Received: 2 January 2023 | Accepted: 23 March 2023

DOI: 10.1111/ene.15810

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Lipids and amyotrophic lateral sclerosis: A two-sample Mendelian randomization study

Kailin Xia[1,2,3,4,5] | Veronika Klose[3] | Josef Högel[2] | Tao Huang[6] | Linjing Zhang[1,4,5] | Johannes Dorst[2] | Dongsheng Fan[1,4,5] | Albert C. Ludolph[2,3]

[1]Department of Neurology, Peking University Third Hospital, Beijing, China

[2]Department of Neurology, Ulm University, Ulm, Germany

[3]German Center for Neurodegenerative Diseases (DZNE), Ulm, Germany

[4]Beijing Key Laboratory of Biomarker and Translational Research in Neurodegenerative Diseases, Beijing, China

[5]Key Laboratory for Neuroscience, National Health Commission/Ministry of Education, Peking University, Beijing, China

[6]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China

Correspondence
Dongsheng Fan, Department of Neurology, Peking University Third Hospital, Beijing, China.
Email: dsfan@sina.com

Albert C. Ludolph, Department of Neurology, Ulm University, Ulm, Germany.
Email: albert.ludolph@rku.de

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81873784 and 82071426; the Clinical Cohort Construction Program of Peking University Third Hospital, Grant/Award Number: BYSYDL2019002

Abstract

Objective: Previous observational studies revealed a potential but partially controversial relation between lipid metabolism and the risk of amyotrophic lateral sclerosis (ALS), potentially prone to bias. Therefore, we aimed to study whether lipid metabolism involves genetically determined risk factors for ALS through Mendelian randomization (MR) analysis.

Methods: Using genome-wide association study summary-level data for total cholesterol (TC) ($n = 188,578$), high-density lipoprotein cholesterol (HDL-C) ($n = 403,943$), low-density lipoprotein cholesterol (LDL-C) ($n = 440,546$), apolipoprotein A1 (ApoA1) ($n = 391,193$), apolipoprotein B (ApoB) ($n = 439,214$), and ALS (12,577 cases and 23,475 controls), we implemented a bidirectional MR study to evaluate a genetic relation between lipids and ALS risk. We performed a mediation analysis to assess whether LDL-C is a potential mediator on the pathway from traits of LDL-C-related polyunsaturated fatty acids (PUFAs) to ALS risk.

Results: We identified genetically predicted increased lipid levels to be associated with the risk of ALS, whereby elevated LDL-C had the most potent effect (OR 1.028, 95% CI 1.008–1.049, $p = 0.006$). The effect of increased levels of apolipoproteins on ALS was similar to their corresponding lipoproteins. ALS did not cause any changes in lipid levels. We found no relation between LDL-C-modifying lifestyles and ALS. The mediation analysis revealed that LDL-C could act as an active mediator for linoleic acid, with the mediation effect estimated to be 0.009.

Conclusions: We provided high-level genetic evidence verifying the positive link between preclinically elevated lipid and ALS risk that had been described in previous genetic and observational studies. We also demonstrated the mediating role of LDL-C in the pathway from PUFAs to ALS.

KEYWORDS
amyotrophic lateral sclerosis, genetics, instrumental variables, lipids, Mendelian randomization

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with poor overall survival of 3–5 years due to muscle weakness and respiratory failure [1]. The causes of ALS are complex and largely unknown, among which genetic factors are the best explored. Since the causality of specific gene variants is unknown, few promising disease-modifying therapies based on genetic findings are available. Therefore, identifying genetically defined risk factors for ALS is of interest, which may provide a better understanding of ALS and reveal potential strategies in disease prevention.

