

Supplemental Online Content

Association of Plasma High-Density Lipoprotein Cholesterol and Mortality in Healthy Older Adults

Table S1: Information of 309 variants used in the polygenic risk score for HDL-C.

Table S2: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality ASPREE: Excluding the US population, participants reporting high physical activity and adjustment for weight change from baseline to annual visit 2 (HR, 95% CI)

Table S3: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality excluding those with a history of prostate cancer and testosterone supplements ASPREE (HR, 95% CI), only males

Table S4: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality excluding those who were taking hormone replacement therapy ASPREE (HR, 95% CI), only females

Table S5: Baseline characteristics of participants: Overall, and high-density lipoprotein cholesterol (HDL-C) category in the UK Biobank cohort

Table S6: Association between baseline HDL and mortality in the UK Biobank: Caucasians only, Excluding those reporting high physical activity (HR, 95% CI)

Table S7: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality adjusted for HDL-C-PRS in the Aspirin in Reducing Events in the Elderly (ASPREE) and the UK Biobank (UKB) cohort (HR, 95% CI)

Table S8: Death endpoint subtype for non-cancer non-cardiovascular cause

Table S9: Comparison of associations between elevated high-density lipoprotein cholesterol (HDL-C) and cause and sex-specific mortality events observed in ASPREE, UKB and other previously published studies.

Table S10: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality in those never drink alcohol UKB (HR, 95% CI) (n=3076, age range 40-73 years)

Fig S1. Distribution of HDL polygenic risk score: A. Aspirin in Reducing Events in the Elderly B. UK biobank

Fig S2. Distribution of HDL cholesterol concentrations in the Aspirin in Reducing Events in the Elderly (ASPREE): A. Males B. Females

Fig S3. Distribution of high-density lipoprotein cholesterol (HDL-C) concentrations in the UK Biobank (UKB): A. Males B. Females

Fig S4. Nonlinear association between high-density lipoprotein (HDL) cholesterol levels in men in the UK Biobank (UKB): A. all-cause mortality, B. Cancer mortality, C. CVD mortality and D. noncancer-non-CVD mortality

Fig S5. Nonlinear association between high-density lipoprotein (HDL) cholesterol levels in women in the UK Biobank (UKB): A. all-cause mortality, B. Cancer mortality, C. CVD mortality and D. noncancer-non-CVD mortality

Supplementary Method: Validation cohort (UK Biobank)

Table S1: Information of 309 variants used in the polygenic risk score for HDL-C.

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
1:23734350	rs1767141	A	C	-0.0263027
1:26902388	rs6668958	T	G	0.0203878
1:27236212	rs17162330	T	C	0.0412983
1:28344980	rs12144891	A	G	0.0167868
1:40028180	rs4660293	A	G	0.04
1:63113719	rs1168089	T	C	-0.0153
1:93584606	rs4847399	A	G	-0.0216
1:107549245	rs2878349	A	G	-0.0149869
1:109817590	rs12740374	T	G	0.0453754
1:110082886	rs7550711	T	C	-0.0489667
1:110163879	rs28362581	A	G	-0.0275937
1:110470764	rs333947	A	G	-0.0266884
1:150940625	rs267738	T	G	-0.0239485
1:156700651	rs12145743	T	G	-0.0139968
1:172346548	rs1011731	A	G	0.0134303
1:178515312	rs4650994	A	G	-0.0193124
1:182157235	rs2243976	A	G	0.0289208
1:205631767	rs16856110	A	G	0.0199
1:219631981	rs6694509	T	C	-0.0194876
1:220970593	rs2807834	T	G	-0.0238182
1:230295691	rs4846914	A	G	0.0468203
1:230416744	rs1043900	A	G	0.0233713
1:234853406	rs558971	A	G	-0.0138399
2:272203	rs11553746	T	C	0.015806
2:622827	rs2867125	T	C	0.0172779
2:3634753	rs4850047	T	C	0.0201487
2:21231524	rs676210	A	G	0.0617334
2:21288321	rs562338	A	G	0.0177805
2:53992622	rs36020289	C	G	0.0462
2:65281401	rs12990465	T	C	0.0263
2:165528876	rs13389219	T	C	0.0327
2:203519783	rs6435161	T	G	0.0177
2:227093745	rs2943641	T	C	0.0391
3:11619958	rs11712666	A	G	-0.0140681
3:12359049	rs2067819	A	G	0.0211455
3:12434901	rs2292101	T	C	-0.0438087
3:36979042	rs6777217	A	G	-0.0129
3:47045846	rs2305637	T	C	-0.0263536
3:50093209	rs6762477	A	G	0.0232478
3:52532118	rs13326165	A	G	0.0213334
3:53125922	rs11242	T	C	0.0150055
3:123190731	rs35000036	T	C	-0.0132
3:136006576	rs1279840	T	C	0.028

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
3:152171870	rs3773910	C	G	-0.0168785
3:156798732	rs900399	A	G	-0.0213473
3:185510613	rs7633675	T	G	0.0133307
3:185818882	rs4234589	A	G	0.0222339
4:858332	rs11248051	T	C	-0.019
4:26062990	rs10019888	A	G	0.0243
4:69591612	rs293429	T	C	-0.0133
4:88064431	rs10023050	A	G	-0.0152213
4:89741269	rs3822072	A	G	-0.0214017
4:100014805	rs2602836	A	G	0.012717
4:103184239	rs112519623	A	G	-0.0471894
4:103188709	rs13107325	T	C	-0.077677
4:157670537	rs6855363	T	C	-0.0185
5:53297611	rs7735253	A	G	-0.021011
5:55806751	rs459193	A	G	0.0264681
5:55861786	rs9686661	T	C	-0.0343413
5:67714246	rs4976033	A	G	0.0134382
5:74997756	rs10057967	T	C	-0.0205455
5:132349654	rs4705986	T	G	-0.0348
5:153363334	rs390299	A	G	-0.0145304
5:158022041	rs2434612	A	G	0.0225494
5:170459675	rs7730898	A	G	-0.0183
6:31105413	rs1265099	A	G	0.0169989
6:31526080	rs184070214	A	G	-0.0445304
6:31903804	rs9332739	C	G	-0.0290151
6:32667119	rs3135006	T	C	-0.0194957
6:33774394	rs2894342	A	C	0.0145871
6:34194866	rs1759645	T	C	0.0239333
6:34268107	rs16885998	T	G	0.0505644
6:34824636	rs11755393	A	G	0.0303751
6:35467891	rs41270076	T	C	0.0385584
6:41987451	rs4711698	T	C	0.0179812
6:42932715	rs2274517	T	C	0.0155937
6:43758873	rs6905288	A	G	-0.0295443
6:43785255	rs35349911	T	C	-0.0138489
6:43806609	rs881858	A	G	-0.0138468
6:109246891	rs2754820	A	G	0.0196214
6:109574095	rs884366	A	G	-0.0143481
6:116325142	rs3756772	T	C	0.0128002
6:127452935	rs2745353	T	C	-0.0201705
6:137076010	rs6925103	T	C	-0.0121453
6:139839423	rs643381	A	C	0.0207997
6:161006077	rs41272114	T	C	0.0663301
6:161082461	rs1652507	T	C	0.0460033
7:1083777	rs1997243	A	G	-0.0222054

