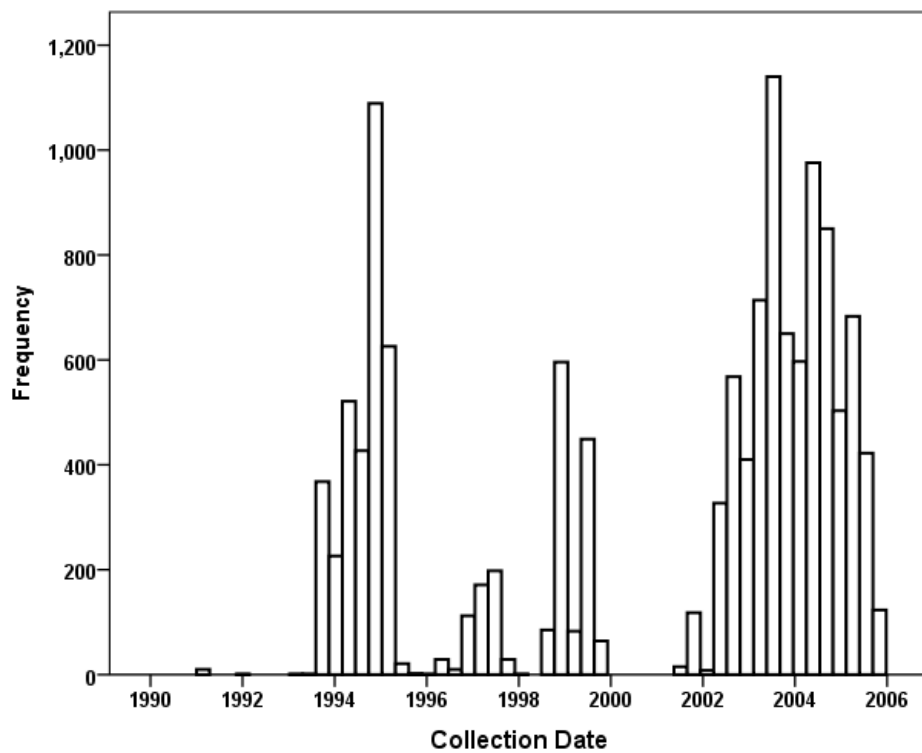
Supplementary Figure 2. Comparison of estimated linear effects (beta coefficients from Cox regression) on mortality for selected biochemical tests, with estimates for all-cause mortality (white columns), cancer mortality (blue columns), cardiovascular disease mortality (green columns) and mortality from other stated causes (purple columns). Error bars show standard errors for the beta coefficients.