Lipids constitute a fundamental energy supplier and play an essential role in many cellular processes, including apoptosis, autophagy, and intracellular signaling [2]. Apolipoproteins are indispensable constituents of lipoproteins and are responsible for maintaining structural stability and lipid transport. The main component of high-density lipoprotein cholesterol (HDL-C) is apolipoprotein A1 (ApoA1) [3], whereas apolipoprotein B (ApoB) is the primary apolipoprotein in low-density lipoprotein cholesterol (LDL-C) [4]. Circulating lipid levels are significantly determined by inheritance with heritability up to 59% [5]. Some, but not all, epidemiological studies indicate that premorbid higher levels of circulating lipids were associated with the risk of ALS [6–8]. These inconsistent results may be due to varying sample sizes, interference of confounders, and reverse causal relations. Randomized control trials (RCTs) are generally needed to overcome the limitations of observational studies. However, RCTs investigating the effects of premorbid lipid metabolism on the risk of ALS have rarely been conducted to date.

Mendelian Randomization (MR) is a statistical approach for investigating relations between an exposure and an outcome based on instrumental genetic variables (IVs) and genome-wide association studies (GWASs) of summary-level data [9]. By simulating RCTs with naturally grouped risk alleles, the MR approach can produce weighted controls to account for reverse causality and confounders [10]. Recently, Chen et al. and Zeng et al. independently found a significant association between pre-existing elevated LDL-C and the risk of ALS via MR approaches, which may be caused by shared genes [11, 12]. However, the powers of both MR studies were limited due to the relatively small sample sizes of the respective GWASs. Furthermore, the relation between apolipoproteins and ALS remains poorly explored. Similarly, the effect of LDL-C-modifying lifestyles on ALS are not clear. For example, exercise is known to have a beneficial effect on individuals with dyslipidemia, but the association between exercise and risk of ALS is controversial [13–15]. Polyunsaturated fatty acids (PUFAs) are strongly involved in the synthesis and decomposition of LDL-C and are also an essential part of lipid metabolism [16]. Both dietary intake levels and serum concentration of PUFAs were suggested to be associated with ALS risk [17–19]. Investigating the relation between PUFAs and ALS by MR and exploring the role of LDL-C may provide further support for the association between LDL-C and ALS. Therefore, to systematically evaluate the effects of genetically determined lipid and apolipoprotein levels on ALS and to assess the potential effect of lipid-modifying lifestyles on the risk of ALS, we conducted a bidirectional, two-sample, MR analysis based on the largest GWASs to date.

METHODS

Study design

We performed this study under a two-sample, bidirectional, MR analysis framework. All data used in this study were GWAS summary results from the European population. First, we calculated whether or not there was a bidirectional association between lipid levels and risk of ALS. Then we evaluated the effect of adjustable LDL-C-modifying lifestyles on ALS. Lastly, we performed a network MR analysis to assess the mediation role of LDL-C in the association between PUFAs and ALS due to the evidence that PUFAs may be relevant for ALS (Figure S1).

Data sources and instrument selection

We obtained genetic data for total cholesterol (TC) from the Global Lipids Genetics Consortium (GLGC) containing 188,578 individuals from 37 cohorts after quality control [20]. We extracted the GWASs summary-level data of LDL-C, HDL-C, ApoA1, and ApoB from the UK Biobank (UKBB), performed by Tom G. Richardson et al. separately [21] by including 393,193 to 441,016 individuals. Through adjustment for age and sex, a linear mixed model was utilized in this study for enhanced power and fewer false positives [22]. Single nucleotide polymorphisms (SNPs) independently associated with the exposures ($p < 5 \times 10^{-8}$, at $r^2 < 0.001$) were selected as candidate IVs. For those SNPs missing corresponding information in the ALS data, we searched proxies with $r^2 > 0.8$ using the publicly available online tools SNiPA [23] and LDlink [24]. If these IVs had no reported proxies, we excluded them. To make the results more robust, we additionally found proxies for those lipids related SNPs declared as palindromic. Overall, we identified 76 IVs for TC, 272 IVs for HDL-C, 139 IVs for LDL-C, 236 IVs for ApoA1, and 152 IVs for ApoB.