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
7:6449496	rs2303361	T	C	-0.0237664
7:17911038	rs10282707	T	C	-0.0258393
7:26397239	rs1534696	A	C	0.0185192
7:36170883	rs2726070	A	G	-0.0171845
7:50305863	rs4917014	T	G	-0.0138
7:72856430	rs1178979	T	C	-0.0335
7:129663496	rs11556924	T	C	0.0126053
7:130466854	rs972283	A	G	0.0275923
7:150217309	rs3735080	T	C	-0.0136905
7:150521026	rs7787577	A	G	0.0314351
8:9183339	rs11774381	T	C	-0.0277809
8:9183596	rs4841132	A	G	-0.108003
8:10643164	rs9657541	T	C	-0.0246395
8:19805708	rs1801177	A	G	-0.119999
8:19813180	rs264	A	G	0.0325237
8:19813529	rs268	A	G	0.237858
8:19824492	rs13702	T	C	-0.0589478
8:19831977	rs17091872	A	G	-0.0559013
8:19854773	rs2410622	T	C	-0.0263574
8:19860161	rs6983170	T	C	0.0932811
8:19861854	rs6651485	A	G	0.0538949
8:19865175	rs2083637	A	G	-0.0484456
8:19889872	rs7837677	T	C	-0.0336313
8:19928160	rs10106652	A	G	0.0306335
8:19930682	rs34859606	C	G	-0.0194426
8:19941145	rs6586892	A	C	0.0359656
8:19955920	rs6983999	A	T	0.0239463
8:71099094	rs4512408	T	C	0.0255
8:106357374	rs2957447	A	G	0.0138
8:116599199	rs2293889	T	G	-0.0304473
8:121868551	rs4871137	T	G	-0.0212605
8:126449406	rs17405319	T	C	-0.0252089
8:126484526	rs2954026	T	G	-0.0493033
9:15305378	rs581080	C	G	0.037
9:107557315	rs13292026	A	G	-0.0437128
9:107562804	rs2230808	T	C	-0.0236144
9:107578620	rs76881554	A	G	-0.16407
9:107586753	rs2066714	T	C	-0.0514204
9:107657070	rs3905000	A	G	-0.0547365
9:107661150	rs10120087	A	C	0.0444376
9:107665978	rs1800978	C	G	0.0573747
9:107669073	rs13284054	T	C	0.0541049
9:107690450	rs1800977	A	G	0.0256097
9:117148430	rs10733608	T	G	0.0139419
9:136155000	rs635634	T	C	0.0145

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
10:8601074	rs11255744	T	C	-0.018197
10:17260290	rs10904908	A	G	-0.0117604
10:46013277	rs970548	A	C	-0.0245
10:94839642	rs2068888	A	G	0.0205217
10:101912064	rs2862954	T	C	-0.0172692
10:113940329	rs2792751	T	C	0.0277199
10:114048792	rs2148489	T	C	0.0222912
10:115789375	rs7076938	T	C	0.0172093
11:823586	rs140201358	C	G	0.052292
11:2936952	rs16928809	A	G	-0.024642
11:13355770	rs6486121	T	C	-0.0151899
11:14276999	rs2303975	A	G	0.0192409
11:27667202	rs925946	T	G	-0.0121835
11:32481177	rs7927401	T	C	-0.0210055
11:47258853	rs3824866	T	C	0.0331259
11:47298360	rs326214	A	G	-0.0247953
11:47663049	rs10838738	A	G	0.0192826
11:61599347	rs61897793	A	G	0.0238054
11:61609750	rs174583	T	C	-0.0424279
11:64031241	rs35169799	T	C	-0.0395875
11:65561468	rs644740	T	C	0.0159728
11:68703959	rs622082	A	G	0.0154999
11:75455021	rs499974	A	C	-0.0254142
11:109995944	rs746463	T	C	-0.0165067
11:116611827	rs180349	A	T	0.0171474
11:116633947	rs10488698	A	G	0.044709
11:116648917	rs964184	C	G	0.132066
11:116701354	rs138326449	A	G	0.715545
11:116707044	rs138407155	A	T	0.355531
11:116838130	rs12281729	A	C	0.0769114
11:116896155	rs10892063	A	C	0.0418259
11:116973929	rs12269901	C	G	0.0267786
11:117183650	rs593245	T	C	0.0146071
11:122522375	rs7941030	T	C	-0.022857
11:126228659	rs4937122	T	G	0.0316876
12:20473758	rs7134375	A	C	0.0215003
12:20591332	rs7134150	A	G	-0.0313866
12:26443030	rs4963975	A	G	-0.0197903
12:49399132	rs1126930	C	G	-0.0372583
12:53866619	rs784563	T	G	0.0152786
12:57792580	rs11613352	T	C	0.0226244
12:101873956	rs2373459	T	C	0.0159672
12:109937534	rs7298565	A	G	0.0279893
12:111884608	rs3184504	T	C	-0.024342
12:121420807	rs1183910	A	G	0.0126543

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
12:122963550	rs12369179	T	C	-0.030961
12:123200768	rs1798192	T	G	-0.0193286
12:123491572	rs940904	A	G	-0.0226219
12:124404718	rs12317176	T	C	-0.0224079
12:124505444	rs863750	T	C	-0.0171575
12:125083696	rs12230272	A	G	0.0223347
12:125261593	rs838880	T	C	-0.0248875
12:125283766	rs10773105	T	C	-0.0255327
12:125292360	rs150728540	A	C	0.475574
12:125299542	rs5891	T	C	0.0776071
12:125327384	rs7306660	A	G	-0.0285815
12:125380232	rs7298751	A	G	-0.0425878
13:41609047	rs17532301	A	G	-0.0266
14:65914867	rs10483776	A	G	0.0153122
14:70783943	rs8021180	A	G	0.014198
14:74250126	rs13379043	T	C	-0.0175699
14:105277209	rs4983559	A	G	-0.0252
15:41847176	rs9944249	T	G	-0.0132233
15:43820717	rs55707100	T	C	-0.0934007
15:58646332	rs4622454	T	C	0.0205337
15:58674695	rs4775041	C	G	0.0388498
15:58676119	rs16940147	A	G	0.0498861
15:58678869	rs117901517	T	C	0.0377591
15:58682690	rs34718390	A	G	0.0528082
15:58683366	rs1532085	A	G	0.0620128
15:58686809	rs7165077	T	C	-0.0273046
15:58690048	rs6494003	A	G	0.0927457
15:58702941	rs16940233	T	C	-0.0478432
15:58721447	rs12912415	A	G	0.0400102
15:58730571	rs6494006	T	C	0.0436024
15:58731395	rs17301746	T	C	0.087949
15:58751877	rs936960	T	G	0.0524001
15:58779039	rs1869138	T	C	-0.0281074
15:58838010	rs6083	A	G	-0.016189
15:58857378	rs17269397	A	G	-0.0261116
15:59010962	rs424346	T	C	0.0544735
15:61955338	rs12148597	A	G	-0.0157745
15:63414083	rs34317102	A	C	-0.019028
15:63970456	rs2228510	T	C	-0.0117381
15:90214777	rs139271800	A	G	-0.2482
16:985891	rs7202647	T	C	0.017
16:11403893	rs12928822	T	C	0.0179
16:53800954	rs1421085	T	C	0.0282437
16:54410447	rs12929759	A	G	0.0182545
16:55029160	rs4238772	A	G	0.0285827

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
16:56883438	rs8044753	A	G	0.0247609
16:56921840	rs36049418	A	G	0.0655532
16:56937262	rs11648751	T	C	-0.0303659
16:56949168	rs37029	A	G	-0.0242036
16:56985139	rs9989419	A	G	-0.0336365
16:56985514	rs72786786	A	G	0.0576565
16:56986976	rs76315536	T	C	0.161449
16:56994894	rs4783961	A	G	0.0260019
16:56995236	rs1800775	A	C	0.0317126
16:56995935	rs34065661	C	G	-0.484692
16:56999258	rs7203984	A	C	0.0740872
16:57005479	rs1532624	A	C	0.112757
16:57005550	rs12708974	T	C	-0.0857298
16:57007353	rs5883	T	C	0.167389
16:57007451	rs289714	A	G	0.0821681
16:57015091	rs5880	C	G	-0.137781
16:57383759	rs506829	T	C	0.0192122
16:60419220	rs16962034	T	G	-0.0157044
16:67714560	rs7202185	A	G	-0.0372704
16:67928042	rs16942887	A	G	0.0742214
16:71669624	rs1345868	A	C	0.0144331
16:81524274	rs12443634	A	C	-0.0312639
17:7462969	rs3803800	A	G	-0.0134
17:26695832	rs2071379	A	G	0.0143
17:37715426	rs11078915	T	C	-0.0267118
17:37813856	rs11869286	C	G	0.0238863
17:37815304	rs11556624	C	G	0.0867316
17:38156712	rs4794822	T	C	-0.0176751
17:41926126	rs72836561	T	C	-0.187459
17:41942109	rs231539	T	C	-0.0357199
17:46022065	rs17679445	A	G	0.0295385
17:47422363	rs11652146	A	G	-0.0171784
17:65870073	rs12602912	T	C	-0.0176127
17:66884879	rs10852765	A	G	0.0156253
17:76395430	rs2292642	T	C	0.0319034
17:76437343	rs2289750	A	G	-0.0282954
18:21161134	rs1788783	T	C	0.015
18:47097398	rs8093249	A	G	0.0336754
18:47109955	rs77960347	A	G	-0.250466
18:47113165	rs117623631	T	C	0.343183
18:47118219	rs3786248	T	C	-0.0589871
18:47160953	rs7241918	T	G	0.0740528
18:47176793	rs4939886	A	G	0.0197515
18:47209143	rs11660468	T	C	0.0253264
18:57942799	rs9956279	T	C	-0.0168

