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Supplementary Table 1	**Adjusted rate ratios (RR) and 95% confidence intervals (CI) for risk of ischaemic stroke (IS; N = 5475) and intracerebral haemorrhage (ICH; N = 4776) by concentrations of major blood lipids in observational analyses in CKB, with and without adjustment for body mass index (BMI)**
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Supplementary Table 1: Adjusted rate ratios (RR) for risk of ischaemic stroke (IS; N = 5475) and intracerebral haemorrhage (ICH; N = 4776) by concentrations of major blood lipids in observational analyses in CKB, with and without adjustment for body mass index (BMI)[a]

Major blood lipids (SD)	RR (95% CI) per SD higher				P for heterogeneity between IS and ICH
	Ischaemic stroke (N = 5475)		Intracerebral haemorrhage (N = 4776)		
	Without BMI	With BMI	Without BMI	With BMI	
LDL-C (0.68 mmol/L)	1.12 (1.07-1.16)	1.10 (1.06-1.15)	0.90 (0.86-0.95)	0.91 (0.87-0.96)	$P=4.2\times10^{-11}$
HDL-C (0.29 mmol/L)	0.93 (0.89-0.97)	0.94 (0.90-0.99)	1.00 (0.96-1.05)	0.98 (0.94-1.02)	P=0.01
Triglycerides[b] 0.58	1.05 (1.00-1.10)	1.03 (0.98-1.08)	0.87 (0.82-0.91)	0.88 (0.84-0.93)	$P=1.3\times10^{-8}$

SD=Standard deviation; CI=Confidence intervals.

[a] Cox regression was used to estimate the rate ratios (95% CI), as shown in column 2, 3, 4, and 5, per SD unit higher concentrations of measured blood lipids. The analyses were stratified by age-at-risk (5-year), sex, and study area, and adjusted for education, smoking, alcohol consumption, physical activity, diabetes, and baseline systolic blood pressure, with and without adjustment for BMI. Chi-square test was used for heterogeneity. All P-values (two-sided) were uncorrected for multiple testing.

[b] Values for triglycerides are natural logarithm of triglyceride measurements.

Supplementary Table 2. Characteristics of the 46 LDL-C associated genetic variants obtained from the Global Lipids Genetics Consortium

