CO-INHERITANCE OF VARIATION IN ALL-CAUSE MORTALITY AND BIOCHEMICAL RISK FACTORS

Supplementary Tables

Supplementary Table 1. Descriptive statistics for study participants, by sex and study.

	Male									Female								
	'SSAGA' Study (1993-1996)			'Anxiety' Study 1996-1992			'NAG' Study 2001-2005			'SSAGA' Study (1993-1996)			'Anxiety' Study 1996-1992			'NAG' Study 2001-2005		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Age (years)	1117	44.9	11.1	741	48.4	15.0	3731	51.1	13.8	2220	46.5	12.0	1146	47.0	14.9	4512	50.4	14.0
BMI (kg/m^2)	1080	25.66	3.47	-	-	-	2992	27.08	4.41	2157	24.96	4.67	-	-	-	3772	26.61	5.63
Creatinine (μmol/l)	888	95.3	12.9	748	104.6	20.4	3766	101.1	18.5	1603	76.8	11.5	1151	83.2	16.2	4552	79.9	15.9
Urea (mmol/l)	888	6.22	1.40	747	6.83	1.72	3762	6.71	1.68	1604	5.33	1.40	1151	5.94	1.63	4546	6.01	1.64
Uric acid (mmol/l)	916	0.383	0.077	748	0.320	0.070	3769	0.346	0.076	1643	0.283	0.072	1153	0.249	0.067	4552	0.262	0.071
Calcium (mmol/l)	888	2.41	0.089	-	-	-	3750	2.46	0.162	1603	2.39	0.095	-	-	-	4547	2.44	0.152
Total Protein (g/l)	887	74.4	4.3	725	77.4	5.0	3720	77.6	4.6	1599	74.1	4.5	1143	77.6	4.8	4503	77.0	4.6
Albumin (g/l)	888	48.9	3.0	748	48.1	3.1	3760	48.8	3.0	1603	47.2	3.1	1153	46.7	2.9	4550	47.5	2.9
Globulins (g/l)	886	25.5	3.6	725	29.4	3.9	3712	28.8	3.9	1599	26.9	3.6	1143	30.9	3.8	4501	29.6	3.7
Bilirubin (g/l)	883	9.7	5.8	744	10.1	5.3	3738	9.9	5.5	1601	7.6	4.2	1147	7.9	4.3	4529	7.9	4.4
log Bilirubin		*0.9330*	*0.2121*		*0.9555*	*0.1990*		*0.9450*	*0.2111*		*0.8347*	*0.1996*		*0.8524*	*0.1932*		*0.8494*	*0.2033*
ALP (u/l)	889	70.2	21.2	-	-	-	3761	77.9	21.3	1602	65.8	21.9	-	-	-	4551	75.1	24.8
AST (u/l)	1046	25.1	13.2	747	34.6	14.7	3769	27.3	11.3	2008	21.1	7.2	1153	29.4	9.5	4553	22.3	9.3
log AST		*1.3715*	*0.1443*		*1.5184*	*0.1265*		*1.4116*	*0.1364*		*1.3018*	*0.1340*		*1.4503*	*0.1209*		*1.3276*	*0.1278*
ALT (u/l)	1046	23.9	26.8	747	33.4	36.5	3769	30.9	19.9	2008	15.8	9.4	1153	23.2	14.3	4553	20.5	12.4
log ALT		*1.3032*	*0.2394*		*1.4590*	*0.2106*		*1.4343*	*0.2107*		*1.1412*	*0.2201*		*1.3164*	*0.1909*		*1.2663*	*0.1826*
GGT (u/l)	1046	30.6	32.9	748	35.2	45.6	3769	39.5	44.0	2008	18.3	16.5	1153	22.1	22.4	4551	24.2	27.9
log GGT		*1.3702*	*0.2869*		*1.4175*	*0.2972*		*1.4803*	*0.2845*		*1.1645*	*0.2715*		*1.2427*	*0.2698*		*1.2801*	*0.2658*
BCHE (u/l)		-	-	748	9403	1950	3768	9750	1941		-	-	1153	8444	1956	4552	8802	1923
Total cholesterol (mmol/l)	1118	5.68	1.05	748	5.63	1.10	3769	5.70	1.06	2221	5.63	1.09	1153	5.62	1.04	4552	5.65	1.04
LDL-C (mmol/l)	994	3.52	0.92	707	3.30	0.93	3530	3.36	0.93	2118	3.38	0.99	1127	3.20	0.90	4472	3.22	0.92
HDL-C (mmol/l)	1062	1.23	0.28	748	1.36	0.37	3769	1.35	0.37	2155	1.55	0.39	1153	1.65	0.45	4552	1.66	0.42
Triglyceride (mmol/l)	1120	2.18	1.55	748	2.20	1.43	3769	2.26	1.42	2221	1.55	1.00	1153	1.71	1.05	4552	1.69	0.96
log Triglyceride		*0.2616*	*0.2515*		*0.2773*	*0.2335*		*0.2898*	*0.2312*		*0.1237*	*0.2301*		*0.1748*	*0.2131*		*0.1735*	*0.2144*
Glucose (mmol/l)	878	5.28	1.22	-	-	-	2571	5.33	2.00	1580	5.11	1.08	-	-	-	3274	4.93	1.54
C-reactive protein (mg/l)		-	-	748	2.90	6.30	3758	3.34	5.78	-	-	-	1153	4.01	6.63	4544	4.21	7.64
log CRP		-	-		*0.1408*	*0.5712*		*0.2581*	*0.4830*		-	-		*0.2616*	*0.6001*		*0.3253*	*0.5389*
Iron (μmol/l)	1030	18.16	5.75	-	-	-	3768	21.52	6.47	2077	17.4	6.8	-	-	-	4552	19.1	6.5
Transferrin (g/l)	1030	2.70	0.40	748	2.46	0.35	3765	2.69	0.35	2076	2.89	0.51	1153	2.67	0.45	4548	2.86	0.45
Saturation (%)	1030	27.3	9.2	-	-	-	3766	32.4	10.6	2076	24.7	10.6	-	-	-	4548	27.4	10.2
Ferritin (mg/l)	1030	240	180	748	218	227	3766	260	191	2077	99	108	1153	94	109	4552	113	114
log Ferritin		*2.2571*	*0.3540*		*2.1739*	*0.4113*		*2.3013*	*0.3410*		*1.8151*	*0.4177*		*1.7727*	*0.4354*		*1.8921*	*0.3908*

