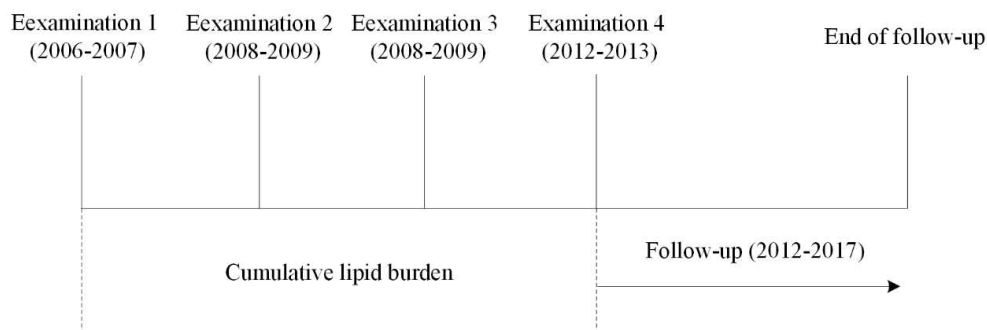


Supplementary Materials

Supplementary Figure S1. Diagram of the study



Supplementary Table S1. Hazard Ratios and 95% Confidence Intervals of

Myocardial Infarction according to different cumulative burden of lipid parameters.

Myocardial Infarction			Model 1	Model 2	Model 3
	Events N=272	Incidence Rate	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
TG burden					
0	168	0.53	Reference	Reference	Reference
1	39	0.99	2.05(1.44-2.48)	2.03(1.42-2.89)	1.63(1.09-2.28)
2	31	0.79	1.68(1.15-2.58)	1.70(1.16-2.50)	1.53(1.04-2.26)
3	34	0.86	1.95(1.34-2.83)	1.83(1.25-2.69)	1.61(1.09-2.38)
p for trend			0.13	0.21	0.50
TC burden					
0	96	0.44	Reference	Reference	Reference
1	44	0.60	1.35(0.94-1.92)	1.36(0.95-1.95)	1.35(0.95-1.94)
2	60	0.82	1.77(1.28-2.44)	1.74(1.26-2.41)	1.67(1.20-2.31)
3	72	0.99	2.19(1.61-2.97)	2.15(1.57-2.94)	2.01(1.47-2.75)
p for trend			< 0.0001	< 0.0001	< 0.0001
LDL-C burden					
0	74	0.45	Reference	Reference	Reference
1	56	0.62	1.46(1.03-2.07)	1.54(1.08-2.20)	1.54(1.08-2.20)
2	61	0.67	1.51(1.07-2.11)	1.61(1.14-2.69)	1.57(1.11-2.22)
3	81	0.89	1.84(1.34-2.53)	1.95(1.41-2.69)	1.88(1.36-2.59)
p for trend			< 0.0001	< 0.0001	< 0.0001
HDL-C burden					
0	240	0.60	Reference	Reference	Reference
1	15	1.20	1.86(1.10-3.13)	1.90(1.12-3.19)	1.80(1.07-3.04)

2	9	0.72	1.14(0.58-2.21)	1.15(0.59-2.24)	1.05(0.54-2.04)
3	8	0.64	0.97(0.48-1.96)	1.00(0.49-2.02)	0.89(0.44-1.81)
<i>p</i> for trend			0.61	0.56	0.87
Non-HDL-C burden					
0	46	0.32	Reference	Reference	Reference
1	54	0.55	1.66(1.12-2.47)	1.75(1.17-2.60)	1.71(1.15-2.54)
2	61	0.62	1.80(1.23-2.64)	1.86(1.26-2.75)	1.77(1.20-2.62)
3	111	1.12	3.20(2.27-4.52)	3.24(2.28-4.60)	2.94(2.06-4.19)
<i>p</i> for trend			< 0.0001	< 0.0001	< 0.0001

Model 1 was adjusted for age, sex,

Model 2 was adjusted for model 1 plus BMI (≥ 30 , 25-29.9, 18.5-24.9, < 18.5) and physical activity, smoker, alcohol intake.

Model 3 was adjusted for model 2 plus history of hypertension, diabetes mellitus, hypercholesterolemia

Supplementary Table S2. Hazard Ratios and 95% Confidence Intervals of Death according to different cumulative burden of lipid parameters.

