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Mendelian randomization implies no direct causal association between leukocyte telomere length and amyotrophic lateral sclerosis

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We employed Mendelian randomization (MR) to evaluate the causal relationship between leukocyte telomere length (LTL) and amyotrophic lateral sclerosis (ALS) with summary statistics from genome-wide association studies ($n \sim 38,000$ for LTL and $\sim 81,000$ for ALS in the European population; $n \sim 23,000$ for LTL and $\sim 4,100$ for ALS in the Asian population). We further evaluated mediation roles of lipids in the pathway from LTL to ALS. The odds ratio per standard deviation decrease of LTL on ALS was 1.10 (95% CI 0.93–1.31, $p = 0.274$) in the European population and 0.75 (95% CI 0.53–1.07, $p = 0.116$) in the Asian population. This null association was also detected between LTL and frontotemporal dementia in the European population. However, we found that an indirect effect of LTL on ALS might be mediated by low density lipoprotein (LDL) or total cholesterol (TC) in the European population. These results were robust against extensive sensitivity analyses. Overall, our MR study did not support the direct causal association between LTL and the ALS risk in neither population, but provided suggestive evidence for the mediation role of LDL or TC on the influence of LTL and ALS in the European population.

Amyotrophic lateral sclerosis (ALS) is an adult-onset fatal multisystem neurodegenerative disease, leading to substantial public health threat although it is relatively rare worldwide. However, the cause and pathogenesis underlying ALS mostly remains unknown, with few replicable and definitive risk factors and scarce drugs available^{1–4}. The number of ALS cases is predicted to increase dramatically due to population aging in the coming years⁵, which would further aggravate the ALS-associated social and economic burden. Therefore, the identification of its risk factors can provide better understanding of ALS and has the potential to pave the way for therapeutic intervention.

In the past few years the role of telomere in various complex diseases has attracted much attention⁶. Progressive telomere shortening occurs in all dividing normal cells due to incomplete synthesis of DNA lagging-strand, oxidative damage and other factors, which ultimately leads to cellular growth arrest or apoptosis that is thought to be an initial proliferative barrier to tumor development in humans⁷. Indeed, recent studies suggested that leukocyte telomere length (LTL) was widely relevant to age-related diseases and disorders (e.g. many types of cancer and coronary heart disease)^{8–11}. In particular, it was demonstrated that shorter LTL was associated with various neurodegenerative disorders. For example, a latest study showed LTL at baseline and 18 months was shorter in patients of Parkinson's disease (PD) compared to healthy controls¹², although prior studies found nonsignificant association between LTL and PD (Table 1). In addition, telomere shortening was recognized as an indicator of progression for Alzheimer's disease (AD) (Table 1).

However, the knowledge about the relationship between LTL and ALS is very limited. Previous studies proposed that telomerase inhibition could be a pathogenetic contributor to the neurodegeneration in ALS¹³. A recent study¹⁴, along with ALS animal models¹⁵, offered some evidence that shorter LTL likely decreased the risk

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| NDD | OR/HR (95% CI, <i>p</i>) | <i>N</i> (case/control) | Country | References |
|----------|----------------------------|-------------------------|---------------|------------|
| PD | 0.70 (0.38–1.28, 0.246) | 956/1,284 | EUR and Asian | 74 |
| PD | 0.91 (0.71–1.16, 0.450) | 96/172 | USA | 75 |
| PD | 0.99 (0.77–1.27, 0.535) | 131/115 | Finland | 76 |
| PD | 0.99 (0.88–1.12, 0.875) | 408/809 | USA | 77 |
| PD | 1.30 (0.76–2.17, 0.340) | 28/27 | Japan | 78 |
| ALS | 0.89 (0.68–1.16, 0.400) | 6,100/7,125 | EUR | 9 |
| ALS | 0.92 (0.87–0.97, 0.008) | 1,241/335 | UK | 14 |
| AD | 1.03 (1.01–1.05, 0.012) | 71,880/383,378 | EUR | 79 |
| AD | 1.05 (1.01–1.09, 0.010) | 71,880/383,378 | EUR | 80 |
| AD | 1.19 (1.02–1.41, 0.030) | 17,008/37,154 | EUR | 9 |
| AD | 1.35 (1.12–1.67, 0.002) | 25,580/48,466 | EUR | 81 |
| AD | 1.35 (1.11–1.67, 0.003) | 25,580/48,466 | EUR | 82 |
| AD | 2.70 (1.69–4.17, 1.47E–05) | 860/2,022 | Multiethnic | 83 |
| Dementia | 1.20 (1.00–1.47, 0.058) | 190/1,469 | Multiethnic | 84 |
| Dementia | 5.26 (1.85–14.3, 0.002) | 20/151 | UK | 85 |