Supplementary Table 2. Correlations between age-and sex-adjusted biomarker standardised residuals and polygenic risk scores. Standard errors and p-values are corrected for related subjects. PRS, polygenic risk score; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; BCHE, butyrylcholinesterase; LDL-C, HDL-C, low- and high-density lipoprotein cholesterol; CRP, C-reactive protein.

		PRS1	PRS2	PRS3	PRS4	PRS5	PRS6	PRS7	PRS8
Creatinine	Coefficient	-0.0031	0.0133	0.0188	-0.0015	0.0010	0.0006	-0.0047	-0.0040
	Robust SE	0.0106	0.0105	0.0099	0.0101	0.0102	0.0102	0.0104	0.0105
	p-value	0.773	0.205	0.059	0.882	0.920	0.956	0.653	0.701
Urea	Coefficient	-0.0139	-0.0078	0.0025	-0.0073	-0.0099	-0.0102	-0.0110	-0.0110
	Robust SE	0.0103	0.0104	0.0098	0.0103	0.0103	0.0102	0.0103	0.0103
	p-value	0.179	0.453	0.798	0.480	0.336	0.317	0.284	0.285
Urate	Coefficient	0.0065	0.0220	0.0248	0.0244	0.0345	0.0352	0.0337	0.0346
	Robust SE	0.0115	0.0112	0.0104	0.0111	0.0110	0.0112	0.0111	0.0110
	p-value	0.572	0.050	0.017	0.027	0.0018	0.0017	0.0023	0.0017
Calcium	Coefficient	0.0114	0.0040	-0.0153	-0.0127	0.0014	0.0053	0.0082	0.0069
	Robust SE	0.0112	0.0115	0.0111	0.0109	0.0108	0.0107	0.0107	0.0107
	p-value	0.306	0.725	0.169	0.243	0.894	0.618	0.445	0.517
Total protein	Coefficient	-0.0236	-0.0145	0.0037	0.0118	0.0233	0.0223	0.0194	0.0189
	Robust SE	0.0108	0.0109	0.0104	0.0106	0.0106	0.0107	0.0106	0.0106
	p-value	0.030	0.184	0.719	0.268	0.028	0.037	0.069	0.076
Albumin	Coefficient	-0.0058	-0.0032	-0.0077	-0.0143	-0.0152	-0.0163	-0.0148	-0.0148
	Robust SE	0.0106	0.0107	0.0102	0.0104	0.0105	0.0105	0.0104	0.0104
	p-value	0.582	0.767	0.452	0.168	0.147	0.121	0.154	0.155
Globulins	Coefficient	-0.0217	-0.0133	0.0123	0.0267	0.0399	0.0385	0.0341	0.0334
	Robust SE	0.0112	0.0113	0.0109	0.0110	0.0110	0.0111	0.0111	0.0111
	p-value	0.052	0.239	0.256	0.015	3.09×10^{-4}	5.35×10^{-4}	0.0021	0.0026
Bilirubin	Coefficient	0.0083	-0.0110	-0.0036	-0.0258	-0.0143	-0.0157	-0.0257	-0.0254
	Robust SE	0.0114	0.0114	0.0112	0.0115	0.0116	0.0117	0.0115	0.0115
	p-value	0.466	0.333	0.751	0.025	0.216	0.179	0.026	0.027
ALP	Coefficient	0.0010	-0.0104	0.0129	0.0164	0.0378	0.0389	0.0349	0.0350
	Robust SE	0.0121	0.0124	0.0122	0.0124	0.0125	0.0123	0.0120	0.0120
	p-value	0.931	0.399	0.291	0.187	0.0025	0.0016	0.0038	0.0035
AST	Coefficient	0.0008	0.0035	0.0056	-0.0068	0.0013	0.0003	-0.0025	-0.0020
	Robust SE	0.0102	0.0103	0.0104	0.0104	0.0105	0.0103	0.0103	0.0103
	p-value	0.935	0.733	0.589	0.512	0.902	0.974	0.809	0.845
ALT	Coefficient	0.0062	0.0044	0.0069	-0.0019	0.0136	0.0137	0.0138	0.0141
	Robust SE	0.0108	0.0109	0.0106	0.0107	0.0108	0.0107	0.0106	0.0105
	p-value	0.569	0.690	0.516	0.860	0.208	0.200	0.192	0.180
AST/ALT	Coefficient	-0.0058	-0.0071	-0.0046	-0.0023	-0.0168	-0.0167	-0.0191	-0.0193
	Robust SE	0.0112	0.0111	0.0107	0.0108	0.0107	0.0107	0.0107	0.0108
	p-value	0.604	0.523	0.666	0.831	0.116	0.121	0.076	0.073
GGT	Coefficient	0.0145	0.0102	0.0135	0.0023	0.0251	0.0260	0.0268	0.0265
	Robust SE	0.0111	0.0110	0.0105	0.0108	0.0109	0.0108	0.0107	0.0107
	p-value	0.194	0.353	0.201	0.834	0.021	0.016	0.013	0.014
BCHE	Coefficient	0.0297	0.0333	0.0064	0.0128	0.0087	0.0148	0.0085	0.0082
	Robust SE	0.0123	0.0119	0.0114	0.0120	0.0119	0.0118	0.0119	0.0119
	p-value	0.016	0.0052	0.574	0.286	0.464	0.209	0.477	0.493