Chromosome: position	SNP ID	Effect allele	Non-effect allele	Weight
19:3414088	rs12975319	A	G	-0.0153429
19:7244884	rs10408844	T	C	0.0180243
19:7970635	rs4804833	A	G	-0.0149519
19:8429323	rs116843064	A	G	0.245615
19:8467235	rs2913968	T	C	0.016603
19:11202306	rs6511720	T	G	0.0200513
19:11303554	rs17616661	A	G	0.0257687
19:11347493	rs737337	T	C	0.0570415
19:32917455	rs2111504	A	T	0.0166861
19:33899065	rs731839	A	G	0.0177915
19:45395619	rs2075650	A	G	0.0378654
19:45396973	rs77301115	A	G	-0.0660358
19:45412079	rs7412	T	C	0.0856446
19:45414451	rs439401	T	C	0.0141174
19:45422946	rs4420638	A	G	0.0419678
19:45448465	rs5167	T	G	-0.0375886
19:46307406	rs8111071	A	G	0.0278068
19:47589895	rs2303108	T	C	0.01366
19:52327784	rs3752125	T	C	-0.0204076
19:54759361	rs12975366	T	C	0.0211845
19:54792761	rs386000	C	G	0.0436559
19:54837165	rs12979085	A	G	0.0204138
20:17596155	rs1132274	A	C	-0.0159
20:32648738	rs2268086	A	G	0.0143913
20:33734493	rs1415771	A	G	-0.0129247
20:43042364	rs1800961	T	C	-0.142137
20:44586023	rs3827066	T	C	0.0496205
20:44598670	rs8123864	T	C	0.0477456
20:45592842	rs1211644	T	C	-0.0177758
20:46153148	rs11700063	A	G	0.0205946
20:46340596	rs4239651	T	C	-0.020977
20:56098733	rs6025606	T	C	0.0118726
20:62196253	rs310631	A	C	0.013306
20:62695931	rs6062343	A	G	0.0137017
21:46271452	rs235314	T	C	-0.0149922
21:46901973	rs12482088	A	C	0.0186627
22:21932068	rs181362	T	C	-0.0303378
22:29451671	rs4823006	A	G	-0.0129774
22:30888527	rs17738540	T	C	-0.0184464
22:38569006	rs738322	A	G	-0.0198011
22:44324727	rs738409	C	G	0.0155275

Table S2: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality ASPREE: Excluding the US population, participants reporting high physical activity and adjustment for weight change from baseline to annual visit 2 (HR, 95% CI)

	HDL levels							
	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L
Male					Female			
Excluding the US population (n=15121) ^a								
All-cause	1.03 (0.85, 1.25)	1	0.98 (0.83, 1.16)	1.48 (1.15, 1.90)	0.89 (0.59, 1.34)	1	1.02 (0.86, 1.21)	0.95 (0.76, 1.17)
Cancer	1.10 (0.84, 1.43)	1	0.99 (0.77, 1.26)	1.29 (0.88, 1.90)	0.65 (0.34, 1.24)	1	0.90 (0.69, 1.38)	0.72 (0.52, 1.11)
CVD	0.93 (0.62, 1.37)	1	0.80 (0.54, 1.15)	0.90 (0.46, 1.74)	1.26 (0.60, 2.66)	1	1.09 (0.76, 1.58)	1.45 (0.97, 2.19)
noncancer-nonCVD	1.01 (0.70, 1.45)	1	1.14 (0.84, 1.54)	2.20 (1.47, 3.29)	1.07 (0.49, 2.34)	1	1.23 (0.88, 1.70)	0.99 (0.66, 1.48)
Excluding those reporting high physical activity (n=6082) ^b								
All-cause	1.10 (0.85, 1.42)	1	1.09 (0.85, 1.39)	2.10 (1.47, 3.01)	1.09 (0.71, 1.67)	1	0.98 (0.78, 1.23)	0.83 (0.62, 1.11)
Cancer	1.30 (0.91, 1.88)	1	1.14 (0.78, 1.66)	1.51 (0.80, 2.87)	0.80 (0.56, 1.65)	1	0.80 (0.57, 1.13)	0.54 (0.33, 0.88)
CVD	1.10 (0.66, 1.81)	1	1.04 (0.62, 1.75)	1.68 (0.74, 3.79)	1.75 (0.84, 3.63)	1	0.95 (0.61, 1.49)	1.24 (0.73, 2.09)
noncancer-nonCVD	0.83 (0.51, 1.36)	1	1.05 (0.68, 1.61)	3.05 (1.80, 5.17)	1.04 (0.47, 2.32)	1	1.31 (0.89, 1.92)	0.97 (0.60, 1.59)
Additional adjustment for weight change from baseline to annual visit 2 with other confounding variables (n=16392)								
All-cause	1.03 (0.83, 1.27)	1	0.98 (0.81, 1.20)	1.61 (1.21, 2.13)	1.13 (0.74, 1.72)	1	1.01 (0.82, 1.23)	1.02 (0.88, 1.28)
Cancer	1.18 (0.87, 1.60)	1	1.03 (0.77, 1.37)	1.33 (0.84, 2.09)	0.84 (0.42, 1.67)	1	0.90 (0.67, 1.21)	0.76 (0.52, 1.11)
CVD	0.97 (0.63, 1.49)	1	0.77 (0.50, 1.18)	1.28 (0.67, 2.42)	1.32 (0.59, 2.94)	1	1.07 (0.71, 1.60)	1.40 (0.98, 2.19)

noncancer- nonCVD	0.85 (0.56, 1.29)	1	1.08 (0.76, 1.54)	2.27 (1.45, 3.54)	1.51 (0.74, 3.09)	1	1.16 (0.79, 1.69)	1.21 (0.75, 1.77)
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Adjusted for age, country of birth, BMI, physical activity, alcohol use, smoking status, levels of education, 100mg Aspirin, nonHDL-C, hypertension, diabetes, chronic kidney disease

^acountry of birth was not adjusted ^bphysical activity was not adjusted

Table S3: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality excluding those with a history of prostate cancer and testosterone supplements ASPREE (HR, 95% CI), only males

	HDL levels			
	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L
All cause	1.03 (0.84, 1.25)	1	0.99 (0.82, 1.18)	1.58 (1.22, 2.04)
Cancer	1.11 (0.84, 1.47)	1	0.94 (0.71, 1.33)	1.34 (0.90, 2.02)
CVD	0.86 (0.57, 1.29)	1	0.84 (0.58, 1.23)	0.84 (0.42, 1.68)
Non-cancer non-CVD	1.05 (0.73, 1.51)	1	1.19 (0.87, 1.63)	2.50 (1.68, 3.72)

adjusted for age, ethnic background, BMI, physical activity, smoking status, alcohol consumption, level of education, nonHDL-C, hypertension, diabetes, chronic kidney disease

Table S4: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality excluding those who were taking hormone replacement therapy ASPREE (HR, 95% CI), only females