Table 1. Estimated effect sizes of shorter LTL on neurodegenerative diseases in previous studies. *NDD* neurodegenerative disease, *PD* Parkinson's disease, *ALS* amyotrophic lateral sclerosis, *AD* Alzheimer's disease, *OR* odds ratio, *HR* hazard ratio, *CI* confidence interval, *p* *p* value, *N* sample size, *EUR* European.

of ALS (Table 1). However, it remains uncertain whether such association is causal or not. Because it is rather challenging to determinate causal relationship between LTL and ALS via observational studies or randomized controlled trials (RCT), in this study we resort to another novel statistical approach called Mendelian randomization (MR)^{16,17}. Briefly, depending on single nucleotide polymorphisms (SNPs) as instrumental variables, MR can infer the causal association between an exposure (e.g. LTL) and an outcome (e.g. ALS)^{17,18}. The basic idea behind MR is that the two alleles of a genetic variant are randomly allocated during the process of gamete formation under the Mendel's law; such allocation is analogous to the randomization of subjects in RCT and hence has a powerful control for reverse causality and confounders¹⁹ (Supplementary Fig. S1). Furthermore, the recent success of large-scale genome-wide association studies (GWASs)^{20–24} allows us to choose appropriate SNPs as valid instrumental variables for a variety of exposures for causal inference in MR^{25–27}.

In this study we aim to investigate whether there exists a causal association between LTL and the risk of ALS. To achieve such goal, we conducted the two-sample MR analysis with summary statistics publicly available from GWASs with ~ 38,000 individuals for LTL and ~ 81,000 individuals for ALS in the European population, and with ~ 23,000 individuals for LTL and ~ 4,100 individuals for ALS in the Asian population. Additionally, we further explored the mediation role of lipids in the relationship between LTL and ALS with network MR analysis given the evidence that blood lipids may be relevant to ALS.

Materials and methods

GWAS data sources for LTL, ALS and other relevant traits. We first obtained genetic data for LTL from the ENGAGE Telomere Consortium²¹, where a total of ~ 2.3 million SNPs for 37,684 individuals of European ancestry were contained after quality control (Supplementary Text). In this study LTL was measured as a continuous variable, and the linear additive regression was implemented for each genetic variant to detect the association with LTL²¹. A set of independent associated index SNPs ($p < 5.00E-8$) were selected as candidate instrumental variables for LTL. To minimize the pleiotropic bias of instruments, we applied a conservative manner²⁸ that was previously undertaken in many MR studies^{20,29–32}. Specifically, we would remove index SNPs that were located within 1 Mb of ALS-associated locus (Supplementary Table S1) and that may be potentially related to ALS if their Bonferroni-adjusted *p* values were less than 0.05. Finally, we reserved seven SNPs to serve as instrumental variables. To estimate the causal effect of LTL on ALS, we obtained summary statistics from the largest ALS GWAS that contained ~ 10 million SNPs on 80,610 European individuals (20,806 ALS cases and 59,804 controls)²⁰ (<https://als.umassmed.edu/>). The summary statistics (e.g. marginal effect size, standard error and effect allele) of these instruments are shown in Table 2.

In addition, since ALS and frontotemporal dementia (FTD) often represent a continuous disease spectrum with comorbidity in up to 50% cases, and share common genetic mechanisms^{33–35}, we also explored the causal association between LTL and FTD with MR approaches (Table 3). We removed index SNPs that were associated with FTD³⁶ and reserved six instruments as one instrument was missing in the FTD GWAS data set (Supplementary Tables S2–S3). Furthermore, we attempted to validate whether the identified relationship between LTL and ALS in the European population also holds in the Asian population. Therefore, we performed additional MR analyses with another two GWAS datasets in which both LTL²² and ALS³⁷ were conducted on the Asian individuals (Supplementary Text). Note that, the two sets of index SNPs of LTL from the two populations share no common instruments (Table 2 and Supplementary Table S4).

