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Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults

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Stroke is the second leading cause of death worldwide and accounts for >2 million deaths annually in China[1,2]. Ischemic stroke (IS) and intracerebral hemorrhage (ICH) account for an equal number of deaths in China, despite a fourfold greater incidence of IS[1,2]. Stroke incidence and ICH proportion are higher in China than in Western populations[3–5], despite having a lower mean low-density lipoprotein cholesterol (LDL-C) concentration. Observational studies reported weaker positive associations of LDL-C with IS than with coronary heart disease (CHD)[6,7], but LDL-C-lowering trials demonstrated similar risk reductions for IS and CHD[8–10]. Mendelian randomization studies of LDL-C and IS have reported conflicting results[11–13], and concerns about the excess risks of ICH associated with lowering LDL-C[14,15] may have prevented the more widespread use of statins in China. We examined the associations of biochemically measured lipids with stroke in a nested case-control study in the China Kadoorie Biobank (CKB) and compared the risks for both stroke types associated with equivalent differences in LDL-C in Mendelian randomization analyses. The results demonstrated positive associations of LDL-C with IS and equally strong inverse associations with ICH, which were confirmed by genetic analyses and LDL-C-lowering trials. Lowering LDL-C is still likely to have net benefit for the prevention of overall stroke and cardiovascular disease in China.

A total of 512,891 adults from 10 diverse areas in China were recruited to the CKB prospective study. Among the subset of 489,762 individuals with no prior history of stroke, transient ischemic attack, or CHD at baseline, the mean (s.d.) age was 51 (11) years and 59% were women. Overall, after a median follow-up duration of 9 years, a total of 32,869 incident IS cases and 8,270 incident ICH cases were recorded, yielding age- and sex-adjusted incidence rates of 761 and 187 cases per 100,000 person years, respectively.

Among individuals with no prior history of cardiovascular disease (CVD), cancer, lipid-lowering, anticoagulant, or antiplatelet treatment at baseline, 5,475 IS cases, 4,776 ICH cases, and 6,290 healthy controls were selected for a nested case-control study of incident stroke. At baseline, IS cases, compared with controls, were more likely to be urban residents and smokers, but had similar dietary patterns. Regular consumption of certain animal-based foods, for example, meat and eggs, was less common in ICH cases than in controls, but the distribution of other socio-economic and lifestyle factors were similar (Table 1). The overall mean (s.d.) plasma concentrations of total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C) were 4.6 (0.9) mmol l^{-1}, 2.4 (0.6) mmol l^{-1}, and 1.2 (0.3) mmol l^{-1}, respectively. The median (interquartile range) concentration of triglycerides was 1.6 (1.3) mmol l^{-1}. Stroke cases had higher mean levels of systolic blood pressure (SBP) than controls, but LDL-C and SBP were only weakly correlated ($r = 0.06$).

Plasma concentrations of LDL-C were positively associated with a risk of IS and inversely associated with a risk of ICH, after stratification for age at risk (five-year intervals), study area, and sex, and adjustment for education, smoking, alcohol consumption, physical activity, diabetes, and baseline SBP. Throughout the range examined, that is, 1.7–3.2 mmol l^{-1}, each 1 mmol l^{-1} higher usual LDL-C was associated with a 17% (rate ratio (RR) = 1.17, 95% confidence interval (CI): 1.10–1.25) higher risk of IS, and a 14% (RR = 0.86, 95% CI 0.80–0.92) lower risk of ICH (Fig. 1), which translated into an RR of 0.85 (95% CI 0.80–0.91) for IS and an RR of 1.16 (95% CI 1.08–1.25) for ICH, for each 1 mmol l^{-1} lower LDL-C. These results were unaltered by further adjustment for other lipid fractions (Extended Data Fig. 1) and were generally similar in different subgroups (except for sex, area, and smoking for IS and age and body mass index (BMI) for ICH) (Extended Data Fig. 2).

Plasma concentrations of HDL-C were inversely associated with risk of IS (RR=0.93, 95% CI 0.89–0.97 per 0.3 mmol l^{-1} higher HDL-C), but not with ICH (RR = 1.00, 95% CI 0.96–1.05) (Fig. 1). The associations of LDL-C and HDL-C with IS were independent of each other (Extended Data Fig. 3).

Plasma concentrations of triglycerides were weakly positively associated with a risk of IS (RR = 1.02, 95% CI 1.00–1.04 per 30% higher triglycerides), but were inversely associated with ICH (RR = 0.94, 95% CI 0.92–0.96) (Fig. 1). The risk estimates for IS and ICH for all major blood lipids were largely unaltered after additional adjustment for BMI (Supplementary Table 1). Overall, the associations of LDL-C, HDL-C, and triglycerides with IS differed qualitatively from those for ICH ($P_{\text{heterogeneity}}$ between IS

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Table 1 | Baseline characteristics of participants in the nested case-control study of stroke

	IS cases	ICH cases	Controls
Number of participants	5,475	4,776	6,290
Demographic factors			
Age at baseline, mean (s.d.) (years)	54.3 (10.7)	58.8 (10.7)	56.7 (11.6)
Female (%)	53.1	47.8	47.9
Urban (%)	44.9	22.5	21.2
≥6 years of education (%)	38.6	36.1	38.6
Household income (>20,000 yuan per year) (%)	33.1	29.2	29.5
Lifestyle factors			
Male ever-smokers (%)	64.2	60.6	60.3
Female ever-smokers (%)	3.7	3.3	3.2
Male ever-drinkers (%)	29.1	30.6	29.7
Female ever-drinkers (%)	2.5	2.6	1.9
Physical activity, mean (s.d.) (MET-h per day)	18.1 (14.2)	18.1 (13.1)	18.9 (12.0)
Regular consumption of certain foods[a] *(%)*			
Meat or poultry	38.5	35.6	37.8
Fish or other seafood	5.1	3.8	5.1
Eggs	25.1	21.8	26.8
Fresh fruit	19.9	17.9	21.6
Dairy products	10.0	7.5	10.3
Physical and blood measurements, mean (s.d.)			
SBP (mmHg)	144.1 (34.2)	152.0 (29.5)	134.0 (21.1)
DBP (mmHg)	83.0 (18.8)	87.0 (15.8)	77.3 (11.7)
BMI (kg m^{-2})	23.9 (4.4)	23.5 (3.8)	23.2 (3.4)
Random blood glucose (mmol l^{-1})	6.6 (3.9)	6.5 (3.4)	6.0 (2.8)
Lipid measurements			
Total cholesterol (mmol l^{-1})	4.8 (1.0)	4.5 (1.0)	4.5 (0.9)
LDL-C (mmol l^{-1})	2.5 (0.7)	2.3 (0.7)	2.3 (0.7)
HDL-C (mmol l^{-1})	1.2 (0.3)	1.3 (0.3)	1.3 (0.3)
Triglycerides (mmol l^{-1})[b]	1.7 (1.4)	1.5 (1.2)	1.5 (1.2)
Apolipoprotein B (mg dl^{-1})	85.8 (27.1)	81.7 (21.4)	82.8 (20.4)
Apolipoprotein A1 (mg dl^{-1})	133.9 (29.1)	134.4 (22.7)	134.7 (21.9)
Lipoprotein(a) (nmol l^{-1})[b]	18.3 (36.5)	18.7 (33.3)	18.4 (35.5)
Medical history and health status (%)			
Diabetes	10.5	8.6	5.1
Hypertension[c]	56.8	69.3	37.6
Self-rated poor health status[d]	14.2	15.1	9.4

[a]Regular consumption was defined as consumption of the food groups on at least four days per week. [b]Estimates were median (interquartile range) for triglycerides, and lipoprotein(a). [c]Participants were considered to be hypertensive if they had a measured SBP of at least 140 mmHg or a measured DBP of at least 90 mmHg, or were receiving treatment for hypertension. The latter was defined as those who reported a diagnosis of hypertension by a physician and use of antihypertensives at baseline. [d]Individuals were asked to classify their current general health status compared with others of the same age by responding to the question 'How is your current health status?' If they replied that it was 'poor', they were classified as having 'self-rated poor health status'. MET-h, metabolic equivalent of task-hours; DBP, diastolic blood pressure. Mean (s.d.) values were directly standardized to age (at baseline, 10-year range), sex, and study area structure of the entire study population included, unless otherwise stated.