	HDL levels			
	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L
All cause	1.01 (0.69-1.46)	1	0.99 (0.83-1.17)	0.99 (0.80-1.22)

Cancer	0.81 (0.45-1.47)	1	0.88 (0.68-1.12)	0.70 (0.50-1.01)
CVD	1.35 (0.67-2.76)	1	1.24 (0.87-1.76)	1.63 (1.09-2.40)
Non-cancer non-CVD	1.07 (0.55-2.08)	1	1.00 (0.74-1.37)	1.03 (0.71-1.49)

adjusted for age, ethnic background, BMI, physical activity, smoking status, alcohol consumption, level of education, nonHDL-C, hypertension, diabetes, chronic kidney disease

Table S5: Baseline characteristics of participants: Overall, and high-density lipoprotein cholesterol (HDL-C) category in the UK Biobank cohort

	Overall	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L	p-value
<i>Male</i>						
N (%)	29,735 (100)	5861 (19.7)	18,114 (60.9)	5085 (17.1)	675 (2.3)	
Age, mean (SD), y	66.9 (1.5)	66.9 (1.5)	66.9 (1.5)	66.9 (1.5)	66.9 (1.5)	0.85
Ethnic background						0.007
Caucasian	28594 (96.3)	5581 (95.4)	17,432 (96.3)	49,34 (97.1)	647 (95.8)	
Others	1110 (3.7)	272 (4.7)	662 (3.7)	148 (2.9)	28 (4.2)	
Low activity (walked outside <30 minutes), n (%)	1162 (38.8)	2409 (43.1)	6792 (38.6)	1732 (34.9)	229 (34.9)	<0.001
BMI, mean (SD), kg/m ²	27.6 (3.9)	29.2 (4.1)	27.6 (3.7)	25.9 (3.4)	24.9 (3.3)	<0.001
Current/former smoking, n (%)	17,331 (58.4)	3517 (60.1)	10,427 (57.6)	2975 (58.5)	412 (61.0)	0.004
Current alcohol use, n (%)	27,866 (93.8)	5,218 (89.2)	17,035 (94.2)	4947 (97.3)	666 (98.7)	<0.001
Education, n (%)						<0.001
<12 years of schooling	16,080 (54.1)	3,511 (60.0)	9801 (54.2)	2452 (48.3)	316 (46.8)	
>12 years of schooling	13,624 (45.9)	2342 (40.0)	8293 (45.8)	2630 (51.8)	359 (53.2)	
Hypertension, (%)	20,845 (70.1)	4256 (72.6)	12652 (69.9)	3467 (68.2)	470 (69.6)	<0.001
Chronic kidney disease (eGFR <60ml/min) ^a , (%)	1280 (4.3)	435 (7.4)	704 (3.9)	129 (2.5)	12 (1.8)	<0.001
Diabetes, n (%)	2825 (9.5)	1044 (17.8)	1525 (8.4)	216 (4.3)	40 (5.9)	<0.001
HDL-C PRS, mean (SD), z score (n=29,413)	-0.00 (1.00)	-0.55 (0.94)	0.01 (0.94)	0.50 (0.94)	0.82 (0.99)	<0.001
Total Cholesterol (mg/dl)	206.2 (42.3)	181.9 (40.4)	207.7 (41.0)	224.4 (39.0)	237.9 (38.5)	<0.001
Non-HDL-C (mg/dl)	155.8 (40.3)	146.4 (39.7)	158.6 (40.5)	157.3 (38.9)	148.4 (38.2)	<0.001
<i>Female</i>						
N (%)	33,114 (100)	1171 (3.5)	14733 (44.5)	13322 (40.2)	3888 (11.7)	
Age, mean (SD), y	66.9 (1.5)	66.9 (1.5)	66.9 (1.5)	66.9 (1.5)	66.9 (1.5)	0.92
Ethnic background						<0.001
Caucasian	32,029 (96.8)	1118 (95.7)	14,184 (96.4)	12,942 (97.2)	3785 (97.4)	

	Overall	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L	p-value
Others	1046 (3.2)	52 (4.4)	525 (3.6)	368 (2.8)	101 (2.6)	
Low activity (walked outside <30 minutes), n (%)	13708 (43.0)	537 (49.8)	6359 (45.1)	5357 (41.5)	1455 (38.3)	<0.001
BMI (kg/m ²)	27.2 (4.7)	30.3 (5.4)	28.5 (4.8)	26.2 (4.1)	24.6 (3.7)	<0.001
Current/former smoking, n (%)	13569 (41.0)	512 (43.8)	6009 (40.9)	5416 (40.7)	1632 (42.0)	0.12
Current alcohol use, n (%)	29,134 (88.1)	894 (76.4)	12569 (85.5)	12024 (90.3)	3647 (93.9)	<0.001
Education, n (%)						<0.001
<12 years of schooling	18903 (57.2)	792 (67.7)	9015 (61.3)	7238 (54.4)	1858 (47.8)	
>12 years of schooling	14172 (42.8)	378 (32.3)	5694 (38.7)	6072 (45.6)	2028 (52.2)	
Hypertension, (%)	18,636 (56.3)	640 (54.7)	8299 (56.3)	7490 (56.2)	2207 (56.8)	0.65
Chronic kidney disease, (eGFR <60ml/min) ^a , (%)	1761 (5.3)	118 (10.1)	917 (6.2)	577 (4.3)	149 (3.8)	<0.001
Diabetes, n (%)	1713 (5.2)	246 (21.0)	1065 (7.2)	335 (2.5)	67 (1.7)	<0.001
HDL-C PRS, mean (SD), z score (n=32700)	-0.00 (1.00)	-0.81 (0.96)	-0.28 (0.94)	0.19 (0.94)	0.64 (0.93)	<0.001
Total Cholesterol (mg/dl)	234.1 (44.7)	195.6 (44.8)	225.0 (44.2)	241.3 (41.4)	255.8 (40.7)	<0.001
Non-HDL-C (mg/dl)	171.8 (42.4)	159.2 (44.3)	173.3 (43.6)	172.8 (41.2)	166.0 (40.3)	<0.001

^acalculated from creatinine using CKD-EPI Creatinine Equation (2021)

Table S6: Association between baseline HDL and mortality in the UK Biobank: Caucasians only, Excluding those reporting high physical activity (HR, 95% CI)

	HDL levels							
	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L
Male					Female			
Caucasians only ^a								
All-cause	1.17 (1.09, 1.26)	1	0.99 (0.91, 1.08)	1.39 (1.17, 1.67)	1.32 (1.12, 1.55)	1	0.93 (0.86, 1.00)	0.99 (0.88, 1.11)
Cancer	1.26 (1.14, 1.40)	1	0.99 (0.87, 1.11)	1.38 (1.06, 1.78)	1.18 (0.93, 1.49)	1	0.91 (0.82, 1.00)	0.97 (0.83, 1.14)
CVD	1.15 (0.95, 1.39)	1	0.84 (0.67, 1.08)	1.39 (0.84, 2.30)	2.13 (1.42, 3.20)	1	0.74 (0.57, 0.96)	0.85 (0.57, 1.27)
noncancer-nonCVD	1.07 (0.94, 1.21)	1	1.04 (0.90, 1.19)	1.41 (1.05, 1.90)	1.28 (0.98, 1.66)	1	1.02 (0.99, 1.16)	1.06 (0.87, 1.29)
Excluding those reporting high physical activity ^b								
All-cause	1.18 (1.06, 1.31)	1	0.95 (0.93, 1.09)	1.50 (1.13, 2.00)	1.34 (1.08, 1.66)	1	0.95 (0.85, 1.06)	1.06 (0.89, 1.26)
Cancer	1.23 (1.06, 1.44)	1	0.80 (0.65, 0.98)	1.48 (1.01, 2.21)	1.31 (0.96, 1.78)	1	0.93 (0.80, 1.08)	1.01 (0.80, 1.27)
CVD	1.25 (0.95, 1.66)	1	0.84 (0.56, 1.24)	1.41 (0.62, 3.22)	2.03 (1.15, 3.57)	1	0.78 (0.53, 1.14)	0.97 (0.54, 1.73)
noncancer-nonCVD	1.07 (0.89, 1.29)	1	1.21 (0.98, 1.49)	1.57 (0.99, 2.48)	1.19 (0.83, 1.69)	1	1.03 (0.85, 1.24)	1.17 (0.86, 1.57)

adjusted for age, ethnic background, BMI, physical activity, alcohol use, smoking status, level of education, nonHDL-C, hypertension, diabetes, chronic kidney disease