We note that the ALS cases were sporadic and the European-ALS GWAS adjusted the effect of age in the association analysis (Supplementary Text). The latter indicates that the confounding effect due to age on the

| SNP | GENE | CHR | BP | A1/A2 | LTL | | | | ALS | | | | PVE | F |
|------------|--------|-----|-------------|-------|--------|-------|----------|--------|--------|-------|-------|--------|----------|-------|
| | | | | | BETA | SE | p | N | BETA | SE | p | N | | |
| rs11125529 | TERT | 2 | 54,329,370 | C/A | -0.056 | 0.010 | 4.48E-08 | 37,653 | -0.007 | 0.020 | 0.730 | 80,610 | 8.32E-04 | 31.4 |
| rs10936599 | TERC | 3 | 170,974,795 | T/C | -0.079 | 0.008 | 2.54E-31 | 37,669 | 0.003 | 0.016 | 0.839 | 80,610 | 3.89E-03 | 147.0 |
| rs7675998 | ZNF208 | 4 | 164,227,270 | A/G | -0.074 | 0.009 | 4.35E-16 | 34,694 | -0.005 | 0.016 | 0.747 | 80,610 | 1.94E-03 | 67.6 |
| rs2736100 | NAF1 | 5 | 1,339,516 | A/C | -0.078 | 0.009 | 4.38E-19 | 25,842 | 0.010 | 0.014 | 0.493 | 80,610 | 2.90E-03 | 75.1 |
| rs9420907 | ACYP2 | 10 | 105,666,455 | A/C | -0.069 | 0.010 | 6.90E-11 | 37,653 | 0.050 | 0.019 | 0.011 | 80,610 | 1.26E-03 | 47.6 |
| rs8105767 | RTEL1 | 19 | 22,007,281 | A/G | -0.048 | 0.008 | 1.11E-09 | 37,499 | 0.006 | 0.015 | 0.683 | 80,610 | 9.59E-04 | 36.0 |
| rs755017 | OBFC1 | 20 | 61,892,066 | A/G | -0.062 | 0.011 | 6.71E-09 | 37,113 | -0.005 | 0.022 | 0.831 | 80,610 | 8.55E-04 | 31.8 |

Table 2. Summary information of instrumental variables for LTL and ALS in the European population. *SNP* the label of single-nucleotide polymorphism that served as instrumental variable, *CHR* chromosome, *BP* base position, *A1* effect allele, indicates the allele that is associated with shorter LTL, explaining why all the BETA estimates are negative, *A2* alternative allele, *BETA* SNP effect size, *SE* standard error of the SNP effect size, *p* and *N* are respectively the *p* value and sample size, *PVE* proportion of variance explained by the SNP (i.e. $PVE_i = (\hat{\beta}_i^x)^2 / ((\hat{\beta}_i^x)^2 + \text{var}(\hat{\beta}_i^x) \times N_i)^{86}$, where $\hat{\beta}_i^x$ and $\text{var}(\hat{\beta}_i^x)$ are the estimated effect size and variance for instrument *i*; *F*: *F* statistic (i.e. $F_i = PVE_i(N_i - 1 - k) / (k - k \times PVE_i)^{87,88}$, where N_i is the sample size for instrument *i* and *k* is the number of instruments). Both of PVE and *F* statistic are calculated to validate the issue of weak instruments.

| Traits | Pop | k_1/k_0 | <i>N</i> (case/control) | Data source |
|--------|-------|-----------|-------------------------|------------------------|
| ALS | EUR | | 80,610 (20,806/59,804) | AVS ²⁰ |
| HDL | EUR | 85/87 | 93,561 | GLGC ⁶¹ |
| LDL | EUR | 78/78 | 89,138 | GLGC ⁶¹ |
| TC | EUR | 86/86 | 93,845 | GLGC ⁶¹ |
| TG | EUR | 53/54 | 90,263 | GLGC ⁶¹ |
| LTL | EUR | 7/7 | 37,684 | ENGAGE ²¹ |
| FTD | EUR | | 12,928 (3,526/9,402) | IFGC ³⁶ |
| HDL | EUR | 79/87 | 93,561 | GLGC ⁶¹ |
| LDL | EUR | 66/78 | 89,138 | GLGC ⁶¹ |
| TC | EUR | 76/86 | 93,845 | GLGC ⁶¹ |
| TG | EUR | 47/54 | 90,263 | GLGC ⁶¹ |
| LTL | EUR | 6/7 | 37,684 | ENGAGE ²¹ |
| ALS | Asian | | 4,084 (1,234/2,850) | Benyamin ³⁷ |
| HDL | Asian | 30/31 | 70,657 | Kanai ⁸⁹ |
| LDL | Asian | 21/22 | 72,866 | Kanai ⁸⁹ |
| TC | Asian | 31/32 | 128,305 | Kanai ⁸⁹ |
| TG | Asian | 26/26 | 105,597 | Kanai ⁸⁹ |
| LTL | Asian | 8/10 | 23,096 | SCHS ²² |