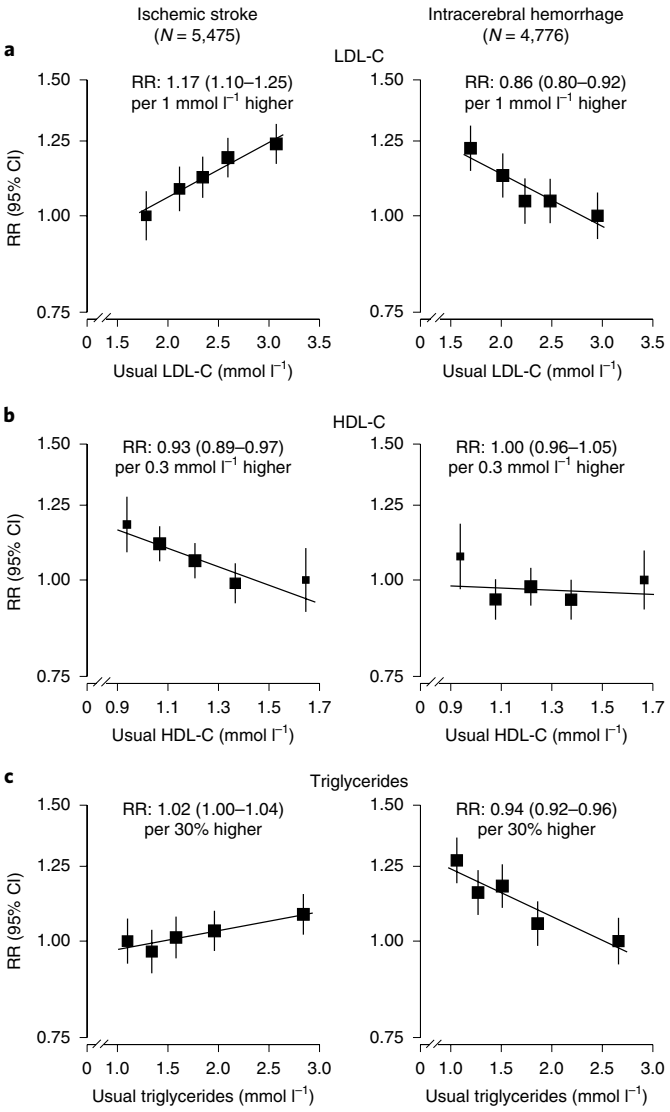

Fig. 1 | Adjusted RRs for risk of IS and ICH by fifths of usual concentrations of LDL-C, HDL-C, and triglycerides in observational analyses in the CKB. a–c, Cox regression was used to estimate the RRs and 95% CIs for IS (N = 5475) and ICH (N = 4776) by fifths of usual LDL-C (**a**), usual HDL-C (**b**), and usual triglycerides (**c**). Each square has an area inversely proportional to the variance of the log risk in the specific group. The line represents the slope from a weighted linear regression with the weights based on the inverse variance of the log RR.

and ICH: $P = 4.2 \times 10^{-11}$, $P = 0.01$, $P = 1.3 \times 10^{-8}$, respectively) (Supplementary Table 1).

Plasma concentrations of LDL-C were strongly correlated with apolipoprotein B ($r = 0.92$) and weakly correlated with lipoprotein(a) ($r = 0.22$). The associations of apolipoprotein B with stroke types were consistent with those for LDL-C. However, lipoprotein(a) was not significantly associated with either IS or ICH (Extended Data Fig. 4), and the risk estimates of LDL-C for both stroke types were unaltered after further adjustment for lipoprotein(a).

A genetic risk score (GRS) comprising 46 single-nucleotide polymorphisms (SNPs) most significantly associated with plasma LDL-C concentrations in the Global Lipids Genetics Consortium (GLGC)[16,17] was constructed as an instrumental variable for LDL-C using previously published methods[18] (see Methods). Supplementary Table 2 also compares the effect sizes of the 46 SNPs on plasma LDL-C concentrations in the CKB with those in the GLGC[17], and shows good concordance for genetically instrumented differences in LDL-C in both Chinese and Western populations. In the CKB, the GRS for LDL-C strongly predicted the plasma concentrations of LDL-C ($P = 7 \times 10^{-247}$), but not HDL-C,

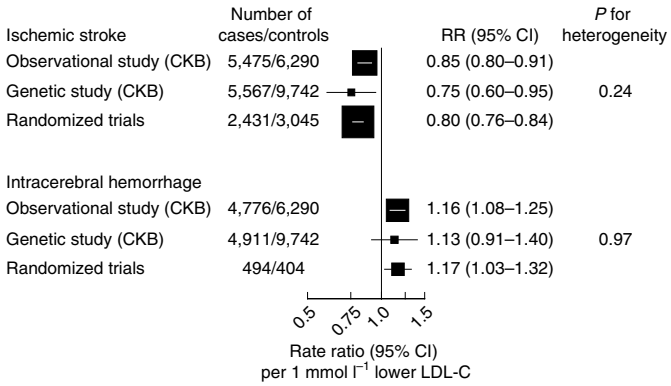

Fig. 2 | Adjusted RRs for risk of IS and ICH associated with 1 mmol l^{-1} lower LDL-C in observational and genetic analyses in the CKB, and in randomized trials of LDL-C-lowering drug treatment in Western populations. The values shown are the RRs (95% CIs) per 1 mmol l^{-1} lower LDL-C concentrations. The number of cases of IS and ICH, and controls in the observational analyses were 5,475, 4,776, and 6,290, respectively; in the genetic analyses, they were 5,567, 4,911, and 9,742, respectively. In the randomized trials, the number of IS cases were 2,431 in the treated and 3,045 in the control groups, and the corresponding numbers of ICH cases were 494 in the treated and 404 in the control groups, respectively. Chi-squared tests were used to test for heterogeneity. Two-sided *P* values were uncorrected for multiple testing.

triglycerides, physical activity, BMI, SBP, or random blood glucose (Extended Data Fig. 5).