We used the summary statistics of ALS GWAS with the largest sample size (cases = 12,577; controls = 23,475) applying a linear mixed model, as this is considered to be more eligible in the ALS GWAS including unignorable imperfectly balanced strata than fixed-effects meta-analysis [25]. Patients were diagnosed with possible, probable, or definite ALS according to the 1994 El Escorial criteria or the revised El Escorial criteria. Seven independently associated SNPs ($p < 5 \times 10^{-8}$ at $r^2 < 0.001$) were selected to be IVs for ALS. To verify the relation between lipids (TC, HDL-C, LDL-C, ApoA1, and ApoB) and ALS, we repeated the analyses with another ALS meta-GWAS based on European ancestry (cases = 27,205; controls = 110,881) [26]. We excluded those lipid-IVs without corresponding information in the ALS data and identified 12 independent SNPs associated with ALS ($p < 5 \times 10^{-8}$ at $r^2 < 0.001$) as ALS-IVs for replicated analysis.

According to previous recommendations [27, 28], different types of LDL-C-modifying lifestyles (nutrition and physical activity) were included. Dietary lifestyles included the intake of non-oily fish or oily fish, cereals, cooked vegetables or salad/raw vegetables (raw vegetables), fresh fruit, coffee, and tea. The exercise lifestyles were defined according to a UKBB questionnaire, based on the types of physical activity done in the past 4 weeks, including strenuous sports (sports that make one sweat or breathe hard), heavy do it yourself (DIY) (weeding, lawn mowing, carpentry, digging), light DIY (pruning, watering the lawn), walking for pleasure (not as a mean of transport), other exercises (swimming, cycling, keep fit, bowling), and none of the above. We retrieved from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk) genetic variants independently associated with corresponding lifestyles [29]. Furthermore, independently genome-wide level significant SNPs ($p < 5 \times 10^{-8}$ at $r^2 < 0.001$) were obtained for linoleic acid (LA), arachidonic acid (AA), α-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) from their corresponding GWASs [30–32]. Among these, ALA, EPA, and DHA were excluded due to their insufficient numbers of IVs.

The phenotypic variance explanation (R^2, $R^2 = 2 \times \text{beta}^2 \times [1-\text{EAF}] \times \text{EAF}/\text{SD}^2$, EAF = effect allele frequency, beta = effect of each SNP on exposures) [33] and *F*-statistics ($F = R^2 \times [N-2]/[1-R^2]$) [34] of each IV were calculated to assess their strength. The summary information of IVs for lipids and PUFAs are in Table S1, and the summary statistics of instruments for LDL-C-modifying lifestyles are in Table S2.

Effect estimation with two-sample MR

We performed the primary analyses with the inverse variance-weighted (IVW) method (multiplicative random effects model). To validate the robustness of our results, the weighted median method, simple median method, MR Egger method, and MR PRESSO method were utilized as sensitivity analyses. The weighted median method yields consistent results when 50% of IVs are valid [35]. The MR PRESSO method identifies outliers with regard to IVs and assesses the effect without outliers [36].

To test for potential pleiotropy of IVs, we employed the following approaches: (1) MR Egger intercepts, to recognize the presence of pleiotropy when the intercept significantly deviates from the origin; (2) Cochran's Q test, assessing the heterogeneity of SNPs enrolled in the IVW estimates; and (3) leave-one-out analysis, to evaluate whether a single SNP drove the association by removing each IV in turn and recalculating the IVW estimates. Bonferroni correction was applied to account for multiple testing. The significance level was set at $p < 0.05/k$, where k is the number of tests using the same dataset (in the first part exploring the association between lipids and ALS, $k = 5$; in the second part exploring the association between lifestyles and ALS, $k = 14$; in the third part exploring the association between PUFAs and LDL-C or ALS, $k = 3$). A *p*-value between $0.05/k$ and 0.05 we considered as a nominal significant level. All analyses were carried out with R software (version 4.2.1), TwoSampleMR package (version 0.5.6) [37], and MR-PRESSO package (version 1.0) [36].

