Supplementary Table S1. Characteristics of the SNPs used as instrumental variables for leukocyte telomere length

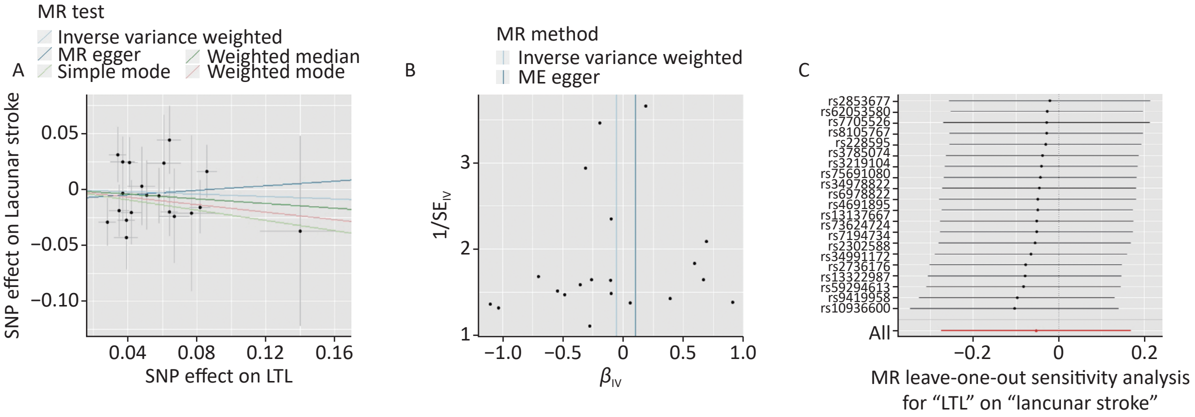
SNP	**Chr**	**Position**	**Proximal Gene**	**EA**	**NEA**	**EAF**	β	***SE***	***P* value**	R^2 **(%)**	***F*-statistic**
rs3219104	1	226562621	*PARP1*	C	A	0.830	0.042	0.006	9.60×10^{-11}	0.049	38.644
rs10936600[d]	3	169514585	*TERC*	T	A	0.243	−0.086	0.006	7.18×10^{-51}	0.271	213.377
rs55749605[b]	3	101232093	*SENP7*	A	C	0.579	−0.037	0.007	2.45×10^{-8}	0.068	53.346
rs13137667	4	71774347	*MOB1B*	C	T	0.959	0.077	0.014	2.43×10^{-8}	0.046	36.102
rs4691895[d]	4	164048199	*NAF1*	C	G	0.783	0.058	0.006	1.58×10^{-21}	0.113	89.096
rs7705526	5	1285974	*TERT*	A	C	0.328	0.082	0.006	5.34×10^{-45}	0.296	233.616
rs2853677[c]	5	1287194	*TERT*	A	G	0.592	−0.064	0.005	3.35×10^{-31}	0.197	155.091
rs2736176[a]	6	31587561	*PRRC2A*	C	G	0.313	0.034	0.005	3.53×10^{-10}	0.051	40.178
rs34991172	6	25480328	*CARMIL1*	G	T	0.068	−0.061	0.010	6.19×10^{-9}	0.047	37.033
rs59294613	7	124554267	*POT1*	A	C	0.293	−0.041	0.005	1.17×10^{-13}	0.069	53.984
rs9419958	10	105675946	*STN1(OBFC1)*	C	T	0.862	−0.064	0.007	5.05×10^{-19}	0.097	76.017
rs228595	11	108105593	*ATM*	A	G	0.417	−0.028	0.005	1.43×10^{-8}	0.039	30.991
rs2302588[d]	14	73404752	*DCAF4*	C	G	0.100	0.048	0.008	1.68×10^{-8}	0.041	32.150
rs3785074	16	69406986	*TERF2*	G	A	0.263	0.035	0.006	4.64×10^{-10}	0.048	37.510
rs62053580	16	74680074	*RFWD3*	G	A	0.169	−0.039	0.007	4.06×10^{-8}	0.042	33.406
rs7194734	16	82199980	*MPHOSPH6*	T	C	0.782	−0.037	0.006	6.94×10^{-10}	0.047	36.628
rs8105767	19	22215441	*ZNF208*	G	A	0.289	0.039	0.005	5.42×10^{-13}	0.063	49.560
rs75691080	20	62269750	*RTEL1/STMN3*	T	C	0.091	−0.067	0.009	5.99×10^{-14}	0.075	58.661
rs73624724[c]	20	62436398	*RTEL1/ZBTB46*	C	T	0.129	0.051	0.007	6.33×10^{-12}	0.058	45.345
rs34978822[a]	20	62291599	*RTEL1*	G	C	0.015	−0.140	0.023	7.26×10^{-10}	0.057	44.828

Note. [a]These two SNPs were excluded from Mendelian randomization analysis due to their multiple pleiotropic associations. [b]SNP which were not available in the lacunar stroke statistics were replaced by rs13322987 (R^2 = 0.9958). [c]These two SNPs were excluded from Mendelian randomization analysis due to linkage disequilibrium. [d]These three SNPs were excluded from Mendelian randomization analysis due to palindromic. SNP, single-nucleotide polymorphism; Chr, chromosome; EA, effect allele; NEA, non-effect allele; EAF, Effect Allele Frequency; SE, standard error of Beta.

Supplementary Table S2. Complementary analysis of association between genetically predicted leukocyte telomere length and risk of lacunar stroke using full set of instrumental variables

Methods	***OR***	**95% *CI***	***P* value**
MR Egger	1.107	0.587–2.088	0.757
Weighted median	0.901	0.652–1.244	0.525
IVW	0.949	0.760–1.184	0.641
Simple mode	0.794	0.454–1.391	0.431
Weighted mode	0.845	0.560–1.274	0.431
MR-PRESSO	0.949	0.777–1.158	0.609

Note. IVW, inverse-variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier; *OR*, odds ratio.



Supplementary Figure S1. Scatter plot (A), funnel plot (B), and leave-one-out analysis (C) for MR analysis of leukocyte telomere length and lacunar stroke using full set of instrumental variables. LTL indicates leukocyte telomere length; SNP, single nucleotide polymorphisms; MR, Mendelian randomization.