^aethnic background not adjusted ^bphysical activity not adjusted

Table S7: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality adjusted for HDL-C-PRS in the Aspirin in Reducing Events in the Elderly (ASPREE) and the UK Biobank (UKB) cohort (HR, 95% CI)

	HDL levels							
	<40 mg/dl <1.03 mmol/L N = 1233	40-60 mg/dl 1.03-1.55 mmol/L N=5583	60-80 mg/dl 1.55-2.07 mmol/L N=4307	>80mg dl >2.07 mmol/L N=1884	<40 mg/dl <1.03 mmol/L N = 4,468	40-60 mg/dl 1.03- 1.55 mmol/L N= 23,987	60-80 mg/dl 1.55-2.07 mmol/L N= 14,609	>80mg dl >2.07 mmol/L N= 3,717
ASPREE ^a					UKB ^b			
All cause								
Males	0.92 (0.73-1.17)	1	1.05 (0.86-1.29)	1.43 (1.04-1.97)	1.13 (1.05-1.22)	1	1.03 (0.95-1.12)	1.43 (1.20-1.72)
Females	1.10 (0.69-1.76)	1	1.05 (0.83-1.31)	1.03 (0.78-1.38)	1.35 (1.15-1.58)	1	0.93 (0.86-1.01)	1.00 (0.89-1.13)
Cancer mortality								
Males	1.00 (0.72-1.40)	1	1.06 (0.79-1.42)	1.32 (0.82-2.13)	1.24 (1.11-1.37)	1	1.02 (0.90-1.14)	1.38 (1.07-1.79)
Females	0.80 (0.65-1.21)	1	0.89 (0.65-1.21)	0.73 (0.48-1.11)	1.27 (1.01-1.60)	1	0.88 (0.79-0.98)	0.93 (0.79-1.10)
CVD								
Males	0.90 (0.56-1.44)	1	0.90 (0.33-1.38)	0.78 (0.33-1.85)	1.14 (0.94-1.39)	1	0.86 (0.67-1.10)	1.47 (0.89-2.41)
Females	1.84 (0.84-4.04)	1	1.12 (0.69-1.80)	1.73 (0.98-3.06)	2.02 (1.34-3.05)	1	0.72 (0.55-0.95)	0.85 (0.56-1.30)
Non-cancer non-CVD								
Males	0.78 (0.47-1.29)	1	1.17 (0.80-1.67)	2.03 (1.23-3.36)	1.01 (0.89-1.14)	1	1.11 (0.97-1.28)	1.50 (1.12-2.01)
Females	1.11 (0.43-2.85)	1	1.33 (0.86-2.04)	1.18 (0.69-2.03)	1.25 (0.97-1.63)	1	1.07 (0.94-1.22)	1.16 (0.95-1.43)

^aadjusted for age, country of birth, BMI, physical activity, alcohol use, smoking status, level of education, 100mg Aspirin, nonHDL-C, hypertension, diabetes, chronic kidney disease, and HDL PRS z score and principal components for population structure

^badjusted for age, ethnic background, BMI, physical activity, alcohol use, smoking status, level of education, nonHDL-C, hypertension, diabetes, chronic kidney disease, and HDL PRS z score

Table S8: Death endpoint subtype for non-cancer non-cardiovascular cause

Death cause	N (%)
Blood coagulation disorder	1 (0.1)
Dementia	86 (16.0)
GI disease	20 (3.7)
Liver disease	11 (2.0)
Multi-organ failure/nonspecific/ Unascertained	42 (7.8)
Neurological disease/disorder	45 (8.4)
Renal disease	15 (2.8)
Respiratory (excl. infective pneumonia)	87 (16.2)
Sepsis/Infection (incl, infective pneumonia)	56 (10.4)
Suicide	4 (0.7)
Trauma	56 (10.4)
Other/Unknown/No information	115 (21.4)

Table S9: Comparison of associations between elevated high-density lipoprotein cholesterol (HDL-C) and cause and sex-specific mortality events observed in ASPREE, UKB and other previously published studies.

Study	Age	Males				Females			
		All-cause	CVD	Cancer	Other	All-cause	CVD	Cancer	Other
ASPREE	>65 years with a mean of 75 years	+++	-	+	+++	-	+	-	-
UK Biobank	>65 years with a mean of 67 years	+++	+	++	+++	-	-	-	-
CANHEART cohort ²	57.2 years	n/a	-	-	+	n/a	-	-	+
Copenhagen City Heart Study and the Copenhagen General Population Study ³	Men: 58 (range 48–68) Women: 57 (range 47–67)	+++	+++	+	+	+	+	+	-
Health and Retirement Study ⁶	>65 years of age with a mean	++	+	n/a	+	++	+	n/a	+

Study	Age	Males				Females			
		All-cause	CVD	Cancer	Other	All-cause	CVD	Cancer	Other
	of 74.4 years								
Combined data from the Norwegian Counties Study (1977–87), the Age 40 Program (1985–99) and the Cohort of Norway (1994–2003). ¹³	aged 20–79 years mean age 45.5 years	++	-	+	++	++	-	+	++

+++ HR >2 and statistically significant, ++ HR >1 and statistically significant, + borderline (near) significant, - not significant, n/a not reported

Table S10: Association between baseline high-density lipoprotein cholesterol (HDL-C) and mortality in those never drink alcohol UKB (HR, 95% CI) (n=3076, age range 40-73 years)

	HDL levels			
	<40 mg/dl <1.03 mmol/L	40-60 mg/dl 1.03-1.55 mmol/L	60-80 mg/dl 1.55-2.07 mmol/L	>80 mg/dl >2.07 mmol/L
All cause				
Males	1.08 (0.79, 1.50)	1	1.18 (0.70, 2.00)	2.94 (0.72, 12.0)
Females	1.14 (0.79, 1.65)	1	0.98 (0.79, 1.22)	1.25 (0.84, 1.85)
Cancer				
Males	1.41 (0.92, 2.14)	1	0.88 (0.37, 2.08)	5.94 (1.42, 24.8)
Females	1.26 (0.81, 1.96)	1	0.81 (0.61, 1.08)	1.32 (0.82, 2.10)
CVD				
Males	-	1	-	-
Females	1.26 (0.27, 5.83)	1	1.39 (0.57, 3.38)	2.02 (0.43, 9.48)
Non-cancer non-CVD				
Males	-	1	-	-
Females	0.91 (0.45, 1.83)	1	1.31 (0.90, 1.90)	0.93 (0.40, 2.18)

adjusted for age, ethnic background, BMI, physical activity, smoking status, level of education, nonHDL-C, hypertension, diabetes, chronic kidney disease

Fig S1. Distribution of HDL polygenic risk score: A. Aspirin in Reducing Events in the Elderly B. UK biobank