Mediation analysis to explore the mediation effect of LDL-C between PUFAs and risk of ALS

We analyzed the mediation effect of LDL-C on the association between PUFAs and risk of ALS via the conservative network MR method [38]. The multivariable MR method was adopted to analyze the effect of exposure on ALS conditional on other exposures in the same model. The indirect effect of PUFAs on ALS potentially mediated by LDL-C was estimated by multiplying the results from MR IVW analysis and multivariable MR analysis. The IVW approach was employed to determine the total effect of each PUFA on ALS. Thus, to explain the effect of PUFAs on risk of ALS, we divided the indirect effect by the total effect, as previously reported [39]. Since only the trait with more than two IVs can be analyzed by the multivariable MR method, EPA and AA were excluded in this mediation analysis due to their insufficient IVs.

RESULTS

Effect of lipids on risk of ALS

A genetically predicted higher level of LDL-C was associated with a 2.8% increased risk of ALS (IVW, odds ratio (OR) = 1.028, 95% confidence interval (CI) 1.008–1.049, $p = 0.006$) per one standard deviation (1-SD) unit increase of LDL-C concentration, yielded by sensitivity MR estimates (weighted median method, OR = 1.040, 95% CI 1.007–1.073, $p = 0.016$; MR Egger method, OR = 1.033, 95% CI 1.003–1.063, $p = 0.035$). The MR PRESSO method showed no outliers in IVs. Cochran's *Q* test suggested heterogeneity of IVs ($p = 0.011$), indicating the potential presence of pleiotropy (Figure 1, Table S3, Figure S2). However, the MR Egger intercept (intercept = −0.002, $p = 0.360$) showed no evidence of directional pleiotropy, suggesting that pleiotropy is unlikely to affect the main estimates. We found that no specific SNP had a decisive role regarding the association between LDL-C and ALS by applying the leave-one-out analysis. The replicated analysis confirmed the pronounced causal relation between LDL-C and ALS (IVW, OR = 1.087, 95% CI 1.010–1.170, $p = 0.025$) (Table S4).

We found evidence of a genetically predicted increase of ApoB concentration as a suggestive risk factor for ALS (IVW, OR = 1.024, 95% CI 1.003–1.046, $p = 0.027$), which is consistent with the effect of elevated LDL-C on ALS. Sensitivity analyses showed a similar trend with wider CIs and less statistical power. The validity of IVs was confirmed as neither pleiotropy (MR Egger intercept = 0.0003, $p = 0.876$) nor heterogeneity (Cochran's $Q = 164.195$, $p = 0.219$). The validated effect of ApoB on ALS through the replicated ALS GWAS yielded a positive association between genetically predicted