Each 1 mmol l^{-1} lower genetically instrumented LDL-C was associated with RRs of 0.75 (95% CI 0.60–0.95) for IS and 1.13 (95 % CI 0.91–1.40) for ICH (Fig. 2). Sensitivity analyses including median-weighted or inverse variance-weighted Mendelian randomization and Mendelian randomization-Egger approaches indicated similar results to those obtained by the main GRS for stroke types (Supplementary Table 3).

In a meta-analysis of the worldwide randomized trials of LDL-C-lowering drug treatment, each 1 mmol l^{-1} lower LDL-C was associated with RRs of 0.80 (95% CI 0.76–0.84) for IS and 1.17 (95% CI 1.03–1.32) for ICH (Fig. 2 and Extended Data Fig. 6). The risk estimates obtained from trials were highly consistent with those in the observational and genetic studies in the CKB ($P_{heterogeneity} = 0.24$ and 0.97, respectively) (Fig. 2).

To assess the net effects (benefits versus hazards) of LDL-C-lowering drug treatment in the Chinese population, we applied the relative risk estimates from the LDL-C-lowering trials to the age-specific absolute risks of stroke types and major coronary events (MCEs, including myocardial infarction and fatal ischemic heart disease) in all CKB participants. The results demonstrated that the predicted number of incident events of IS and MCEs avoided greatly exceeded the excess ICH events by lowering LDL-C by 1 mmol l^{-1} per 10,000 patients treated for 5 years in Chinese adults (Fig. 3). Hence, the findings suggest a net benefit of lowering LDL-C to prevent overall stroke and MCEs in both primary (low-risk individuals) and secondary (individuals at high risk of recurrent vascular events) prevention settings. Moreover, any such net benefits are likely to be greater if all atherosclerotic vascular diseases were to be included.

The present study, including a large number of brain image-confirmed IS and ICH cases in populations without prior history of chronic disease or statin use, demonstrated strong positive associations of LDL-C with IS and equally strong inverse associations with ICH. The causal relevance of LDL-C for both IS and ICH was confirmed by Mendelian randomization analyses in the same study population, which was less susceptible to reverse causality and confounding factors. For LDL-C, the risk estimates for IS were consistent with those observed in Western populations[7], but extended the lower range of LDL-C in the general population down to 1.7 mmol l^{-1}, that is, well below the concentrations typically seen in Western populations. These results suggest that even among those with what is by Western standards, a normal or low LDL-C concentration, lower LDL-C is associated with a lower risk of IS, as it is for CHD[19]. Conversely, lower LDL-C was associated with a higher risk of ICH, irrespective of baseline levels of blood pressure, BMI, or other vascular risk factors. The risk estimates for different stroke types in both observational and genetic analyses in the CKB were similar for equivalent differences in LDL-C in the LDL-C-lowering trials conducted predominantly in Western populations.

Large-scale trials have demonstrated that lowering LDL-C by 1 mmol l^{-1} with statins reduces the risk of IS by about one-fifth[8,15], with similar effect estimates observed for other LDL-C-lowering drug treatments, for example, ezetimibe or evolocumab[9,20,21]. The risk reductions associated with LDL-C-lowering drug treatment observed in the trials were not reliably predicted by previous observational studies[6,22], which included studies predating the widespread use of brain imaging for stroke diagnosis. In contrast, recent reports of Mendelian randomization analyses of LDL-C and IS[23,24] demonstrated significant associations of genetically instrumented LDL-C with IS, consistent with the results of the present study.

The highly consistent results from the observational and genetic analyses in China and the randomized trials conducted chiefly in Western populations now provide reliable evidence that lower LDL-C is causally associated with a higher risk of ICH. Previous studies have suggested that the proportional excess risk of ICH associated with lower LDL-C was confined to individuals with elevated blood pressure[25,26], but this is not supported by the present study, suggesting that the previous reported interaction between cholesterol and SBP for ICH[25,26] could be a chance finding[27]. Randomized trials have reported similar proportional reductions in risk of total stroke with LDL-C-lowering treatment in individuals with hypertension versus those without[28], and with different levels of total cardiovascular risk[8,15]. The mechanisms by which low LDL-C causes ICH are not fully understood. Histopathological studies have suggested that lower cholesterol concentrations may increase permeability of the vessel walls[29,30], causing arterionecrosis, microaneurysms, and ICH[25,30,31].

The present study estimated that each 1 mmol l^{-1} lower LDL-C was associated with approximately 10–20 excess ICH cases in Chinese adults per 10,000 individuals treated for 5 years with commonly available statins, compared with 5–10 ICH cases in North American or European populations[8]. Concerns about the excess risk of ICH associated with LDL-C-lowering treatment have been an obstacle to the more widespread use of statins in China. For example, only <5% of the individuals at high risk of CVD reported regular use of statins in the CKB and other studies in China[32], compared with 66% in most Western countries (for example, Sweden and Canada)[32]. However, in Chinese adults, with higher rates of stroke[4,33,34] and a higher proportion of ICH[4,33], the present study demonstrated that lowering LDL-C still has a net benefit on preventing overall stroke, irrespective of age, prior history of hypertension, or CVD. Moreover, any net beneficial effects of lowering LDL-C are likely to be greater if the trends of increasing IS incidence and decreasing ICH incidence observed over the last two decades continues[5,35], or if the beneficial effects on other occlusive vascular diseases are also included[8,15].

In conclusion, the associations of major blood lipids with stroke differed qualitatively by stroke type. Lower LDL-C concentrations were associated with a lower risk of IS and a higher risk of ICH; the causal relevance of these associations was confirmed by genetic analyses in the same population and by LDL-C-lowering trials in Western populations. Thus, the highly consistent results of observational and genetic analyses in the Chinese population and those of the LDL-