Table 3. GWAS data sets used in our MR analysis in the present study. Here k_1 is the final number of instruments employed in the analysis while k_0 is the number of candidate instruments. *ALS* amyotrophic lateral sclerosis, *FTD* frontotemporal dementia, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TC* total cholesterol, *TG* triglycerides, *LTL* leukocyte telomere length, *Pop* population, *EUR* European, *AVS* the ALS Variant Server, *IFGC* International FTD-Genomics Consortium, *GLGC* Global Lipids Genetics Consortium, *ENGAGE* European Network for Genetic and Genomic Epidemiology, *SCHS* Singapore Chinese Health Study.

causal effect estimation was removed. In addition, given the fact that LTL would shorten progressively with age, to facilitate the explanation of our results, we thus made a sign transformation for effect sizes of those used instrumental variables so that the causal relationship corresponds to *shorter* LTL.

Causal effect estimation via two-sample Mendelian randomization. We implemented the two-sample MR to estimate the causal effect of LTL on ALS via inverse-variance weighted (IVW) methods^{38–41} (Supplementary Text). We also employed the weighted median method⁴², likelihood-based approach⁴³, leave-one-out (LOO) analysis⁴⁴, MR-PRESSO test⁴⁵ and MR-Egger regression^{38,46} as part of sensitivity analyses to validate the robustness of our results. As a supplementary analysis, we further implemented the generalized summary based Mendelian Randomization (GSMR) method⁴⁷ by leveraging possible linkage disequilibrium among instruments, and applied the HEIDI-outlier approach to detect pleiotropic instrumental variables.

| Method | ALS-european | FTD-european | ALS-asian |
|-----------------|-------------------------|--------------------------|--------------------------------------|
| | OR (95% CI, <i>p</i>) | OR (95% CI, <i>p</i>) | OR (95% CI, <i>p</i>) |
| IVW-random | 1.10 (0.92–1.32, 0.284) | 0.81 (0.44–1.48, 0.498) | 0.75 (0.53–1.07, 0.116) |
| IVW-fixed | 1.10 (0.93–1.31, 0.274) | 0.81 (0.44–1.48, 0.498) | 0.75 (0.53–1.07, 0.116) |
| MR-Egger | 1.02 (0.32–3.29, 0.964) | 0.40 (0.01–14.71, 0.516) | 0.61 (0.24–1.56, 0.241) |
| Weighted Median | 1.06 (0.85–1.32, 0.624) | 0.73 (0.35–1.52, 0.400) | 0.67 (0.43–1.05, 0.082) |
| Likelihood | 1.10 (0.92–1.32, 0.290) | 0.81 (0.44–1.48, 0.496) | 0.75 (0.53–1.07, 0.115) |
| GSMR | 1.10 (0.93–1.31, 0.274) | 0.81 (0.44–1.48, 0.498) | 0.73 (0.51–1.05, 0.086) ^a |

Table 4. Association of LTL with the risk of ALS or FTD in the European and Asian populations. The intercept of the MR-Egger regression is 0.006 (95% CI – 0.079–0.090, $p=0.872$), 0.055 (95% CI – 0.214–0.323, $p=0.601$) or 0.026 (95% CI – 0.076–0.128, $p=0.552$), respectively. ^aSeven instruments were finally employed because the genotype of rs41309367 on gene *RTEL1* was missing in the 1,000 Genomes Project.

Mediation analysis to explore the mediation effect of lipids between LTL and ALS/FTD. In our MR analysis, we attempted to provide deeper insight into the relationship between LTL and ALS/FTD by conducting mediation analysis although non-significant causal associations were identified in neither population. Because previous studies showed LTL was associated with blood lipid levels^{48–52} (as would be also confirmed by our results; see below for details), and because there existed evidence for potential causal associations between lipids and ALS^{3,53,54}, we further investigated whether the effect of LTL on ALS/FTD might be mediated through lipids^{55–59} by implementing network MR analysis⁶⁰ with the lipid trait (e.g. HDL, LDL, TC or TG)⁶¹ as mediator (Supplementary Fig. S2 and Supplementary Text). Besides LTL, in the network MR analysis each of lipids should also have a set of instrumental variables (Table 3). The details of selecting instrumental variables for lipids were described elsewhere⁵³. To make the estimated causal effects comparable between the European and Asian populations, following prior work⁵³ we unified the units of lipid in the two populations (Supplementary Text). The summary statistics of instruments for lipids are displayed in Supplementary Tables S5–S9.