Death			Model 1	Model 2	Model 3
	Events N=1343	Incidence Rate	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
TG burden					
0	1008	75.06	Reference	Reference	Reference
1	119	8.86	1.13(0.93-1.37)	1.14(0.94-1.38)	1.08(1.08-1.09)
2	115	8.56	1.20(0.99-1.45)	1.21(1.00-1.47)	1.13(0.93-1.37)
3	101	7.52	1.16(0.95-1.43)	1.18(0.96-1.46)	1.07(0.87-1.32)
<i>p</i> for trend			0.2148	0.1438	0.5116
TC burden					
0	648	48.25	Reference	Reference	Reference
1	203	15.12	0.92(0.78-1.08)	0.93(0.80-1.10)	0.93(0.79-1.09)
2	220	16.38	0.92(0.79-1.07)	0.95(0.82-1.11)	0.92(0.79-1.07)
3	272	20.25	1.13(0.98-1.30)	1.20(1.04-1.39)	1.15(0.99-1.33)
<i>p</i> for trend			0.0066	0.0006	0.0028
LDL-C burden					
0	486	36.19	Reference	Reference	Reference
1	237	17.65	0.98(0.84-1.14)	0.98(0.84-1.14)	0.98(0.84-1.14)
2	244	18.17	0.89(0.76-1.04)	0.90(0.77-1.05)	0.89(0.77-1.04)
3	376	28.00	1.17(1.02-1.33)	1.17(1.02-1.34)	1.14(1.00-1.31)
<i>p</i> for trend			0.0005	0.0003	0.0012
HDL-C burden					

0	1204	89.65	Reference	Reference	Reference
1	52	3.87	1.35(1.02-1.78)	1.36(1.03-1.80)	1.30(0.99-1.72)
2	34	2.53	0.89(0.63-1.25)	0.90(0.64-1.26)	0.83(0.59-1.17)
3	53	3.95	1.28(0.97-1.68)	1.26(0.95-1.66)	1.17(0.89-1.55)
<i>p</i> for trend			0.4047	0.4829	0.9729
Non-HDL-C burden					
0	409	30.45	Reference	Reference	Reference
1	296	22.04	1.06(0.92-1.24)	1.07(0.92-1.25)	1.06(0.91-1.23)
2	281	20.92	0.93(0.80-1.09)	0.97(0.83-1.13)	0.94(0.80-1.09)
3	357	26.58	1.10(0.95-1.27)	1.15(1.00-1.33)	1.07(0.92-1.24)
<i>p</i> for trend			0.0035	0.0005	0.0077

Model 1 was adjusted for age, sex,

Model 2 was adjusted for model 1 plus BMI (≥ 30 , 25-29.9, 18.5-24.9, < 18.5) and physical activity, smoker, alcohol intake.

Model 3 was adjusted for model 2 plus history of hypertension, diabetes mellitus, hypercholesterolemia

Supplementary Table S3. Hazard Ratios and 95% Confidence Intervals of ischemic Stroke according to different cumulative burden of lipid parameters treated as continuous variables.

IS			Model 1	Model 2	Model 3
	Events N=1023	Incidence Rate	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
TG burden					
Quartile 1	180	17.60	Reference	Reference	Reference
Quartile 2	256	25.02	1.24(1.02-1.50)	1.28(1.05-1.55)	1.22(1.00-1.48)
Quartile 3	306	29.91	1.51(1.25-1.82)	1.56(1.29-1.88)	1.47(1.22-1.78)
Quartile 4	281	27.47	1.54(1.27-1.86)	1.58(1.31-1.92)	1.41(1.16-1.72)
<i>p</i> for trend			0.0009	0.0011	0.0642
TC burden					
Quartile 1	190	18.57	Reference	Reference	Reference
Quartile 2	223	21.80	1.24(1.02-1.50)	1.26(1.03-1.53)	1.22(1.00-1.49)
Quartile 3	282	27.57	1.29(1.07-1.55)	1.36(1.13-1.64)	1.31(1.09-1.58)
Quartile 4	328	32.06	1.44(1.20-1.72)	1.54(1.28-1.84)	1.43(1.19-1.72)
<i>p</i> for trend			0.0004	$< .0001$	0.0003
LDL-C burden					
Quartile 1	214	20.92	Reference	Reference	Reference
Quartile 2	234	22.87	1.21(1.00-1.46)	1.22(1.01-1.47)	1.24(1.02-1.49)
Quartile 3	263	25.71	1.52(1.27-1.83)	1.54(1.28-1.85)	1.57(1.30-1.88)