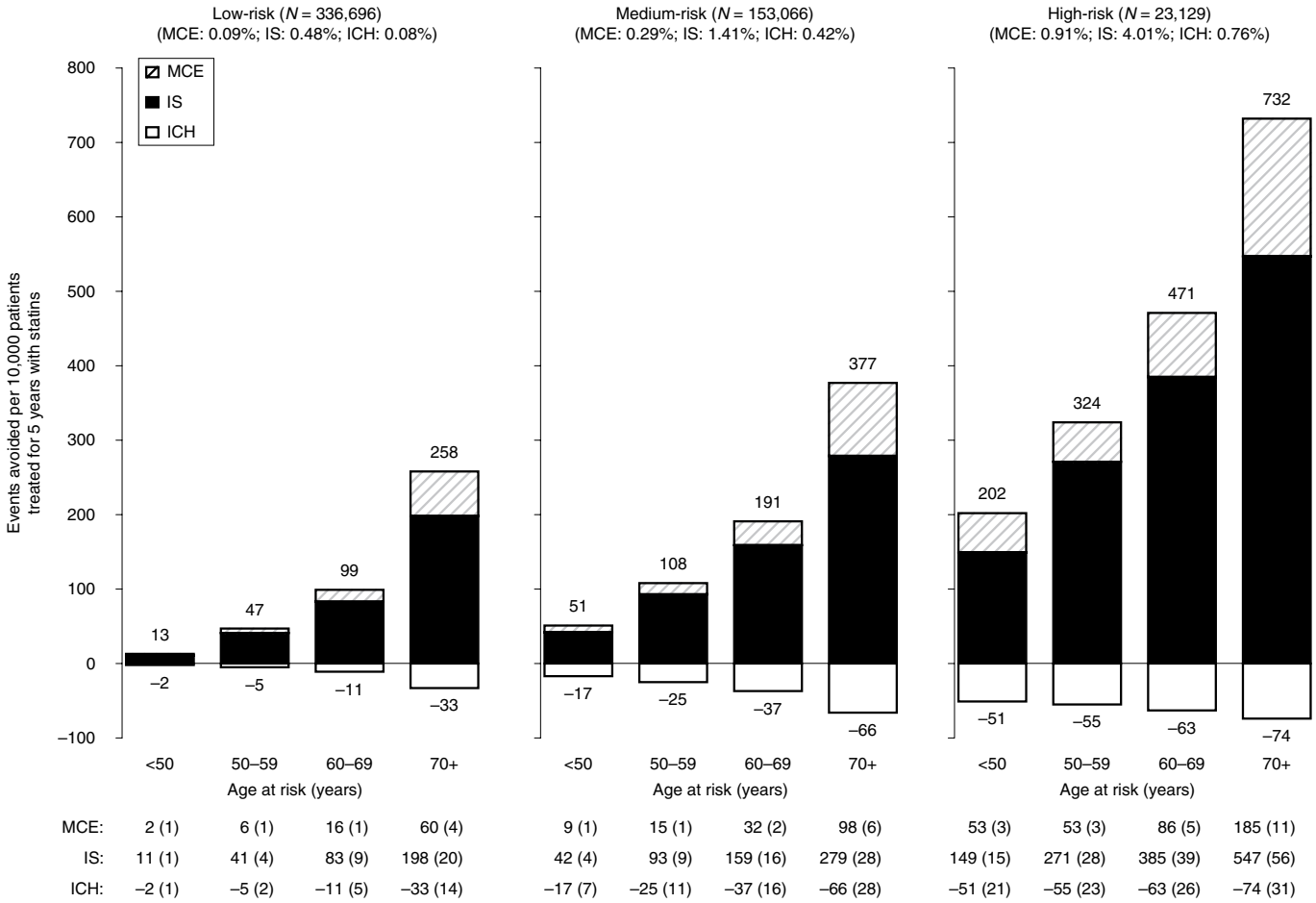

Fig. 3 | Predicted number of events avoided for IS, MCEs, and ICH per 10,000 patients treated by lowering LDL-C by 1 mmol l^{-1} with statins for 5 years in Chinese adults with different levels of vascular risk. The estimated number of events (and their s.d.) avoided by lowering LDL-C by 1 mmol l^{-1}, obtained by applying the RRs from the LDL-C-lowering trials to low-, medium-, and high-risk population subgroups in the CKB, are shown below the figure.

C-lowering trials in Western populations suggest that the excess risk of ICH observed in the trials is probably due to lower concentrations of LDL-C, rather than other factors. Importantly, the results also suggest that lower LDL-C concentrations are still likely to have net benefit for preventing overall stroke and CVD in the Chinese population with high stroke rates. Hence, the results provide support for more widespread use of LDL-C-lowering drug treatment to prevent overall stroke and other vascular diseases both in Chinese and other populations worldwide with low mean LDL-C concentrations.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41591-019-0366-x.

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Author contributions

L.S., R.Clarke, D.B., R.P., and Z.C. designed and planned the analysis and manuscript. L.S. performed the data analyses and wrote the first draft of the manuscript. R.Clarke, D.B., S.P., R.P., and Z.C. provided scientific interpretation of the results and revised the manuscript. R.Clarke, Z.C., L.L., R.P., R.Collins, R.W., J.L., and J.C., as members of the CKB steering committee, designed and supervised the overall conduct of the study and obtained the funding. Y.G., Y.C., Z.B., C.Y., and Z.C. coordinated the data acquisition (for baseline, resurveys, and long-term follow-up). R.W., Y.G., I.M., Z.B., and M.H. coordinated the genotyping analyses in China and the laboratory analyses in Oxford. All authors provided critical comments on the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Methods

CKB study population. The CKB study recruited 512,891 adults aged 30–79 years from 10 diverse areas in China during 2004–2008[36]. At baseline and subsequent resurveys in a 5% random subset, detailed data were collected on medical history (including use of statins), lifestyle characteristics (including smoking, alcohol consumption, physical activity, and diet), and clinical measurements (including blood pressure and anthropometry)[37]. A blood sample was collected from all participants and plasma was separated for long-term storage at −196 °C. All participants were followed up by electronic linkage, via a unique personal identification number, to death and disease registries, and to nationwide health insurance agencies, for cause-specific mortality and morbidity. The accuracy of reported stroke types (IS and ICH) was verified by a review of the original medical records by a panel of certified neurologists and stroke physicians in China. Among the stroke cases selected, >90% were confirmed using brain imaging. The periodic resurvey data were used to correct for regression dilution bias[38]. Approval was obtained from the relevant international, national, and local ethics committees, and all participants provided written informed consent.

Nested case-control study of stroke types. The nested case-control study of incident stroke types included 5,475 IS cases, 4,776 ICH cases, and 6,290 healthy controls. Participants had no prior history of stroke, CHD, cancer, or use of lipid-lowering, antiplatelet, or anticoagulant drug treatment. Controls were selected among those who were free of diagnosis of stroke of any type, or unspecified type, myocardial infarction, or other CHD, by the censoring date. To avoid selecting any individual as a control who may later become a case, the cases were ranked by the reverse of the dates on which they developed an ICH event (starting with the most recent and working backwards to the earliest cases)[39]. The same controls were used for both IS and ICH cases. Plasma lipid concentrations were measured, with samples randomly ordered by disease status, using AU680 Chemistry Analyzers (Beckman Coulter), which provided direct homogenous assays for LDL-C and HDL-C, and enzymatic color assays for total cholesterol and triglycerides. Plasma concentrations of apolipoprotein B, apolipoprotein A1, and lipoprotein(a) were measured by immunoturbidimetric assays. Genotyping was carried out using an Affymetrix Axiom array, involving 800,000 SNPs, customized for the Chinese population.

GRS for LDL-C. In the Mendelian randomization analyses, a GRS for LDL-C was constructed using all available SNPs from the largest published genome-wide meta-analysis (the GLGC)[17] on lipids, which discovered 157 loci associated with lipids. Within 1-Mb intervals of these 157 loci, 185 independent ($r^2 < 0.05$) SNPs were associated ($P < 5 \times 10^{-8}$) with LDL-C, HDL-C, or triglycerides[16], including 76 SNPs associated with LDL-C ($P < 5 \times 10^{-8}$), of which 68 had the most extreme P values for LDL-C. Only 46 of these 68 SNPs were directly genotyped on the Affymetrix Axiom array in the CKB. Hence, the GRS for LDL-C was restricted to those 46 SNPs most strongly associated with LDL-C and having the largest differences between LDL-C and the other lipid fractions (Supplementary Table 2). For each variant, the effect allele was defined as the allele associated with higher LDL-C concentrations in the GLGC. The GRS was calculated by summing the number of effect alleles carried by each participant, weighted by the reported effect size of each variant on LDL-C concentrations in the GLGC.