		PRS1	PRS2	PRS3	PRS4	PRS5	PRS6	PRS7	PRS8
Total cholesterol	Coefficient	0.0438	0.0326	0.0098	0.0173	0.0268	0.0251	0.0270	0.0266
	Robust SE	0.0111	0.0108	0.0103	0.0104	0.0107	0.0107	0.0105	0.0105
	p-value	8.36×10^{-5}	0.0024	0.343	0.098	0.012	0.019	0.010	0.012
LDL-C	Coefficient	0.0507	0.0428	0.0193	0.0201	0.0314	0.0314	0.0308	0.0312
	Robust SE	0.0114	0.0110	0.0106	0.0107	0.0108	0.0108	0.0107	0.0107
	p-value	8.49×10^{-6}	1.03×10^{-4}	0.069	0.061	0.0037	0.0038	0.0039	0.0035
HDL-C	Coefficient	-0.0337	-0.0434	-0.0231	-0.0326	-0.0313	-0.0307	-0.0239	-0.0249
	Robust SE	0.0112	0.0114	0.0110	0.0110	0.0107	0.0107	0.0108	0.0108
	p-value	0.0026	1.45×10^{-4}	0.035	0.0031	0.0034	0.0042	0.027	0.021
Triglyceride	Coefficient	0.0196	0.0225	0.0082	0.0331	0.0346	0.0313	0.0318	0.0312
	Robust SE	0.0113	0.0109	0.0106	0.0104	0.0106	0.0106	0.0105	0.0105
	p-value	0.082	0.040	0.439	0.0015	0.0011	0.0032	0.0025	0.0029
Glucose	Coefficient	0.0033	0.0091	0.0005	-0.0015	0.0154	0.0124	0.0122	0.0108
	Robust SE	0.0129	0.0119	0.0127	0.0131	0.0130	0.0125	0.0125	0.0125
	p-value	0.791	0.446	1.000	0.920	0.237	0.320	0.330	0.390
CRP	Coefficient	-0.0658	-0.0354	-0.0125	0.0187	0.0258	0.0305	0.0326	0.0322
	Robust SE	0.0117	0.0114	0.0107	0.0111	0.0112	0.0114	0.0115	0.0115
	p-value	1.99×10^{-8}	0.0019	0.242	0.093	0.021	0.0075	0.0046	0.0053
Iron	Coefficient	0.0218	0.0053	0.0026	0.0079	0.0128	0.0126	0.0133	0.0134
	Robust SE	0.0109	0.0105	0.0106	0.0109	0.0108	0.0107	0.0106	0.0106
	p-value	0.046	0.615	0.804	0.468	0.236	0.240	0.210	0.206
Transferrin	Coefficient	-0.0213	-0.0196	-0.0120	0.0008	0.0038	0.0077	0.0057	0.0057
	Robust SE	0.0109	0.0110	0.0108	0.0108	0.0110	0.0110	0.0107	0.0108
	p-value	0.051	0.076	0.270	0.938	0.728	0.483	0.597	0.595
Saturation	Coefficient	0.0269	0.0111	0.0069	0.0083	0.0112	0.0109	0.0123	0.0125
	Robust SE	0.0111	0.0111	0.0109	0.0114	0.0115	0.0114	0.0111	0.0111
	p-value	0.015	0.317	0.525	0.468	0.328	0.338	0.267	0.259
Ferritin	Coefficient	0.0212	0.0213	0.0107	0.0139	0.0158	0.0223	0.0237	0.0239
	Robust SE	0.0108	0.0104	0.0100	0.0102	0.0102	0.0101	0.0101	0.0101
	p-value	0.049	0.042	0.282	0.176	0.119	0.028	0.019	0.018

Supplementary Table 3.