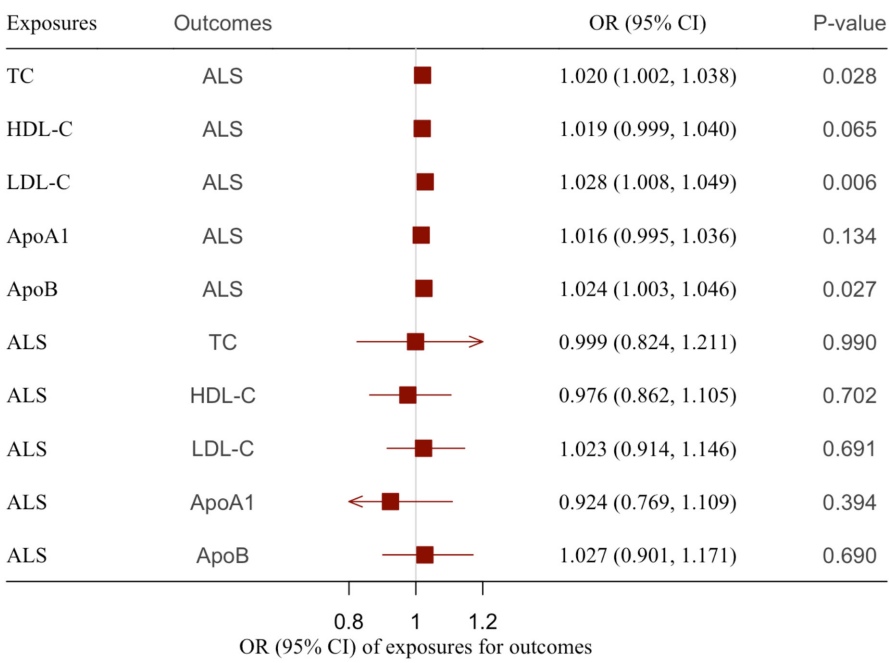

FIGURE 1 Associations of genetically predicted lipid levels and risk of amyotrophic lateral sclerosis using inverse variance-weighted Mendelian randomization analyses. 95% confidence interval beyond the range is indicated by an arrow. ALS, amyotrophic lateral sclerosis; Apo, apolipoprotein; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TC, total cholesterol.

elevated ApoB and the risk of ALS (OR = 1.108, 95% CI 1.024–1.199, $p = 0.011$) (Table S4).

Genetically increased TC likewise showed a nominally significant association with the risk of ALS. The effect size of elevated TC on ALS was between LDL-C and HDL-C with an IVW OR of 1.020 (95% CI 1.002–1.038, $p = 0.028$). Cochran's Q statistic ($p = 0.019$) suggested IVs' substantial pleiotropy. The replicated analysis verified the suggestive effect of increased TC on the risk of ALS (IVW, OR = 1.088, 95% CI 1.018–1.163, $p = 0.013$).

Regarding HDL-C and ApoA1, we found insufficient evidence for a causal relation with ALS risk. The IVW method showed a 1.9% increased risk of ALS per 1 SD unit increase of HDL-C concentration (95% CI 0.999–1.040, $p = 0.065$) and a 1.6% increased risk of ALS per 1 SD unit increase of ApoA1 concentration (95% CI 0.995–1.036, $p = 0.134$). Other MR approaches yielded similar estimates (Table S3). MR Egger intercept observed apparent horizontal pleiotropy interference for HDL-C (intercept = 0.004, $p = 0.042$). Cochran's Q test revealed evident heterogeneity for both HDL-C ($p = 0.0001$) and ApoA1 ($p = 0.015$). We saw similar associations between HDL-C or ApoA1 and the risk of ALS in the replicated ALS GWAS data (Table S4).

Taken together, our results indicate that genetic factors responsible for elevated lipids (LDL-C, TC and ApoB) increase the risk of ALS, whereby LDL-C seems to play a leading role.

Effect of ALS on lipid levels

In order to examine the effect of ALS on elevated lipids, we performed the MR analyses with ALS as exposure and lipids as outcome variables. Our analysis revealed no evidence for a causal effect of ALS on lipid levels (Table S5, Figure 1, Figure S3). The IVW ORs (95% CI, p-value) were estimated to be 0.999 (0.824–1.211, $p = 0.990$) of ALS on TC, 1.023 (0.914–1.146, $p = 0.691$) on LDL-C, 1.027 (0.901–1.171, $p = 0.690$) on ApoB, 0.976 (0.862–1.105, $p = 0.702$) on HDL-C, and 0.924 (0.769–1.109, $p = 0.394$) on ApoA1. Neither obvious heterogeneity (Cochran's $Q = 4.720$, $p = 0.317$) nor directional pleiotropy (MR Egger intercept = −0.005, $p = 0.717$) were seen regarding the IVs employed in the analysis between ALS and TC. However, potentially these results were influenced by heterogeneity on the effects of ALS on LDL-C, HDL-C, ApoB, and ApoA1. After removing the outliers separately for each estimation, we still did not observe any significant results via the MR PRESSO outlier test. Likewise, no causal effect of ALS on elevated lipids was found with the replicated ALS GWAS data (Table S6).

Effect of LDL-C-modifying lifestyles on risk of ALS

We found that lifestyle (dietary interventions and physical activity) did not affect the risk of ALS. Detailed results are shown in Figure 2 and Table S7. These results were supported by sensitivity analyses. After removing outliers in IVs no significant change was observed.