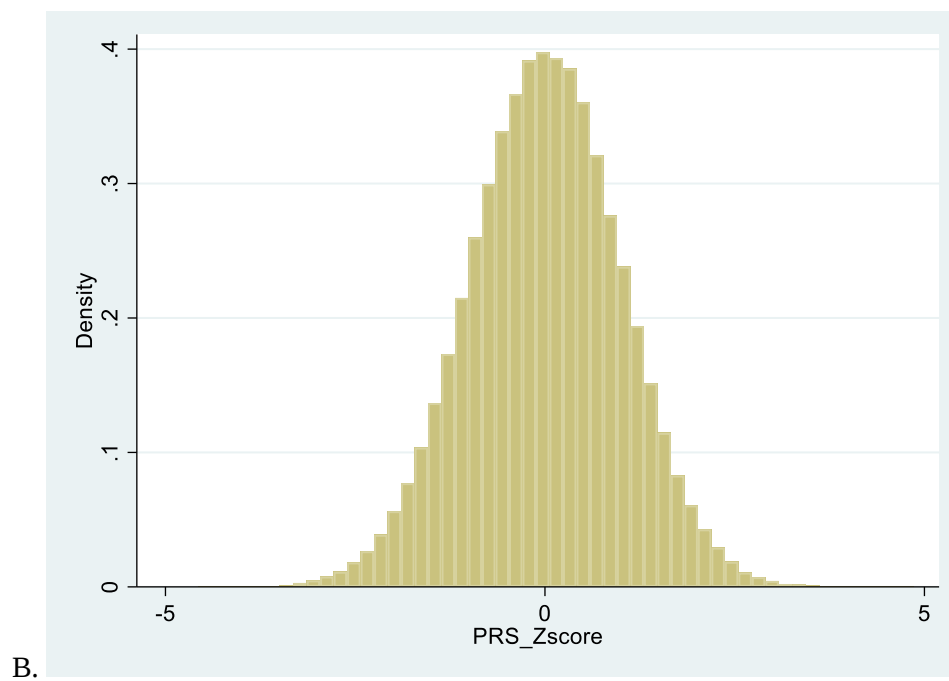
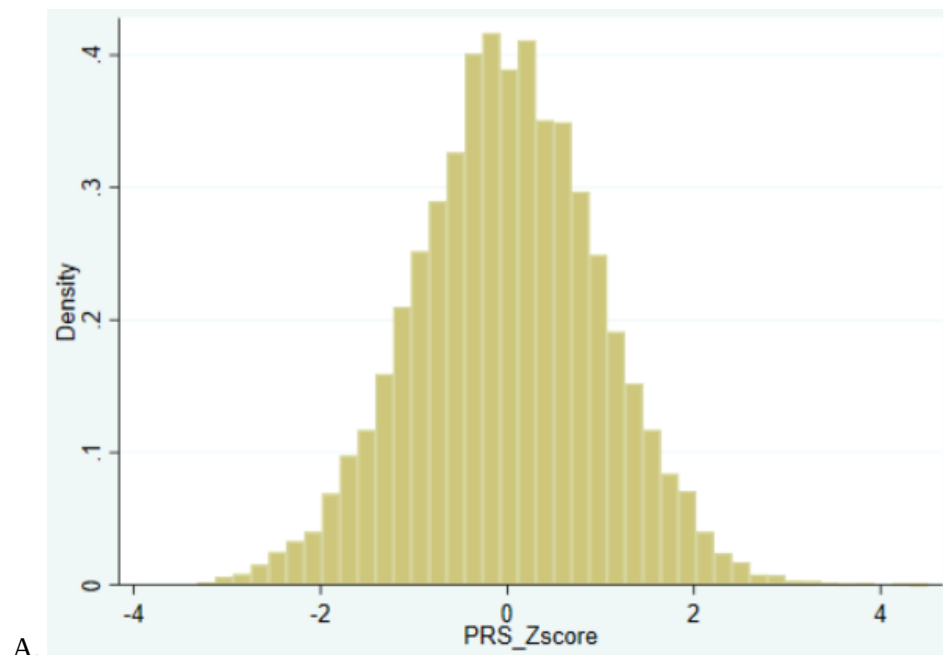


Fig S2. Distribution of HDL cholesterol concentrations in the Aspirin in Reducing Events in the Elderly (ASPREE): A. Males B. Females