Part 1. Comparison of adjusted biochemical test results between groups with and without parental survival information.

a) Mothers' vital status data (alive or died) available (coded as 0, Known) or missing (coded as 1, Unknown/Missing)

Mother death unknown		Urate	Albumin	ALP	GGT	LDL-C	HDL-C	Triglycerides	CRP	Glucose
.00 (Known)	Mean	-0.011	0.002	-0.010	-0.010	0.015	0.009	-0.002	-0.005	-0.010
	N	10533	10485	8797	10962	10814	11223	11223	9607	7027
	Std. Deviation	0.980	1.004	1.000	0.992	0.997	0.991	1.005	1.010	0.940
	Std. Error of Mean	0.010	0.010	0.011	0.009	0.010	0.009	0.009	0.010	0.011
1.00 (Unknown/Missing)	Mean	0.064	-0.009	0.051	0.057	-0.090	-0.053	0.011	0.030	0.061
	N	1833	1814	1705	1888	1846	1914	1914	1715	1157
	Std. Deviation	1.107	0.974	0.997	1.042	1.014	1.049	0.971	0.938	1.304
	Std. Error of Mean	0.026	0.023	0.024	0.024	0.024	0.024	0.022	0.023	0.038
Difference in mean		-0.075	0.010	-0.061	-0.067	0.105	0.062	-0.013	-0.035	-0.071
p-value		0.003	0.682	0.021	0.0075	3.14E-05	0.013	0.599	0.180	0.026

b) Fathers' vital status data (alive or died) available (coded as 0, Known) or missing (coded as 1, Unknown/Missing)

Father death unknown		Urate	Albumin	ALP	GGT	LDL-C	HDL-C	Triglycerides	CRP	Glucose
.00 (Not unknown)	Mean	-0.011	0.001	-0.009	-0.011	0.015	0.008	-0.002	-0.006	-0.012
	N	10482	10433	8755	10910	10764	11171	11171	9566	7004
	Std. Deviation	0.978	1.006	1.001	0.991	0.994	0.991	1.005	1.009	0.938
	Std. Error of Mean	0.010	0.010	0.011	0.009	0.010	0.009	0.010	0.010	0.011
1.00 (Unknown/Missing)	Mean	0.0613	-0.006	0.045	0.061	-0.083	-0.047	0.009	0.032	0.071
	N	1884	1866	1747	1940	1896	1966	1966	1756	1180
	Std. Deviation	1.111	0.967	0.992	1.048	1.027	1.050	0.967	0.946	1.306
	Std. Error of Mean	0.026	0.022	0.024	0.024	0.024	0.024	0.022	0.023	0.038
Difference in mean		-0.072	0.008	-0.054	-0.072	0.097	0.056	-0.010	-0.038	-0.083
p-value		0.0038	0.763	0.039	0.0035	9.49E-05	0.023	0.682	0.147	0.0081

Part 2. Comparison of parental survival between groups with and without biochemical test information (selected on presence or absence of triglyceride results, which was the test with the largest number of results). Availability of triglyceride results was coded as 0 if missing and 1 if available.