Marker	Locus	Chr	Position[a]	Effect Allele	Other Allele	GLGC		CKB[b]	
						Beta	P-value	Beta	P-value
rs10903129	*MACO1*	1	25768937	G	A	0.033	4E-19	0.034	4E-03
rs1998013[c]	*RNU6-830P*	1	55958030	C	T	0.381	4E-67	NA	NA
rs646776	*CELSR2*	1	109818530	T	C	0.161	1E-292	0.209	2E-20
rs267733	*ANXA9*	1	150958836	A	G	0.033	5E-10	-0.013	6E-01
rs2642438	*MARC1*	1	220970028	G	A	0.035	4E-17	0.061	3E-05
rs1367117	*APOB*	2	21263900	A	G	0.119	2E-196	0.102	2E-10
rs515135	*APOB*	2	21286057	C	T	0.139	1E-188	-0.011	6E-01
rs6544713	*ABCG8*	2	44073881	T	C	0.081	6E-85	-0.107	1E-01
rs2710642	*EHBP1*	2	63149557	A	G	0.024	3E-10	0.031	8E-03
rs2030746	*LOC105373585*	2	121309488	T	C	0.021	2E-08	0.006	6E-01
rs2287623	*ABCB11*	2	169830155	G	A	0.022	7E-09	0.031	1E-02
rs1250229	*LOC105373868*	2	216304384	C	T	0.024	8E-09	0.034	2E-01
rs11563251	*UGT1A*	2	234679384	T	C	0.035	2E-08	0.021	3E-01
rs7640978	*CMTM6*	3	32533010	C	T	0.039	1E-08	-0.037	1E-01
rs17345563	*DNAJC13*	3	132209203	A	G	0.036	3E-10	0.016	4E-01
rs7703051	*ANKRD31*	5	74625487	A	C	0.073	5E-85	0.081	3E-14
rs4530754	*CSNK1G3*	5	122855416	A	G	0.028	4E-14	-0.013	2E-01
rs6882076	*TIMD4*	5	156390297	C	T	0.046	5E-33	0.059	1E-06
rs1800562	*HFE*	6	26093141	G	A	0.062	2E-14	-0.012	9E-01
rs1564348	*SLC22A1*	6	160578860	C	T	0.048	3E-22	0.075	4E-01
rs12670798	*DNAH11*	7	21607352	C	T	0.034	7E-16	0.019	7E-02
rs4722551	*LOC105375199*	7	25991826	C	T	0.039	7E-16	0.031	3E-01
rs2073547	*NPC1L1*	7	44582331	G	A	0.049	5E-23	-0.003	8E-01
rs217386	*NPC1L1*	7	44600695	G	A	0.036	8E-22	0.013	7E-01
rs10102164	*TRMT112P7*	8	55421614	A	G	0.032	3E-12	0.044	7E-04
rs3780181	*VLDLR*	9	2640759	A	G	0.045	1E-09	0.063	3E-03
rs8176720	*ABO*	9	136132873	T	C	0.033	6E-18	0.034	2E-03
rs579459	*ABO*	9	136154168	C	T	0.067	3E-49	0.088	9E-12
rs174532	*MYRF*	11	61548874	A	G	0.035	5E-17	0.068	6E-01
rs1535	*FADS2*	11	61597972	A	G	0.053	3E-43	0.041	2E-04
rs11220462	*ST3GAL4*	11	126243952	A	G	0.059	3E-23	0.029	1E-02
rs1186380	*RPL12P33*	12	121376416	C	T	0.024	1E-08	0.015	2E-01
rs1169288	*HNF1A*	12	121416650	C	A	0.038	9E-21	0.018	1E-01
rs4942486	*BRCA2*	13	32953388	T	C	0.024	3E-11	0.041	2E-04
rs8017377	*NYNRIN*	14	24883887	A	G	0.031	3E-15	0.062	8E-03
rs2000999	*TXNL4B*	16	72108093	A	G	0.065	1E-45	0.033	6E-03
rs314253	*ASGR1*	17	7091650	T	C	0.024	2E-10	0.031	5E-03
rs4791641	*PFAS*	17	8161149	C	T	0.021	5E-08	-0.007	6E-01
rs6511720	*LDLR*	19	11202306	G	T	0.221	3E-289	0.184	3E-03
rs688	*LDLR*	19	11227602	T	C	0.054	9E-48	0.077	6E-08
rs6859	*NECTIN2*	19	45382034	A	G	0.084	1E-101	-0.041	5E-04
rs7254892	*NECTIN2*	19	45389596	G	A	0.485	8E-365	0.702	9E-246
rs492602	*FUT2*	19	49206417	G	A	0.029	3E-14	0.043	5E-01
rs364585	*LINC01722*	20	12962718	G	A	0.025	4E-11	-0.003	8E-01
rs2328223	*LOC107985440*	20	17845921	C	A	0.031	2E-09	0.021	1E-01
rs5763662	*MEMR3*	22	30378703	T	C	0.077	2E-10	0.022	2E-01

Chr.=Chromosome; Effect alleles are given as the LDL-C raising allele in the Global Lipids Genetics Consortium data[49,50];
[a] Genomic coordinates were in Build hg19;
[b] The analyses were conducted in 17,567 CKB participants with available data. General linear regression was used to estimate SD differences in LDL-C (after rank-inverse-normal transformation) per 1 effect allele, adjusted for sex, age, age-squared, and case status. The analyses were performed for each study area, and the overall estimates were obtained by inverse-variance-weighted meta-analyses. All P-values (two-sided) were uncorrected for multiple testing.
[c] Monogenic in the present study.

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Supplementary Table 3: Summary-level Mendelian randomisation sensitivity analyses of associations of genetically-instrumented LDL-C with risk of ischaemic stroke (N = 5567) and intracerebral haemorrhage (N = 4911) in CKB[a]

Methods	Ischaemic stroke (N = 5567)					Intracerebral haemorrhage (N = 4911)				
	Beta	SE	LCI	UCI	P-value	Beta	SE	LCI	UCI	P-value
Main analyses:	0.282	0.117	0.054	0.511	0.015	-0.122	0.109	-0.337	0.092	0.264
Sensitivity analyses:										
Weighted median	0.126	0.122	-0.114	0.366	0.304	-0.072	0.114	-0.296	0.152	0.530
Inverse-variance weighted method	0.210	0.114	-0.014	0.433	0.066	-0.099	0.100	-0.295	0.097	0.322
MR-Egger (Causal estimates)	0.101	0.131	-0.156	0.359	0.440	-0.056	0.118	-0.287	0.174	0.631
MR-Egger (Intercept)	0.011	0.007	-0.002	0.024	0.112	-0.004	0.006	-0.016	0.008	0.484

SE=standard error; LCI=lower confidence interval; UCI=upper confidence interval.