Results

Causal effect of LTL on ALS and FTD. A total of seven instrumental variables of LTL were employed in the European population (Table 2). All the selected instruments collectively explain about 1.26% phenotypic variation of LTL and all the *F* statistics are above 10 (ranging from 31.4 to 147.0 with an average of 62.3) (Table 2), which rules out the possibility of weak instrument bias^{28,39,62}. With the fixed-effects IVW method, we observe that the odds ratio (OR) per standard deviation (SD) decrease of LTL (~30 base pair per year) on ALS is 1.10 (95% confidence interval [CI] 0.93–1.31, $p=0.274$) in the European population and 0.75 (95% CI 0.53–1.07, $p=0.116$) in the Asian population (Table 4). We also fail to detect statistically significant causal relationship between LTL and FTD in the European population, with the OR per SD decrease of LTL on FTD estimated to be 0.81 (95% CI 0.44–1.48, $p=0.498$) (Table 4).

We now validated the causal effect of LTL on ALS estimated above through various sensitivity analyses. Here, we mainly focused on the relationship between LTL and ALS in the European population (Table 4). The weighted median and maximum likelihood methods generate similar null causal effect estimates. In particular, the OR is estimated to be 1.06 (95% CI 0.85–1.32, $p=0.624$) by the weighted median method and 1.10 (95% CI 0.92–1.32, $p=0.290$) by the maximum likelihood approach. Both the LOO (Supplementary Table S10) and MR-PRESSO analyses indicate that no instrument outliers exist (see also Fig. 1). The MR-Egger regression provides little evidence of horizontal pleiotropy as its intercept is not significantly deviated from zero (0.006, 95% CI – 0.079–0.090, $p=0.872$). The results of sensitivity analyses for LTL and ALS in the Asian population as well as for LTL and FTD in the European population are summarized in Supplementary Tables S11–S12.

Finally, we conducted GSMR with genotypes of 503 European individuals or 504 Asian individuals in the 1,000 Genomes Project as reference panel⁶³. It is shown that GSMR generates consistent causal effect estimates with previous results (Table 4), again supporting the null association between LTL and ALS/FTD. In addition, the HEIDI-outlier approach does not detect any instruments that exhibit apparent pleiotropic effects, implying the observed association between LTL and ALS/FTD would be not confounded by pleiotropy.

Mediation analysis of the role between LTL, lipids and ALS/FTD. Although we do not find statistically significant evidence that LTL causally influences ALS/FTD in the direct biological pathway, we cannot fully exclude the probability that LTL may impact ALS/FTD via other indirect pathways. We selected six or eight index association SNPs to serve as instrumental variables for LTL on lipids in the European and Asian populations, respectively. In the European population, the causal effects per SD decrease of LTL on HDL and TG are 0.08 (95% CI 0.03–0.14, $p=0.005$) and – 0.10 (95% CI – 0.15 to – 0.04, $p=0.001$), respectively (Table 5). However, HDL and TG are not associated with ALS, implying there may be no indirect effects of LTL on ALS mediated by HDL or TG.

On the other hand, the causal effect per SD decrease of LTL on LDL and TC are – 0.06 (95% CI – 0.12–0.00, $p=0.057$) and – 0.06 (95% CI – 0.12–0.00, $p=0.052$), respectively, both of which are marginally significant at the level of 0.05. Moreover, in the European population these two lipids are causally associated with ALS: the ORs per SD decrease of LDL (~37.0 mg/dL) and TC (~42.6 mg/dL) on ALS are – 0.11 (95% CI – 0.17 to – 0.05, $p=3.41E-04$) and – 0.10 (95% CI – 0.16 to – 0.04, $p=0.002$), respectively. Therefore, based on the basic