LDL-C as a mediator between PUFAs and ALS

We found significant associations between genetically increased PUFAs and the risk of elevated LDL-C (Table S8). With the IVW approach, the causal effects (beta value) of elevated LA and AA on LDL-C were 0.508 ($p = 0.004$) and 0.019 ($p = 7.37 \times 10^{-19}$), respectively. Evaluating the causal relationship between PUFAs and ALS, genetically predicted elevated LA was associated with an increased risk of ALS (beta = 0.033, $p = 2.42 \times 10^{-6}$) (Table S9). Therefore, based on the principle of classical mediation inference, we deduced that

Risk factors	No. of SNPs	OR (95% CI)	P-value
Diet			
Non-oily fish intake	10	1.161 (0.905, 1.488)	0.240
Oily fish intake	57	0.953 (0.881, 1.030)	0.227
Cereal intake	36	0.988 (0.891, 1.096)	0.826
Cooked vegetable intake	17	0.936 (0.757, 1.157)	0.541
Raw vegetable intake	15	0.999 (0.774, 1.291)	0.995
Fresh fruit intake	49	0.977 (0.874, 1.092)	0.678
Coffee intake	34	0.966 (0.884, 1.057)	0.453
Tea intake	38	0.955 (0.874, 1.045)	0.316
Physical activity			
Types of physical activity in last 4 weeks: Strenuous sports	6	1.358 (0.594, 3.103)	0.468
Types of physical activity in last 4 weeks: Heavy DIY	16	0.860 (0.608, 1.218)	0.396
Types of physical activity in last 4 weeks: Light DIY	11	1.043 (0.763, 1.426)	0.792
Types of physical activity in last 4 weeks: Walking for pleasure	19	1.113 (0.87, 1.423)	0.394
Types of physical activity in last 4 weeks: Other exercises	13	1.157 (0.737, 1.816)	0.528
Types of physical activity in last 4 weeks: None of the above	5	0.964 (0.108, 8.586)	0.974

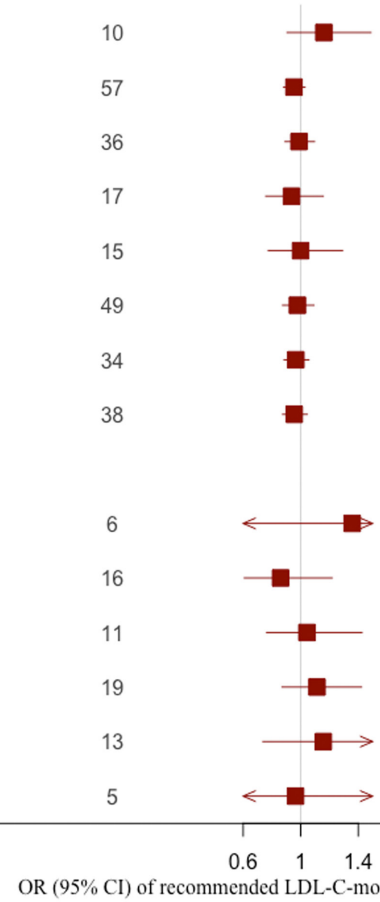

FIGURE 2 Associations of genetically predicted low-density lipoprotein cholesterol-modifying lifestyles and the risk of amyotrophic lateral sclerosis using inverse variance-weighted Mendelian randomization analyses. 95% confidence interval beyond the range is indicated by an arrow. CI, confidence interval; DIY, do it yourself; OR, odds ratio; SNP, single nucleotide polymorphism; TC, total cholesterol.

LDL-C might be a potential mediator on the pathway between LA and the risk of ALS. In multivariable MR analysis, the effect of an increased LDL-C level on the risk of ALS was 0.017. Thus, the indirect effect of elevated LA on ALS risk mediated by LDL-C was 0.009, explaining 27.3% of the total effect.