LDL-C-lowering trials. LDL-C-lowering trials were identified by searching PubMed, the Cochrane Central Register of Controlled Trials, and the ClinicalTrial.gov database, from 1994–2018 using the terms 'statin', 'ezetimibe', 'PCSK9', and 'cardiovascular disease'. Consistent with the criteria used in the Cholesterol Treatment Trialists' Collaboration (meta-analysis of 27 trials of 174,000 participants)[15], additional trials (published before 16 November 2018) were identified if they: (1) assessed an unconfounded intervention to lower LDL-C concentrations; (2) had scheduled duration ≥ 2 years; and (3) included ≥ 1,000 participants. Overall, nine studies (Cholesterol Treatment Trialists' Collaboration meta-analysis[15] plus eight additional ones[9,14,20,21,40–43]) were identified, but two trials were excluded due to a lack of information on different stroke types[40,41].

Statistical analysis. For the observational analyses, a Cox regression analysis was used to calculate the RR and 95% CI of incident stroke types associated with usual plasma lipid concentrations after correction for regression dilution bias. Participants were categorized into fifths of usual lipid concentrations to assess the shape of associations with different stroke types. General linear regression was used to estimate the strength of such associations, weighted by the inverse variance of the logRR. All analyses were stratified by age at risk (5-year), sex, and study area, with adjustment for education, smoking, alcohol consumption, physical activity, diabetes, and baseline SBP. For categorical variables with more than two levels, risk estimates were accompanied by a group-specific 95% CI, representing the statistical information derived only for such groups[44]. The RRs were reported for clinically achievable differences of 1 mmol l^{-1} for LDL-C, 0.3 mmol l^{-1} for HDL-C, 30% for triglycerides, and also for a 1 s.d. higher plasma concentration for each lipid fraction. Additional sensitivity analyses included adjustment for adiposity (to avoid over-adjustment for blood lipids in the primary analyses)[45].

For the genetic analysis, linear or Cox regression analyses were used to assess the associations between GRS and continuous or binary traits, after adjustment for sex, age, and age^2. All analyses were conducted separately by study area, with overall effects estimated using an inverse variance-weighted meta-analysis of the area-specific results. The effects of each 1 mmol l^{-1} lower genetically instrumented LDL-C on different stroke types were estimated using the ratio method[46]. Sensitivity analyses included median-weighted inverse variance-weighted Mendelian randomization and Mendelian randomization-Egger approaches that provide consistent causal estimates from summary data for multiple genetic variants under different statistical assumptions.

For a meta-analysis of randomized trials, the study-specific RRs were scaled to each 1 mmol l^{-1} lower LDL-C for the risk of IS and ICH, using mean LDL-C differences between allocated treatment groups at about 1 year of follow-up. Summary RRs were estimated using an inverse variance-weighted average of the study-specific results[47].

To predict the number of events avoided by lowering LDL-C by 1 mmol l^{-1}, the age-specific rates of IS, ICH, and MCEs (including myocardial infarction and fatal ischemic heart disease) in the CKB were estimated for different levels of background vascular risk (Supplementary Table 4). Hypertension was defined as measured SBP of at least 140 mmHg, or a measured diastolic blood pressure of at least 90 mmHg, or receiving drug treatment for hypertension[48]. Low-risk populations were defined as those with no measured hypertension or prior history of CVD. Medium-risk populations were defined as those with measured hypertension, but with no prior history of CVD. High-risk populations were defined as those with prior history of CVD. The absolute numbers were calculated assuming that lowering LDL-C by 1 mmol l^{-1} reduces the risk of IS and MCEs by 20% (95% CI 16–24%) and 24% (95% CI: 21–27%), respectively[15], and increases the risk of ICH by 17% (95% CI 3–32%) as shown by the results from the LDL-C-lowering trials in this report, with the incidence rates of events reported in all individuals in the CKB. All P values were two-sided. All analyses were conducted using SAS version 9.3 and all figures were produced using R version 3.3.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

R.Clarke, D.B., L.L., and Z.C. have full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. Data from the baseline survey, first resurvey, and cause-specific mortality are available to all bona fide researchers (www.ckbiobank.org). Additional data can also be made available on a collaborative basis by contacting the study investigators. All data requests are reviewed monthly by the CKB Data Access Committee, which is composed of senior scientists from Beijing and Oxford.