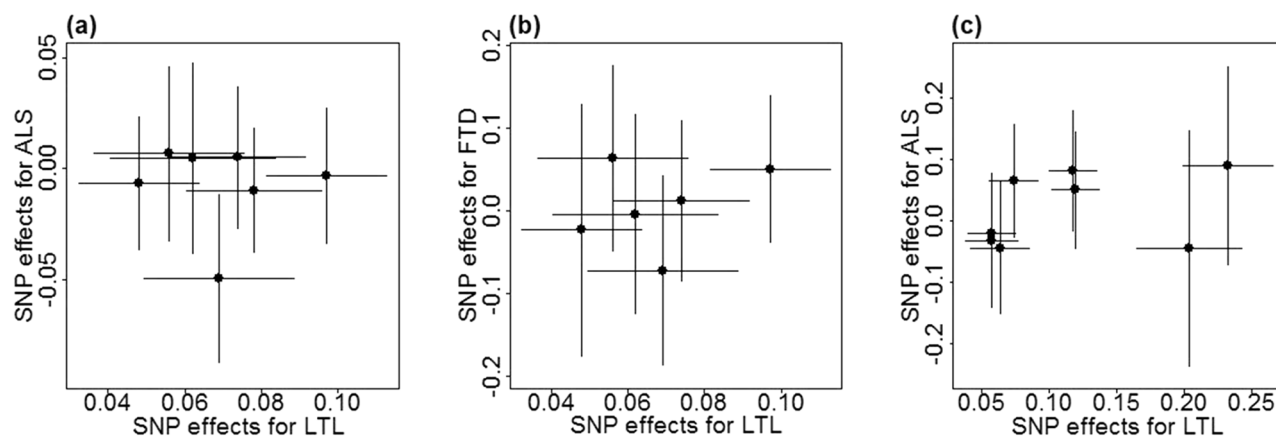


Figure 1. Relationship between effect sizes on LTL and ALS/FTD for SNPs served as instrumental variables. Results are shown for seven SNPs of ALS (a) and six SNPs of FTD (b) in the European population. Results are also displayed for eight SNPs of ALS in the Asian population (c). In each panel, horizontal/vertical lines represent the 95% confidence intervals.

| Pop | Exposure | Mediator | <i>a</i> | SE (<i>a</i>) | <i>p</i> | Mediator | Outcome | <i>b</i> | SE (<i>b</i>) | <i>p</i> | Exposure | Outcome | <i>c</i> | SE (<i>c</i>) | <i>p</i> |
|-------|----------|----------|---------------|-----------------|--------------|----------|---------|---------------|-----------------|-----------------|----------|---------|----------|-----------------|----------|
| EUR | LTL | HDL | 0.082 | 0.029 | 0.005 | HDL | ALS | 0.013 | 0.039 | 0.743 | LTL | ALS | 0.097 | 0.089 | 0.274 |
| | LTL | LDL | -0.060 | 0.031 | 0.057 | LDL | ALS | -0.110 | 0.031 | 3.41E-04 | LTL | ALS | 0.097 | 0.089 | 0.274 |
| | LTL | TC | -0.059 | 0.031 | 0.052 | TC | ALS | -0.098 | 0.032 | 0.002 | LTL | ALS | 0.097 | 0.089 | 0.274 |
| | LTL | TG | -0.095 | 0.028 | 0.001 | TG | ALS | -0.045 | 0.044 | 0.309 | LTL | ALS | 0.097 | 0.089 | 0.274 |
| | LTL | HDL | 0.082 | 0.029 | 0.005 | HDL | FTD | -0.035 | 0.125 | 0.786 | LTL | FTD | -0.208 | 0.308 | 0.498 |
| | LTL | LDL | -0.060 | 0.031 | 0.057 | LDL | FTD | -0.139 | 0.107 | 0.196 | LTL | FTD | -0.208 | 0.308 | 0.498 |
| | LTL | TC | -0.059 | 0.031 | 0.052 | TC | FTD | -0.142 | 0.104 | 0.172 | LTL | FTD | -0.208 | 0.308 | 0.498 |
| | LTL | TG | -0.095 | 0.028 | 0.001 | TG | FTD | -0.018 | 0.140 | 0.898 | LTL | FTD | -0.208 | 0.308 | 0.498 |
| Asian | LTL | HDL | -0.020 | 0.022 | 0.366 | HDL | ALS | 0.108 | 0.129 | 0.404 | LTL | ALS | -0.284 | 0.180 | 0.116 |
| | LTL | LDL | 0.003 | 0.023 | 0.898 | LDL | ALS | -0.234 | 0.131 | 0.073 | LTL | ALS | -0.284 | 0.180 | 0.116 |
| | LTL | TC | -0.002 | 0.014 | 0.911 | TC | ALS | -0.276 | 0.214 | 0.197 | LTL | ALS | -0.284 | 0.180 | 0.116 |
| | LTL | TG | 0.018 | 0.014 | 0.214 | TG | ALS | 0.160 | 0.195 | 0.414 | LTL | ALS | -0.284 | 0.180 | 0.116 |