[a] The Betas and SEs were estimated using published methods with R package[51], per 1 mmol/L higher concentrations of genetically-instrumented LDL-C. All P-values (two-sided) were uncorrected for multiple testing.

Supplementary Table 4: Age-specific rates of ischaemic stroke, intracerebral haemorrhage, and major coronary events in the CKB prospective study, by different levels of background vascular risk

Age at risk	Ischemic stroke				Intracerebral hemorrhage				Major coronary events			
	Person-years	No. of events	Rates (% p.a.)	Events avoided	Person-years	No. of events	Rates (% p.a.)	Excess events	Person-years	No. of events	Rates (% p.a.)	Events avoided
Low-risk (n=336,696)												
<50	1,258,546	1,356	0.11	11 (1)	1,261,482	324	0.03	-2 (1)	1,262,025	209	0.02	2 (0)
50-60	979,911	4,041	0.41	41 (4)	990,273	538	0.05	-5 (2)	990,637	507	0.05	6 (1)
60-70	558,263	4,636	0.83	83 (9)	571,871	739	0.13	-11 (5)	572,227	753	0.13	17 (1)
≥70	226,053	4,470	1.98	198 (20)	240,434	929	0.39	-33 (14)	240,596	1,149	0.48	60 (4)
Overall	3,022,772	14,503	0.48	48 (5)	3,064,060	2,530	0.08	-7 (3)	3,065,485	2,618	0.09	11 (1)
Medium-risk (n=153,066)												
<50	228,332	960	0.42	42 (4)	229,893	459	0.2	-17 (7)	230,589	158	0.07	9 (1)
50-60	408,045	3,788	0.93	93 (9)	416,966	1,238	0.3	-25 (11)	419,006	513	0.12	15 (1)
60-70	404,001	6,427	1.59	159 (16)	422,308	1,860	0.44	-37 (16)	424,513	1,090	0.26	32 (2)
≥70	258,092	7,191	2.79	279 (28)	281,546	2,183	0.78	-66 (28)	282,573	2,212	0.78	98 (6)
Overall	1,298,469	18,366	1.41	141 (15)	1,350,713	5,740	0.42	-36 (15)	1,356,680	3,973	0.29	37 (2)
High-risk (n=23,129)												
<50	9,394	140	1.49	149 (15)	9,666	58	0.6	-51 (21)	9,720	41	0.42	53 (3)
50-60	37,871	1,025	2.71	271 (28)	40,387	262	0.65	-55 (23)	40,739	173	0.42	53 (3)
60-70	64,497	2,486	3.85	385 (39)	72,127	534	0.74	-63 (26)	72,534	500	0.69	86 (5)
≥70	57,237	3,129	5.47	547 (56)	69,696	604	0.87	-74 (31)	69,428	1,029	1.48	185 (11)
Overall	169,000	6780	4.01	401 (41)	191,876	1,458	0.76	-65 (27)	192,421	1,743	0.91	113 (7)
Total	***4,490,241***	***39,649***	***0.88***	***88 (9)***	***4,606,649***	***9,728***	***0.21***	***-18 (8)***	***4,614,586***	***8,334***	***0.18***	***23 (1)***

Low-risk: no measured hypertension, or prior history of cardiovascular disease (coronary heart disease, stroke or transient ischemic attack); Medium-risk: with measured hypertension, but with no prior history of cardiovascular disease; High-risk: with prior history of cardiovascular disease. Participants were considered to have measured hypertension if they had measured systolic blood pressure of at least 140 mm Hg or a measured diastolic blood pressure of at least 90 mm Hg or were receiving treatment for hypertension. The latter was defined as those who reported a diagnosis of hypertension by a physician and use of anti-hypertensives at recruitment.

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