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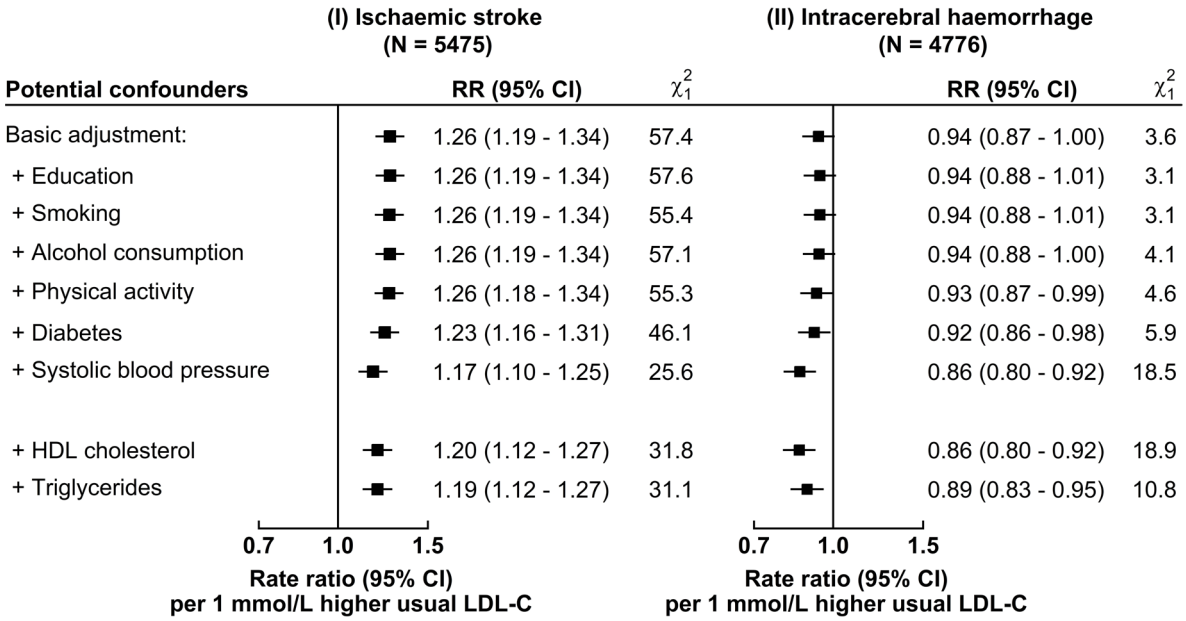
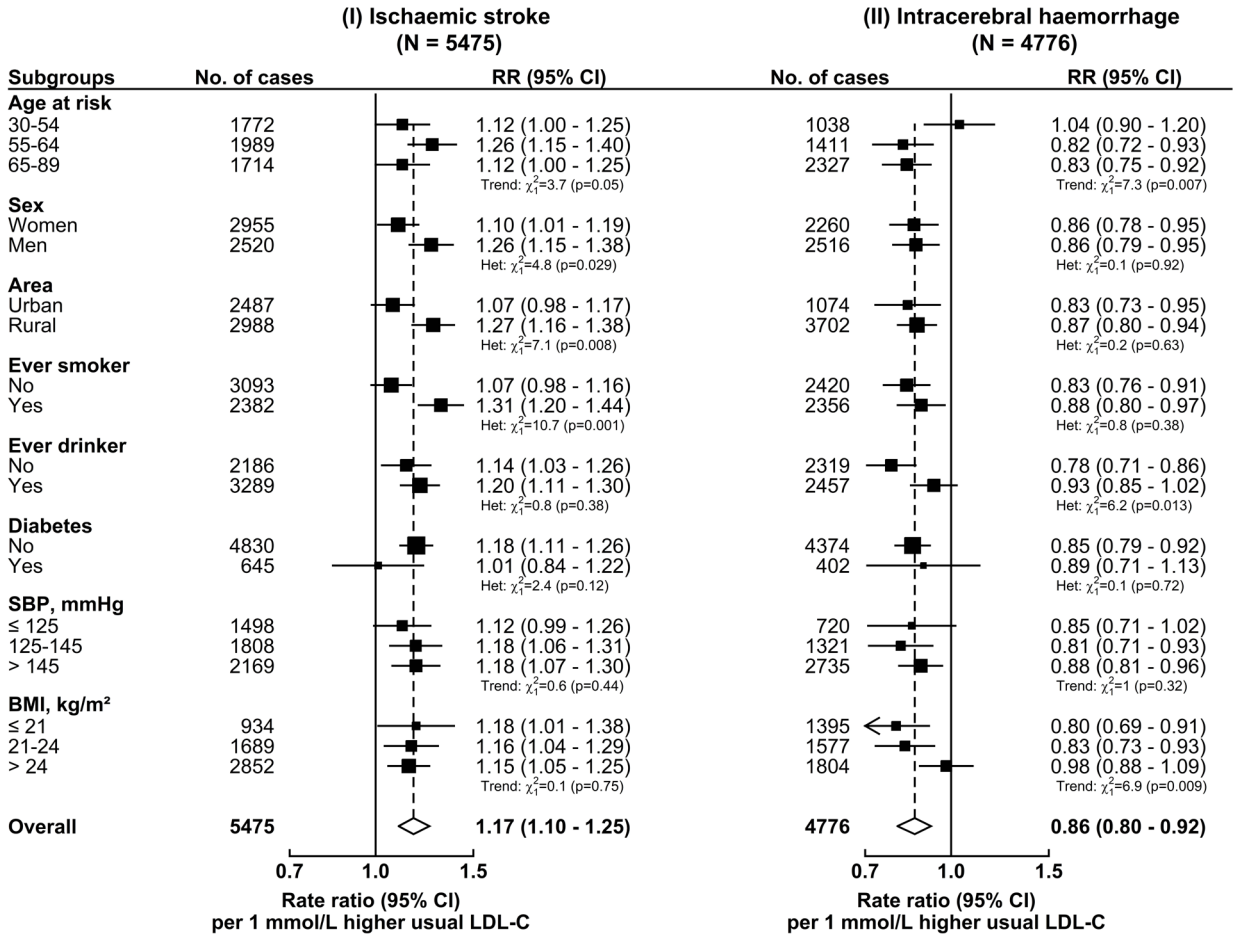
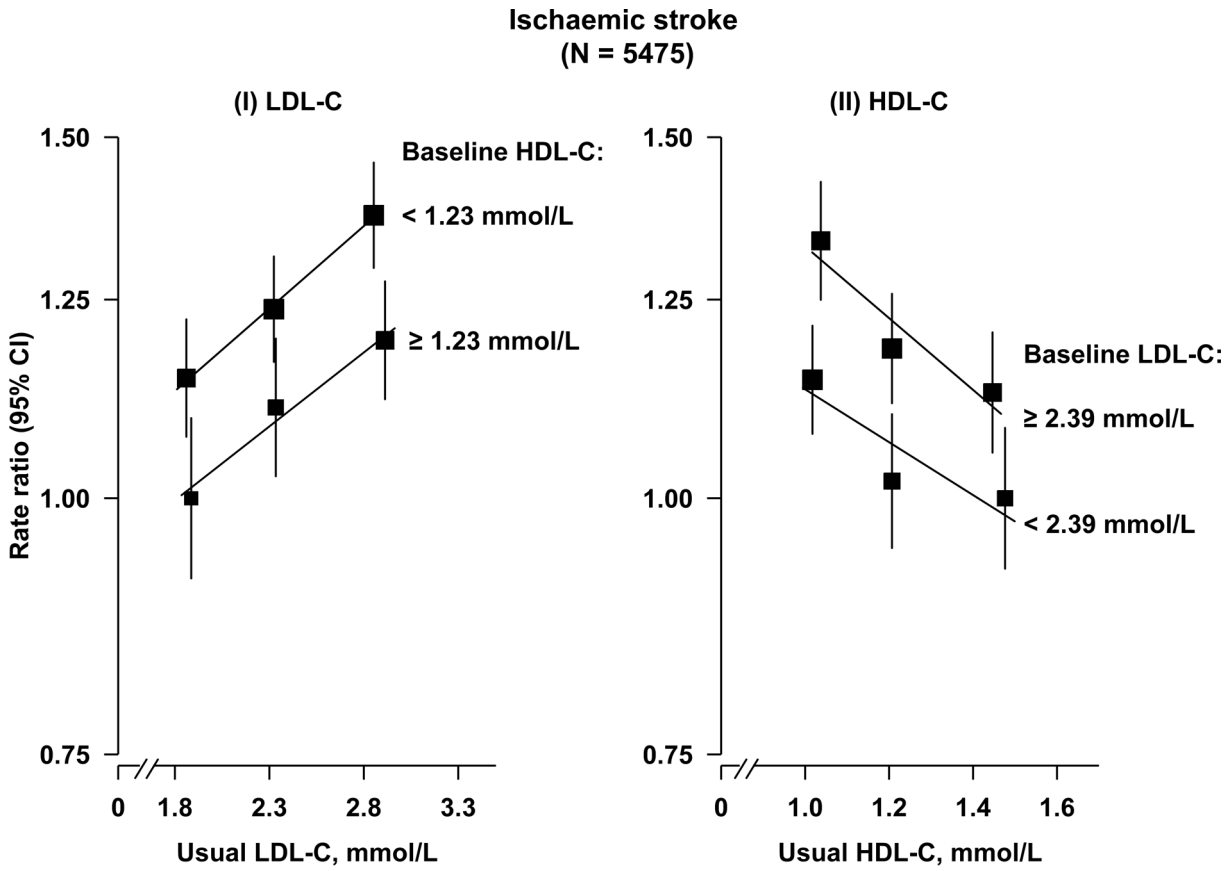