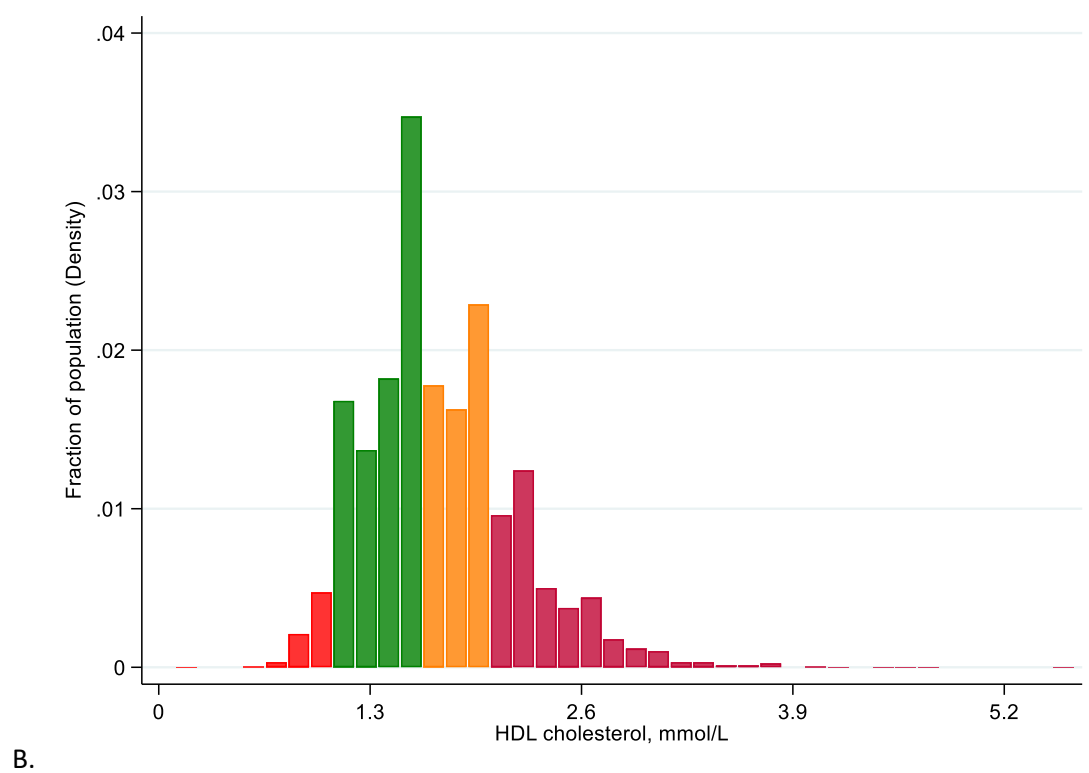
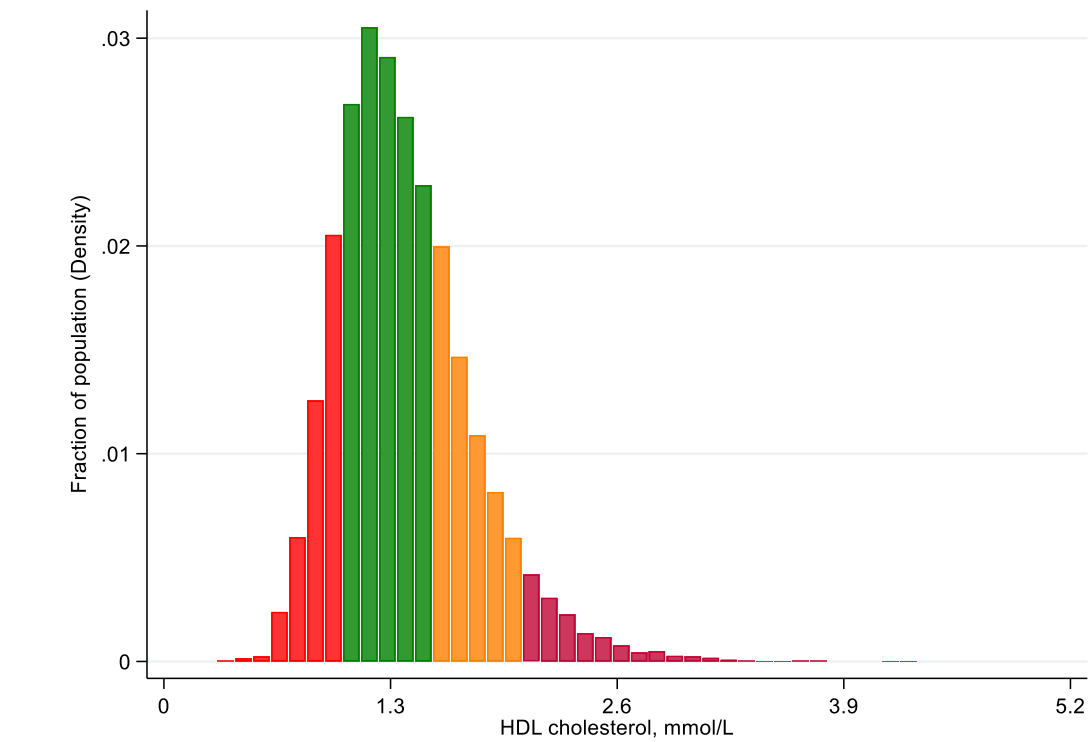
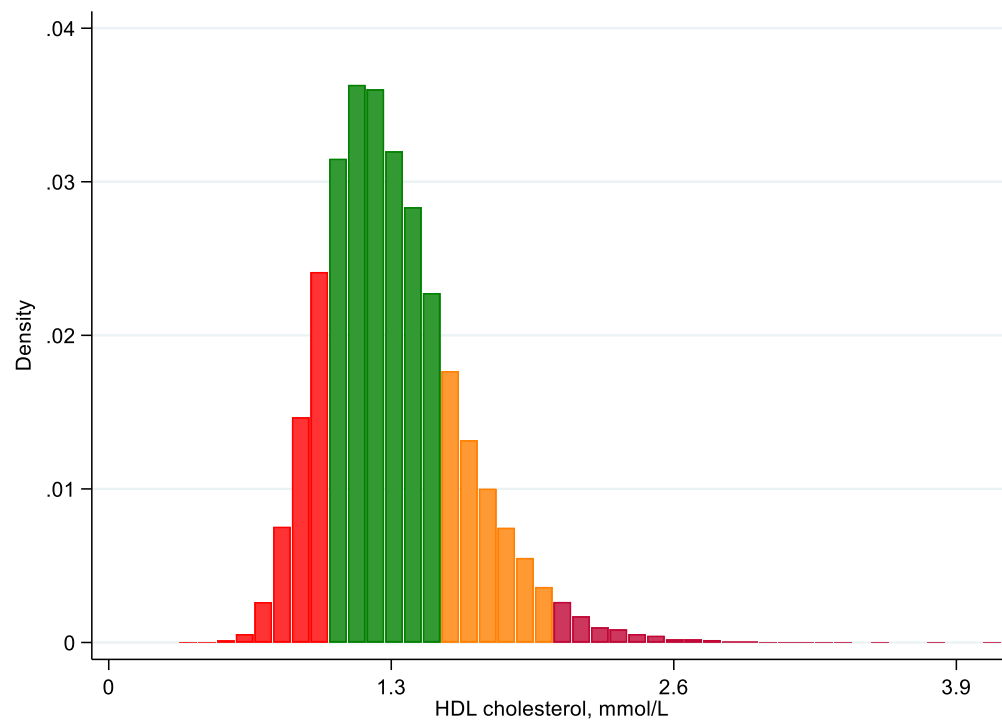
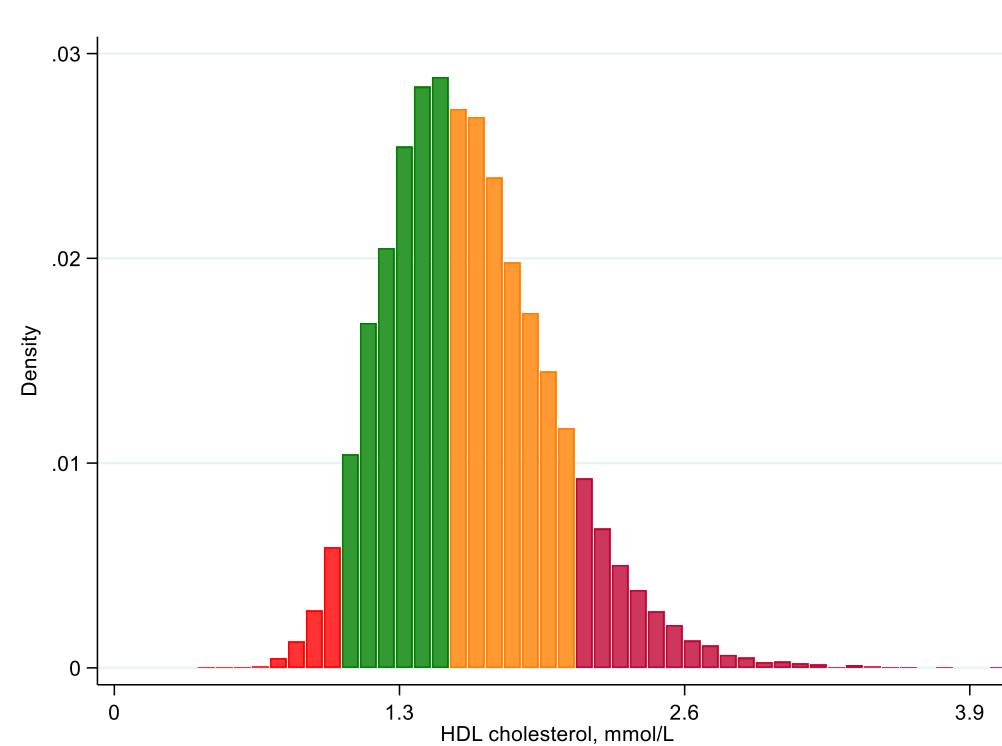


Fig S3. Distribution of high-density lipoprotein cholesterol (HDL-C) concentrations in the UK Biobank (UKB): A. Males B. Females



A



B

Figure S4. Nonlinear association between high-density lipoprotein (HDL) cholesterol levels in men in the UK Biobank (UKB): A. all-cause mortality, B. Cancer mortality, C. CVD mortality and D. noncancer-non-CVD mortality