Quartile 4	312	30.50	1.40(1.18-1.67)	1.45(1.21-1.74)	1.46(1.22-1.74)
<i>p</i> for trend			<.0001	<.0001	<.0001
HDL-C burden					
Quartile 1	247	24.14	Reference	Reference	Reference
Quartile 2	261	25.51	1.04(0.87-1.23)	1.05(0.88-1.25)	1.03(0.87-1.23)
Quartile 3	222	21.70	0.82(0.68-0.98)	0.80(0.66-0.96)	0.78(0.65-0.94)
Quartile 4	293	28.64	1.04(0.88-1.23)	1.02(0.85-1.21)	0.94(0.79-1.13)
<i>p</i> for trend			0.8303	0.6817	0.2768
Non-HDL-C burden					
Quartile 1	179	17.50	Reference	Reference	Reference
Quartile 2	223	21.80	1.29(1.06-1.57)	1.30(1.07-1.59)	1.27(1.04-1.55)
Quartile 3	275	26.88	1.30(1.08-1.58)	1.35(1.11-1.63)	1.30(1.08-1.58)
Quartile 4	346	33.82	1.54(1.28-1.85)	1.62(1.35-1.95)	1.52(1.26-1.83)
<i>p</i> for trend			<.0001	<.0001	<.0001

Model 1 was adjusted for age, sex,

Model 2 was adjusted for model 1 plus BMI (≥ 30 , 25-29.9, 18.5-24.9, < 18.5) and physical activity, smoker, alcohol intake.

Model 3 was adjusted for model 2 plus history of hypertension, diabetes mellitus, hypercholesterolemia

Supplementary Table S4: Subgroup analyses of association between cumulative

LDL burden and risk of ischemic stroke, stratified by one time point of LDL level in the last examination (2012-2013 examination).

Ischemic stroke	Events (%)	Model 1	Model 2	Model 3
LDL < 2.6 mmol/ L in the last examination				
0	166(9.09)	Ref.	Ref.	Ref.
1	110(21.96)	1.15(1.02-1.44)	1.13(1.02-1.47)	1.09(0.90-1.45)
2	87(17.37)	1.30(1.12-1.66)	1.27(1.07-1.72)	1.11(1.01-1.69)
3	138(17.58)	1.38(1.10-1.43)	1.24(1.06-1.50)	1.12(1.04-1.47)
LDL \geq 2.6 mmol/ L in the last examination				
0	49(9.39)	Ref.	Ref.	Ref.

1	102(19.54)	1.63(1.16-2.30)	1.62(1.14-2.29)	1.66(1.17-2.36)
2	125(23.95)	1.29(0.93-1.80)	1.24(0.88-1.74)	1.25(0.89-1.75)
3	246(47.13)	1.77(1.30-2.40)	1.71(1.25-2.34)	1.69(1.23-2.31)

Model 1 was adjusted for age, sex,

Model 2 was adjusted for model 1 plus BMI (≥ 30 , 25-29.9, 18.5-24.9, < 18.5) and physical activity, smoker, alcohol intake.

Model 3 was adjusted for model 2 plus history of hypertension, diabetes mellitus, hypercholesterolemia

Supplementary Table S5. Baseline characteristics of participants with cumulative LDL-C burden < 0 vs > 0 in this sub-analysis of the Kailuan cohort

Variable	cumLDL-C < 0 (n = 16,600)	cumLDL-C > 0 (n = 27,236)	p-value
N (%)	37.87	62.13	
Age, years	59.42(51.67-66.75)	61.09(53.75-68.23)	$< .0001$
Women, %	4184(25.20)	6712(24.64)	0.1874
HDL cholesterol, mmol/L	1.33(1.11-1.58)	1.33(1.13-1.57)	0.2163
LDL cholesterol, mmol/L	1.95(1.52-2.39)	2.77(2.32-3.29)	$< .0001$
Triglyceride, mmol/L	1.11(0.78-1.74)	1.33(0.98-1.98)	$< .0001$
Total Cholesterol, mmol/L	4.55(4.05-5.10)	5.27(4.69-5.96)	$< .0001$
nonHDL, mmol/L	3.17(2.69-3.71)	3.91(3.31-4.58)	$< .0001$
Systolic blood pressure, mm Hg	128.00(118.00-140.00)	130.00(120.00-140.67)	$< .0001$
hsCRP, mg/L	0.90(0.30-1.85)	1.09(0.37-2.15)	$< .0001$
Body mass index, kg/m ²	24.48(22.49-26.79)	24.96(23.03-27.31)	$< .0001$

Diabetes Mellitus, %	742(4.53)	1393(5.17)	0.0029
Hypertension, %	2709(16.54)	4575(16.99)	0.2265
Hypercholesterolemia, n (%)	779(4.76)	1624(6.03)	<.0001
Never smoker, %	10776(65.81)	18457(68.56)	<.0001
Antiplatelet therapy, %	56(0.34)	103(0.38)	0.4904
Antihypertensive medication, %	1897(11.43)	3183(11.69)	0.4112
Antidiabetic medication, %	477(2.87)	961(3.53)	0.0002
Lipid-lowering medication, %	107(0.64)	264(0.97)	0.0003