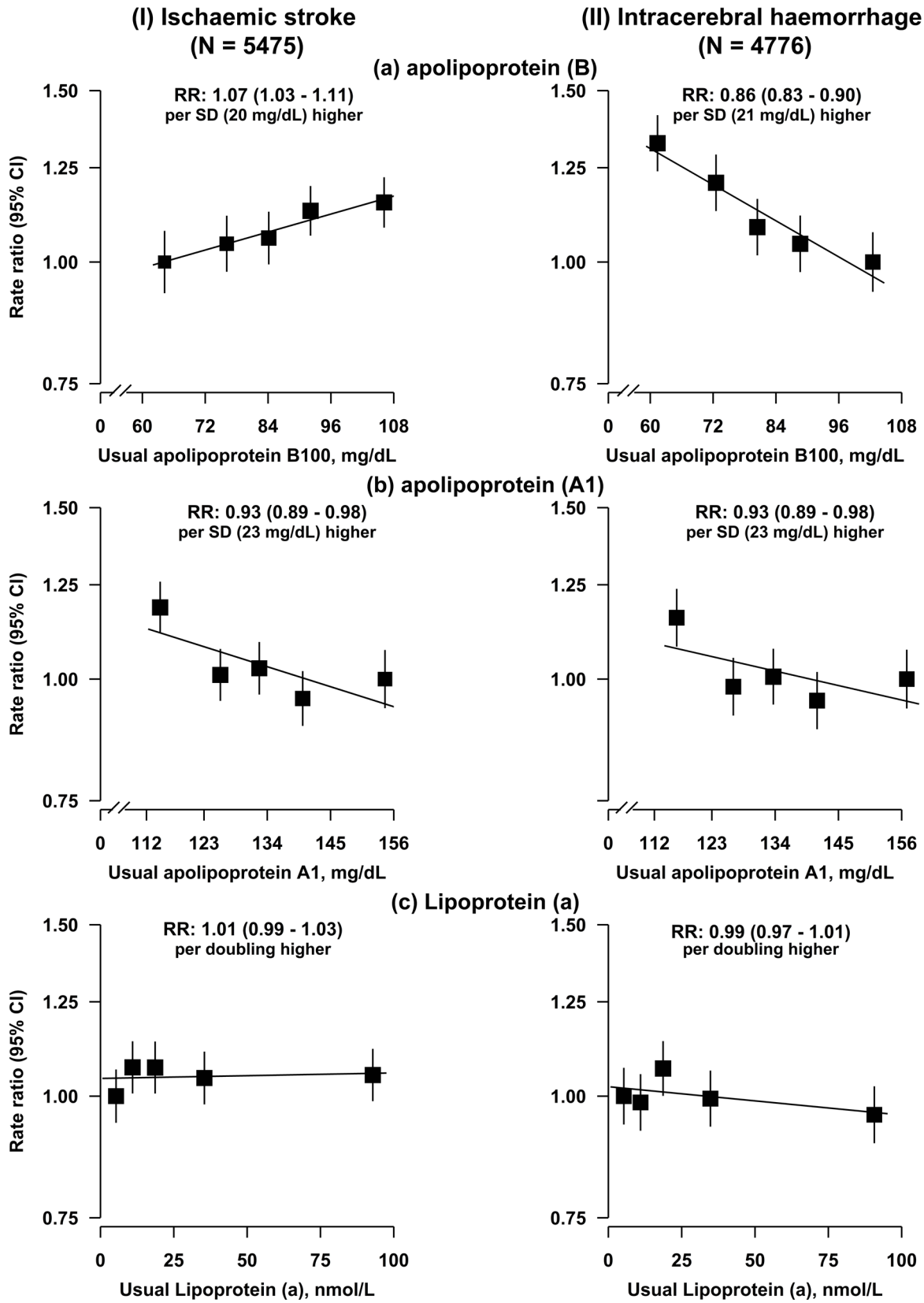
Extended Data Fig. 1 | Effect of progressive adjustment for potential confounders on the risk of IS and ICH with usual LDL-C. Cox regression was used to estimate adjusted RRs (95% confidence intervals (CI)) for the risk of different stroke types per 1 mmol l^{-1} higher concentrations of usual LDL-C. Each square has an area inversely proportional to the variance of the log risk. The horizontal lines represent the 95% CIs.



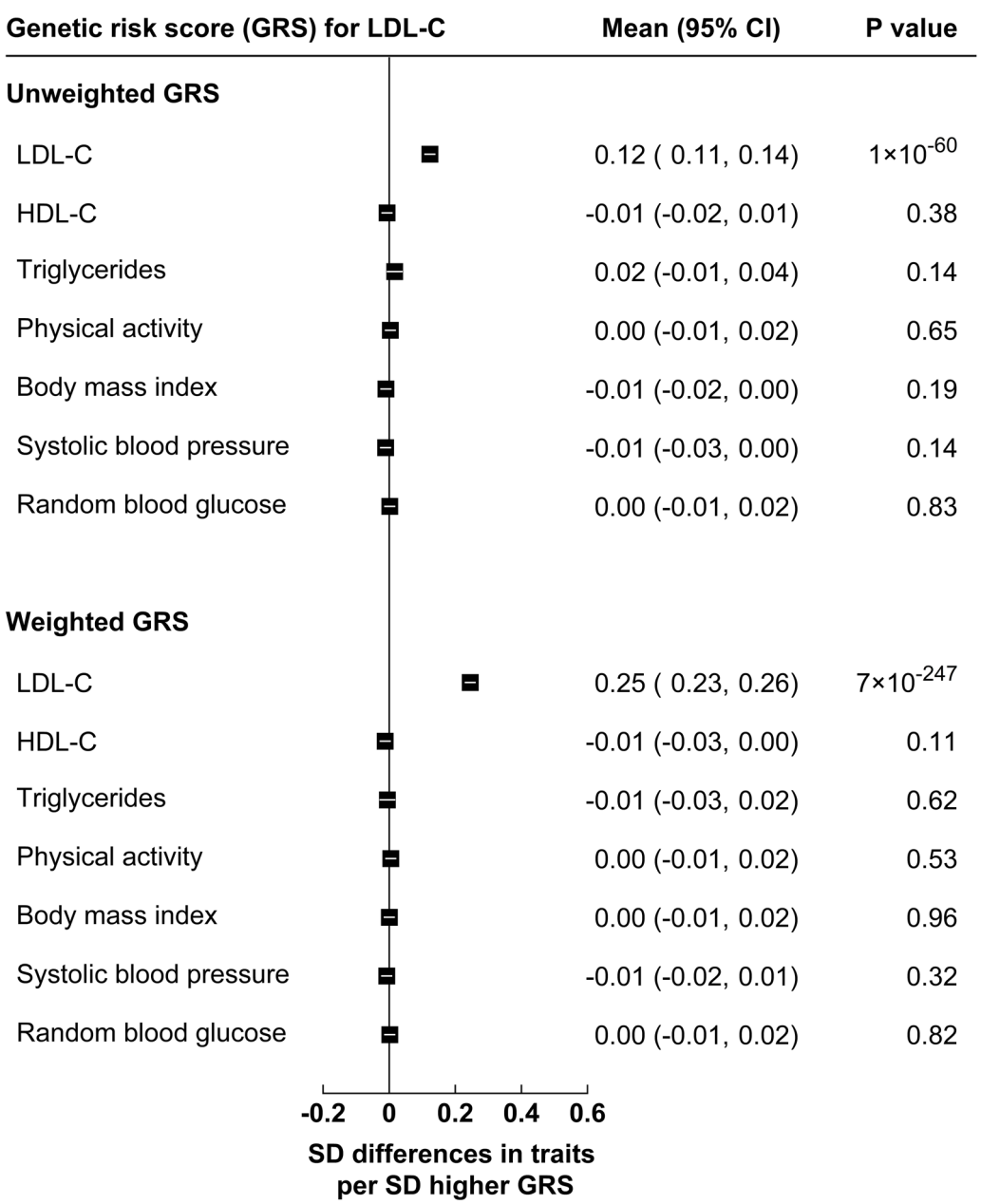
Extended Data Fig. 2 | Associations of usual LDL-C with risk of IS and ICH in population subgroups at baseline. Cox regression was used to estimate the adjusted RRs (95% CIs) for the risk of different stroke types per 1 mmol l^{-1} higher concentrations of usual LDL-C. Chi-squared tests were used to assess heterogeneity and trend; the d.f. are provided as subscripts. All two-sided *P* values were uncorrected for multiple testing. Symbols and conventions as in Extended Data Fig. 1.