There was no significant difference in reported survival for either mothers or fathers between participants with and without triglyceride results.

					95.0% CI for HR	
Mothers' survival	B	SE	Sig.	HR	Lower	Upper
Triglyceride missing	0.011	0.025	0.672	1.011	0.962	1.061

					95.0% CI for HR	
Fathers' survival	B	SE	Sig.	HR	Lower	Upper
Triglyceride missing	0.020	0.020	0.315	1.020	0.981	1.061

Part 3. Comparison of Hazard Ratios (HR) for parental survival by age of study participants at the time of blood collection. Participants were divided at the approximate median age at time of blood collection and associations between the age- and sex-adjusted standardised biochemical test results and survival of their mothers and fathers were estimated separately for participants aged up to 49 years and those 50 or over.

For all tests except urate (in the fathers but not the mothers) the 95% confidence intervals for the HR estimates overlapped.

Mothers survival

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Urate	0.078	0.038	0.040	1.081	1.003	1.164
50 and above	Urate	0.077	0.020	1.46E-04	1.080	1.038	1.124

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Albumin	-0.025	0.036	0.480	0.975	0.909	1.046
50 and above	Albumin	-0.078	0.023	5.91E-04	0.925	0.884	0.967

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	ALP	-0.046	0.039	0.233	0.955	0.885	1.030
50 and above	ALP	0.037	0.025	0.132	1.038	0.989	1.089

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	GGT	0.059	0.034	0.085	1.061	0.992	1.135
50 and above	GGT	0.015	0.021	0.469	1.016	0.974	1.059

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	LDL-C	0.023	0.036	0.512	1.024	0.955	1.098
50 and above	LDL-C	-0.037	0.021	0.082	0.964	0.925	1.005

Fathers survival

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Urate	0.123	0.024	3.98E-07	1.131	1.079	1.186
50 and above	Urate	0.039	0.018	0.030	1.040	1.004	1.077

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Albumin	-0.045	0.023	0.050	0.956	0.915	1.000
50 and above	Albumin	-0.015	0.020	0.450	0.985	0.947	1.024

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	ALP	0.039	0.025	0.118	1.040	0.990	1.092
50 and above	ALP	0.048	0.021	0.019	1.050	1.008	1.093

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	GGT	0.071	0.022	0.0014	1.074	1.028	1.121
50 and above	GGT	0.037	0.018	0.044	1.038	1.001	1.075

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	LDL-C	0.086	0.023	2.03E-04	1.090	1.041	1.140
50 and above	LDL-C	0.033	0.019	0.076	1.033	0.997	1.072

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	HDL-C	-0.096	0.037	0.0091	0.909	0.846	0.976
50 and above	HDL-C	-0.092	0.021	1.10E-05	0.913	0.876	0.951

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	HDL-C	-0.102	0.024	1.55E-05	0.903	0.862	0.946
50 and above	HDL-C	-0.041	0.018	0.020	0.960	0.927	0.994

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Triglycerides	0.065	0.033	0.051	1.067	1.000	1.138
50 and above	Triglycerides	0.055	0.022	0.013	1.056	1.012	1.102

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Triglycerides	0.074	0.022	6.59E-04	1.077	1.032	1.124
50 and above	Triglycerides	0.030	0.019	0.102	1.031	0.994	1.069

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	CRP	0.113	0.037	0.0020	1.120	1.042	1.203
50 and above	CRP	0.062	0.026	0.018	1.064	1.011	1.120

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	CRP	0.071	0.023	0.0024	1.074	1.026	1.125
50 and above	CRP	0.030	0.023	0.194	1.031	0.985	1.078

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Glucose	0.078	0.043	0.068	1.081	0.994	1.175
50 and above	Glucose	-0.015	0.024	0.537	0.985	0.940	1.033

						95.0% CI for HR	
Age		B	SE	Sig.	HR	Lower	Upper
Up to 49	Glucose	0.077	0.028	0.0064	1.080	1.022	1.142
50 and above	Glucose	0.018	0.022	0.407	1.018	0.975	1.064