Table 5. Three directions of the relation with exposure to mediator, mediator to outcome and exposure to outcome. *Pop* population, *EUR* European, *LTL* leukocyte telomere length, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TC* total cholesterol, *TG* triglycerides, *ALS* amyotrophic lateral sclerosis, *FTD* frontotemporal dementia, *p* *p* value, The effect size and the standard error of the relationship with Exposure to Mediator, Mediator to Outcome and Exposure to Outcome are denoted as *a*, *b*, *c* and SE(*a*), SE(*b*), SE(*c*), respectively. The marginally significant causal association between LTL and LDL/TC and the significant causal association between LDL/TC and ALS in the European population are shown in bold.

principle of the classical mediation inference, we can reasonably state that there likely exists potential indirect effect of LTL on ALS mediated by LDL ($ab = 0.007$ and $p = 0.079$) or TC ($ab = 0.006$ and $p = 0.092$) (Table 6). More specifically, in terms of the suggestive evidence of mediation effects displayed above, in the European population we can conclude that shorter LTL can reduce the LDL/TC level, which in turn results in the lower risk of ALS. However, we fail to repeat such mediation association for ALS in the Asian population or for FTD in the European population (Tables 5, 6).

Finally, we examined whether the lack of detectable non-zero causal effect of LTL on ALS is due to the lack of statistical power. We calculated the statistical power to detect an OR of 1.10 or 1.20 (approximately equal the estimated causal effects above) per SD decrease of LTL on the risk of ALS following an analytic approach (<https://cnsgenomics.shinyapps.io/mRnd/>)⁶⁴. It is shown the estimated statistical power is only 15% or 44% (Fig. 2), indicating we have low to moderate power to identify such causal effect with current sample sizes if LTL is indeed causally associated with the risk of ALS.

Discussion

In the present study we have implemented a comprehensive two-sample MR analysis to dissect whether there exists causal relationship between LTL and the risk of ALS. To our knowledge, this is the first MR study to investigate the relationship between LTL and ALS using statistical genetic approaches via summary statistics available from large-scale GWAS. We found that an indirect effect of LTL on ALS might be mediated by LDL or TC, although our MR analysis did not support the existence of direct causal association between LTL and

| Pop | Exposure | Mediator | Outcome | ab (S_{ab}) | 95% CI | Z | p |
|-------|----------|----------|---------|----------------------|---------------------|--------------|--------------|
| EUR | LTL | HDL | ALS | 0.001 (0.003) | -0.005-0.007 | 0.354 | 0.724 |
| | LTL | LDL | ALS | 0.007 (0.004) | -0.001-0.014 | 1.754 | 0.079 |
| | LTL | TC | ALS | 0.006 (0.003) | -0.001-0.013 | 1.682 | 0.092 |
| | LTL | TG | ALS | 0.004 (0.004) | -0.004-0.012 | 1.021 | 0.307 |
| | LTL | HDL | FTD | -0.003 (0.010) | -0.022-0.016 | -0.298 | 0.766 |
| | LTL | LDL | FTD | 0.008 (0.007) | -0.005-0.022 | 1.194 | 0.232 |
| | LTL | TC | FTD | 0.008 (0.007) | -0.005-0.022 | 1.227 | 0.220 |
| | LTL | TG | FTD | 0.002 (0.013) | -0.023-0.027 | 0.134 | 0.893 |
| Asian | LTL | HDL | ALS | -0.002 (0.002) | -0.006-0.002 | -1.048 | 0.295 |
| | LTL | LDL | ALS | -0.001 (0.004) | -0.009-0.008 | -0.157 | 0.875 |
| | LTL | TC | ALS | 0.001 (0.002) | -0.004-0.005 | 0.223 | 0.824 |
| | LTL | TG | ALS | 0.003 (0.003) | -0.003-0.009 | 0.916 | 0.360 |

Table 6. Mediation analysis of the role between telomere length, lipids and ALS/FTD. *Pop* population, *EUR* European, *LTL* leukocyte telomere length, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TC* total cholesterol, *TG* triglycerides, *ALS* amyotrophic lateral sclerosis, *FTD* frontotemporal dementia, ab the mediation effect, S_{ab} standard error of the mediation effect, CI, Z and p represent confidence interval, Z statistic and p value, respectively. The marginally significant mediated effect of LTL on the risk of ALS by LDL or TC are shown in bold.