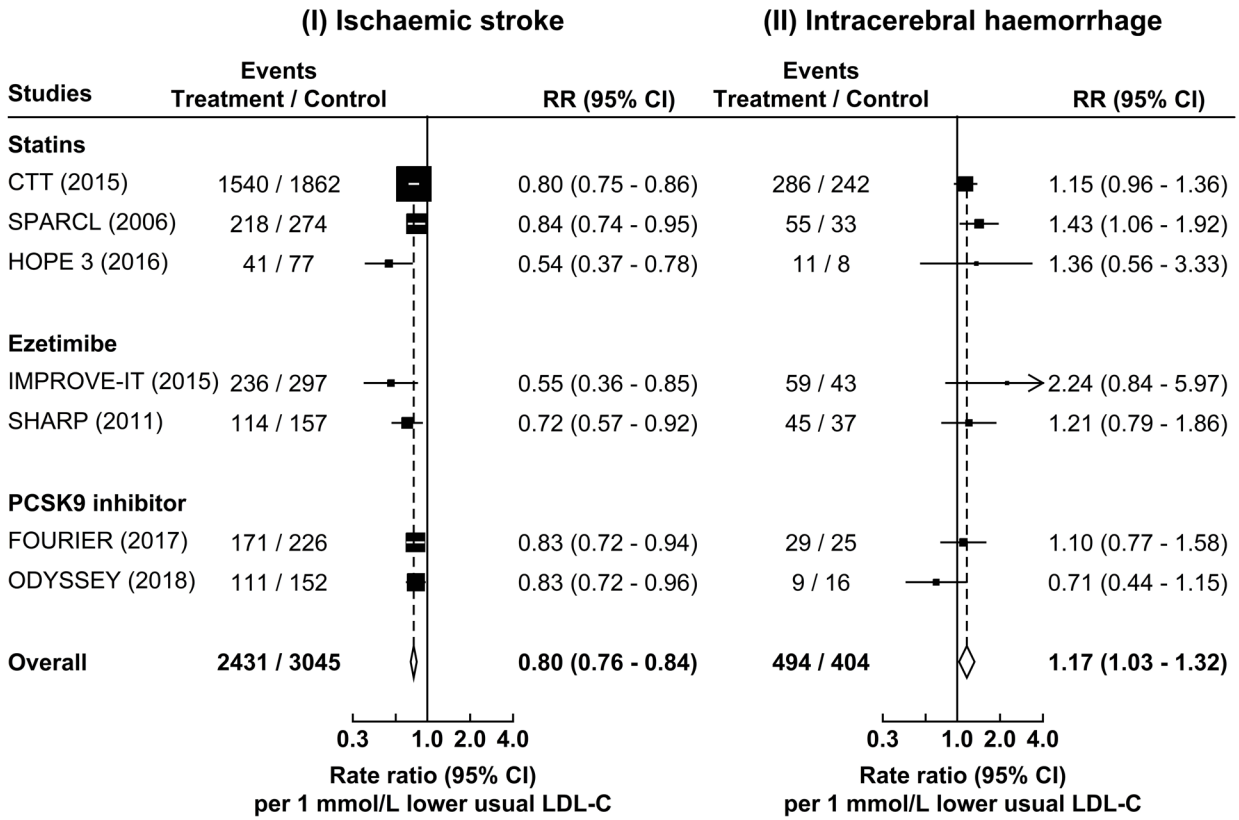
Extended Data Fig. 3 | Adjusted RRs for the risk of IS by usual concentrations of LDL-C and HDL-C in observational analyses in the CKB. Symbols and conventions as in Extended Data Fig. 1. The number of IS cases and controls were 5,475 and 6,290, respectively.



Extended Data Fig. 4 | Adjusted RRs for the risk of IS and ICH by usual concentrations of apolipoprotein B and A1, and lipoprotein(a) in observational analyses in the CKB. a–c, Cox regression was used to estimate the RRs (95% CIs) for IS (N = 5,475) and ICH (N = 4,776) by fifths of usual apolipoprotein B (**a**), usual apolipoprotein A1 (**b**), and usual lipoprotein(a) (**c**), respectively. The line represents the slope from a weighted linear regression with the weights based on the inverse variance of the log RR. Symbols and conventions as in Extended Data Fig. 1.



Extended Data Fig. 5 | Associations of the GRS for LDL-C with major vascular risk factors. The analyses were conducted in 17,567 CKB participants with available data, adjusted for sex, age, age^2, and case status. General linear regression was used to estimate s.d. differences in all traits (after rank inverse normal transformation) per 1 s.d. higher GRS. All two-sided *P* values were uncorrected for multiple testing.



Extended Data Fig. 6 | Meta-analysis of randomized trials of LDL-C-lowering treatment with statins, ezetimibe, or PCSK9 inhibitor and risk of IS and ICH. Study-specific RRs (95% CI) were obtained from the published results of the LDL-C-lowering trials. The overall RRs (95% CIs) were obtained by inverse variance-weighted meta-analysis of the study-specific RRs per 1 mmol l^{-1} lower LDL-C concentration.

nature research

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Reporting Summary

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When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

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☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	No commercial software was used for data collection.
Data analysis	All analyses were conducted using SAS. Figures were plotted using R.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Copies of the CKB data on the baseline visit, first resurvey visit, and cause-specific mortality for the first 10 years of follow-up are available to any bona fide researchers (see: www.ckbiobank.org) and additional data on biochemical and genetic markers and non-fatal disease outcomes are available on a collaborative basis with CKB investigators.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	5,475 IS cases, 4,776 ICH cases and 6,290 controls.
Data exclusions	Exclusions included prior history of CVD, and use of statins, antiplatelet, or anticoagulant drug treatment
Replication	Analyses involved associations of directly measured plasma levels of LDL-C, HDL-C, and triglycerides with stroke types. Associations of stroke types with directly measured plasma levels of LDL-C were replicated with genetically-instrumented differences in LDL-C and randomised trials, each for 1 mmol/L difference in plasma LDL-C concentration.
Randomization	All biochemical and genetic analyses were performed after randomly allocating cases and controls.
Blinding	All biochemical and genetic analyses were performed blindly to case-control status after randomly allocating cases and controls.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	A nested case-control study of Chinese adults with ischaemic stroke, intracerebral haemorrhage, and shared controls were recruited from the China Kadoorie Biobank (CKB). The mean age of participants in CKB was 51 years and 59% were women. The overall mean plasma LDL-C concentration was 2.4 (SD 0.6) mmol/L.
Recruitment	Participants in CKB were recruited from 10 areas (5 urban/5 rural) in China in 2004-2008 with an overall response rate of 30%.