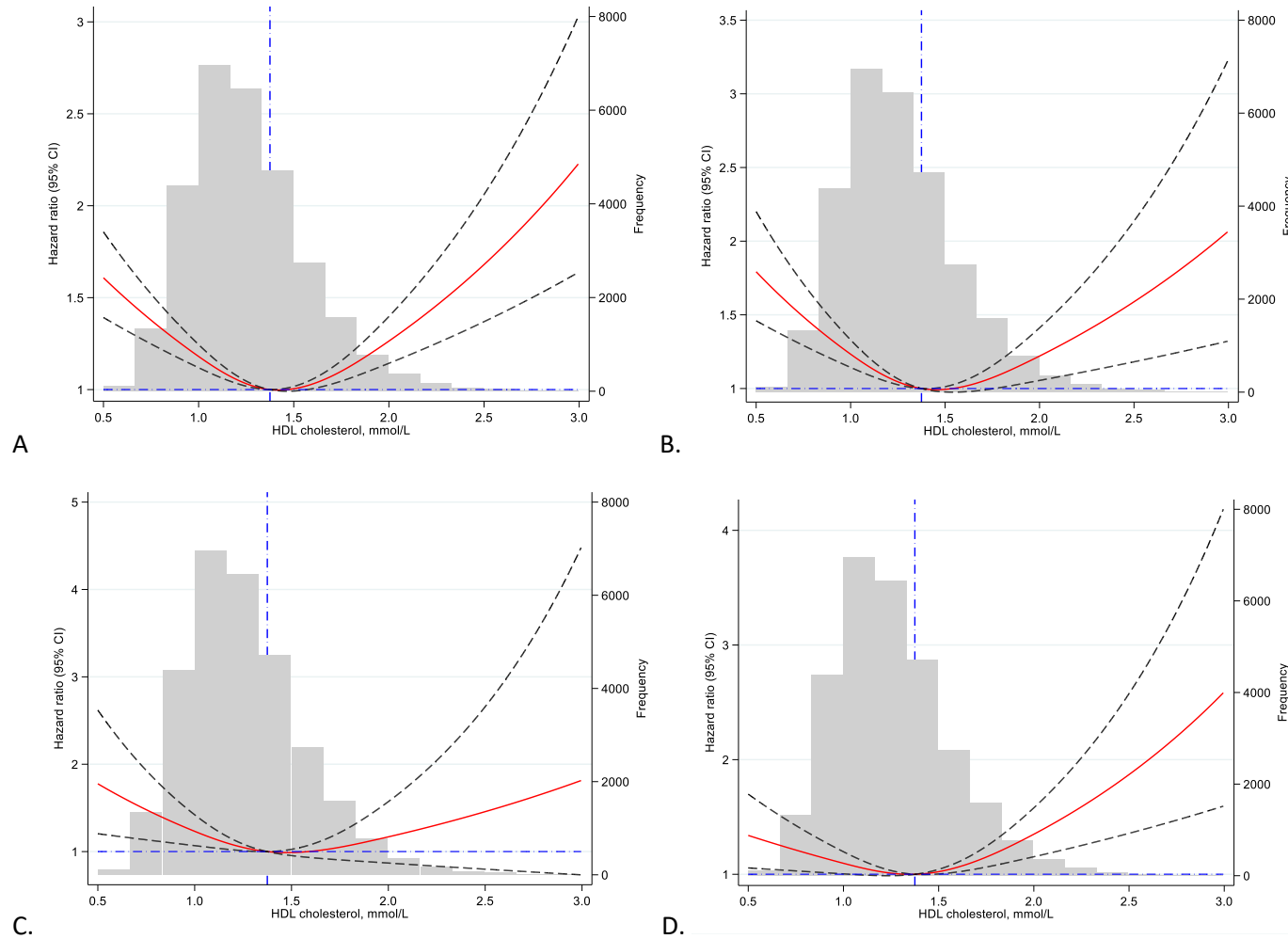
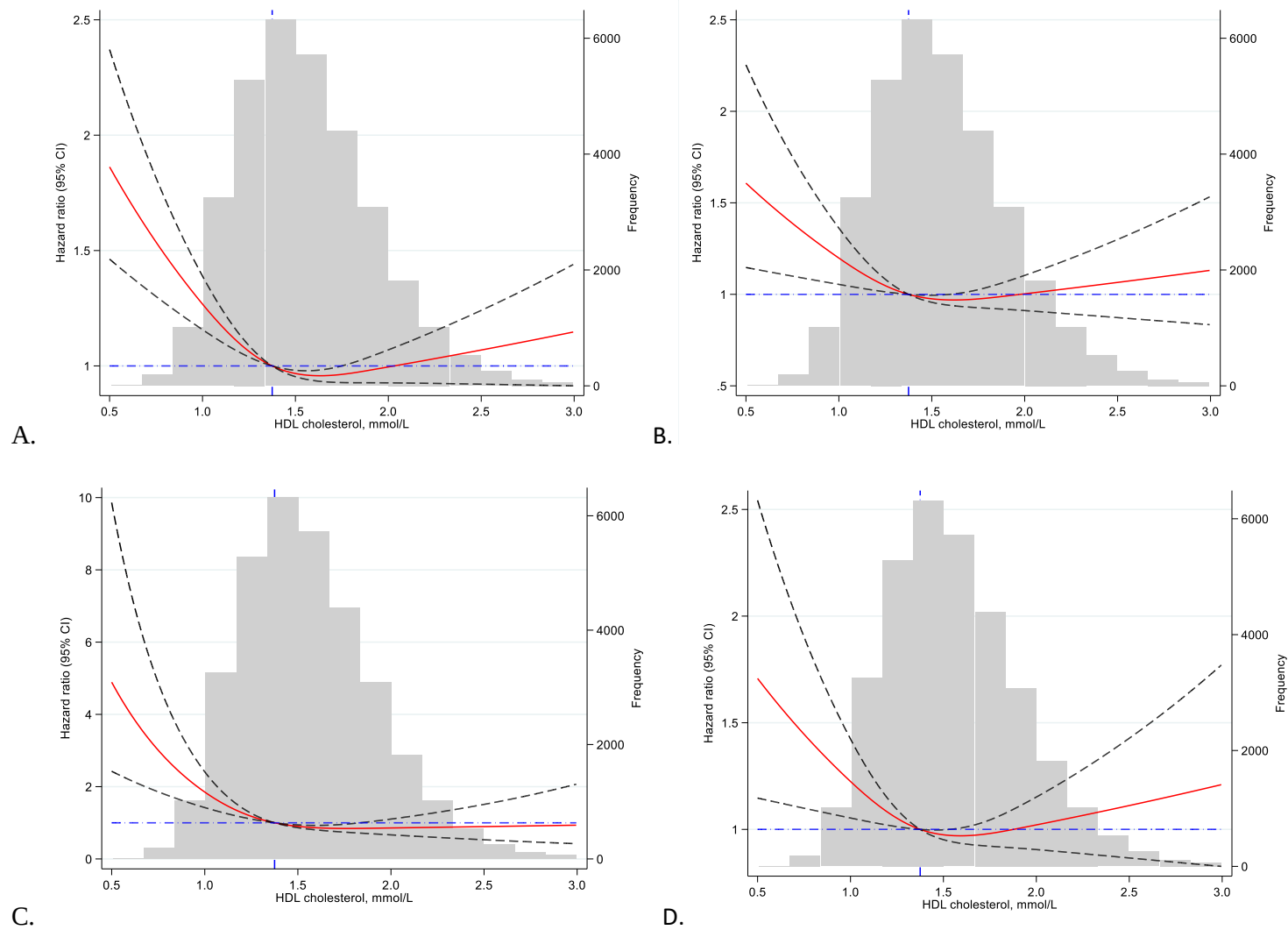


Figure S5. Nonlinear association between high-density lipoprotein (HDL) cholesterol levels in women in the UK Biobank (UKB): A. all-cause mortality, B. Cancer mortality, C. CVD mortality and D. noncancer-non-CVD mortality



Supplementary Method: Validation cohort (UK Biobank)

Participants exclusion criteria from UK Biobank

We included participants at enrolment without a history of diagnosed cardiovascular events (across all hospital inpatient records, based on codes of “Diagnoses - ICD10”; UK Biobank data-field: 41270). Excluded participants were with a record of diagnosed cardiovascular events earlier than at first enrolment using ICD10:

I200, I208, I209, I210, I211, I212, I214, I219, I220, I221, I228, I229, I240, I248, I249, I251, I253, I258, I259, I460, I469, I601, I602, I603, I604, I609, I610, I611, I615, I619, I632, I633, I634, I635, I638, I639, I64, I500, I501, I509, I739, I743, I745, I440, I441, I442, I443, I446, I447, I48, I480, I481, G450, G451, G458, G459

Participants with dementia at enrolment were also excluded using ICD10:

A810, F00, F000, F001, F002, F009, F01, F010, F011, F012, F013, F018, F019, F02, F020, F021, F022, F023, F024, F028, F03, F051, F106, G30, G300, G301, G308, G309, G310, G311, G318, I673

Identification of all-cause and cause-specific mortality from UK Biobank

We used underlying (primary) cause of death by ICD10 (UK Biobank data-field: 40001) and contributory (secondary) causes of death by ICD10 (UK Biobank data-field: 40002) to identify cause-specific mortality.

ICD 10 codes for cardiovascular disease:

I200, I208, I209, I210, I211, I212, I214, I219, I220, I221, I228, I229, I240, I248, I249, I251, I253, I258, I259, I460, I469, I601, I602, I603, I604, I609, I610, I611, I615, I619, I632, I633, I634, I635, I638, I639, I64, I500, I501, I509, I739, I743, I745, I440, I441, I442, I443, I446, I447, I48, I480, I481, G450, G451, G458, G459

ICD 10 codes for cancer:

C00 to C97, D00 to D48

ICD 10 codes for noncancer non-CVD mortality:

Any mortality apart from the codes associated with CVD and cancer mortality were included here.