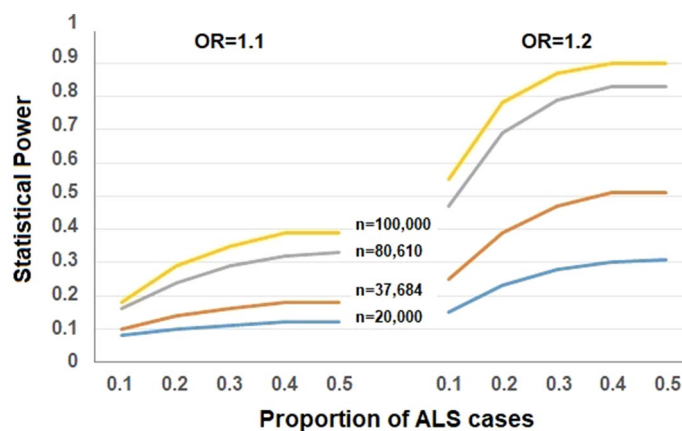


Figure 2. Statistical power calculation for the causal effect of LTL on ALS estimated with the method proposed in⁶⁴. In the calculation, the total phenotypic variance explained by instrumental variables was 1.26% and the proportion of ALS cases varied from 0.1 to 0.5, the significance level was 0.05, the sample size was 20,000, 37,684, 80,610 or 100,000, and the OR = 1.10 or 1.20.

ALS/FTD. These findings were robust to the choice of statistical methods and were carefully validated through various sensitivity analyses.

Our results are not fully consistent with those in previous studies (Table 1). For example, previous studies displayed distinct association in direction and magnitude between LTL and ALS in the European population^{9,14}. Compared to those prior work, our study has the advantage of larger sample size (20,806/59,804 vs. 6,100/7,125 and 1,241/335) and thus holds higher power. In addition, we recognize that the estimated causal effect of shorter LTL on ALS had an opposite direction in the two populations although they were non-significant in neither population. Given the substantial difference of ALS in clinical features and molecular mechanisms between European and Asian populations⁶⁵⁻⁶⁹, this finding may not be unexpected. As little has been known about the causal factors for ALS to date¹, our study therefore contributes considerably to the research area on the relationship between LTL and the risk of ALS, and has potential implication for the therapeutic intervention of ALS.

Besides revealing the null causal relationship between LTL and ALS in the two populations, our study also, at least in part, offers empirical evidence for several questions that were previously unanswered. First, we also validated that the causal association did not hold between LTL and FTD, which might be partly due to the fact that FTD and ALS share extensive similarities in clinical manifestation and genetic foundation³³⁻³⁵. Second, unlike previous studies, the mediation analysis was performed, which provided suggestive evidence supporting the mediation role of LDL or TC in the causal pathway from LTL to ALS in the European population. Therefore, interventions by targeting LDL or TC can be considered as a potential promising manner to counteract the effect of LTL changes on the risk of ALS.

Of course, our study is not without drawbacks. In addition to the general MR limitations similar to other work (e.g. the linear effect assumption), other potential shortcomings should be mentioned^{17,18,70}. First, in our study telomere length measured in blood leukocytes was employed; however, LTL may be not representative of telomere length in tissues that are most relevant to ALS. Second, we note that the Asian-ALS GWAS and the European-FTD GWAS did not adjust the effect of age in their association analyses (Supplementary Text), which may bias our estimates because telomere length would become short with age. However, we cannot examine the causal effect between LTL and ALS/FTD stratified by the age group^{1,6} as it is impossible for us to obtain individual-level GWAS datasets due to privacy concerns. Third, as *C9orf72*, *TARDBP* and *FUS* are known to be the most common mutated genes in ALS^{71–73}. Removing ALS patients with mutations in those genes and performing additional sensitivity analysis can shed new lights on the relationship between LTL and ALS in more general population of sporadic ALS cases (note that excluding those special ALS cases might lead to the reduction of statistical power because of decreased sample size). Again, we cannot conduct such analysis as individual datasets are not accessible. Fourth, as shown above, our MR analysis has only limited statistical power; in addition, our mediation analysis showed that the mediated effect of LTL on the risk of ALS by LDL or TC was only marginally significant. Therefore, studies with larger sample size are required to validate our results in both the European and Asian populations.

Conclusions

Our MR study did not support the causal association between LTL and the risk of ALS in neither the European population nor the Asian population, but provided suggestive evidence supporting the mediation role of LDL or TC on the influence of LTL and ALS in the European population.

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Author contributions

P.Z. and H.Z. conceived the idea for the study. P.Z. and Y.G. obtained the data. P.Z. and Y.G. cleared up the datasets; P.Z., T.W. and Y.G. performed the data analyses. P.Z., T.W., Y.G. and X.Y. interpreted the results of the data analyses. The IFGC Consortium provided the FTD summary data that was used in this study. All the authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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