DISCUSSION

Building on the reported association between dyslipidemia and risk of ALS, we explored whether this association was genetically determined by using a bidirectional, two-sample, MR framework. Our study identified increased LDL-C levels as a genetic risk factor for ALS via various MR approaches. Consistently, elevated levels of ApoB and TC also have risk effects on ALS.

Previous MR studies have reported similar results. Zeng et al. examined the effects of TC, HDL-C, and LDL-C on the risk of ALS and found that only LDL-C and ALS were causally associated (OR = 1.14, 95% CI 1.05–1.24, $p = 1.38E{-}3$) [11]. Chen et al. reported the risk effects of TC and LDL-C on ALS using SNPs linked to both LDL-C and TC [12]. Bandres-Ciga et al. also found an independent risk role of high levels of LDL-C on ALS (OR = 1.116, 95% CI 1.03–1.20, $p = 0.003$) [40]. Compared to these studies, our study enrolled lipid-related GWASs based on significantly higher sample sizes (400,000 compared to 190,000 and 100,000, respectively), providing a higher number of IVs with improved statistical power. Besides, we have obtained high-quality European-based ALS GWAS summary data for discovery analyses and the most recent ALS GWAS statistics with the largest sample sizes for replication analyses.

Notably, for the first time, we explored the effects of apolipoproteins on the risk of ALS and revealed there was no genetically predicted association between lipid-modifying lifestyles and ALS. A Swedish study suggested that changes in lipid and apolipoprotein metabolism were associated with ALS risk and may become prodromal symptoms decades before ALS diagnosis [6]. According to our data, ALS seems not to affect lipid levels, supporting the previous polygenic risk score-based finding that ALS risk alleles were not associated with TC, HDL-C, and LDL-C [12] and providing evidence that lipid levels were indeed genetic risk factors for ALS as reported previously [11].

Based on our data, we see LDL-C as the most potent risk factor for ALS, supporting previous evidence [11, 40]. For that reason, we focused on investigating the effects of LDL-C-modifying lifestyles such as dietary and physical activity. A previous Korean study appeared to demonstrate a protective effect of fruit intake on the risk of ALS and the risk of fish intake on ALS supported by 77 participants [41]. However, in our study population, no significant modifying effects of genetically defined lifestyles on the risk of ALS were found, supporting the null association between physical activity and ALS found in previous MR studies [14, 42]. Due to the genetic variants reflecting a lifelong exposure to a biomarker on the outcome, the effect estimated by the MR approach may be different from the effect of the short-term intervention on ALS in the real world.

Serum LDL-C is a downstream product of the metabolism of PUFAs, and an association between PUFAs and ALS has been suggested previously [43]. Therefore, we further studied the possible mediation effect of LDL-C on the pathway from PUFAs to ALS. LA is an essential omega-6 long-chain PUFA and the initial substrate of the biosynthesis of fatty acids [44]. Our findings were consistent with previous studies showing a protective effect of omega-3 PUFAs on ALS [19] and the reverse correlation between the concentrations of omega-6 PUFAs and omega-3 PUFAs [45]. With the conservative network MR method, we were able to show for the first time that 27.3% of the risk effect of LA on ALS could be explained by elevated LDL-C.

In parallel, we explored lipid profiles in asymptomatic ALS gene carriers and implied that 'worse' lipid metabolism profiles were associated with relatively benign ALS mutations [46]. Although both are preclinical studies, the MR study investigated genetic, long-term factors for the risk of disease, while the prospective cohort study focused more on the relation between lipid levels in a relatively short time before disease onset and ALS prognosis. Therefore, both studies describe different scenarios with the latter coming to similar conclusions as previous studies [6, 47].

The following limitations should be mentioned: The IVs for LDL-C-modifying lifestyles and PUFAs are limited, which may weaken the statistical power and robustness of our results. We adopted various MR approaches to test for potential pleiotropy in IVs to overcome this deficiency, including the MR Egger method, weighted median method, MR PRESSO method, and Cochran's *Q* test. Moreover, in order to provide high statistical power and broadly acceptable conclusions, ALS GWASs employed in most ALS-related MR studies involved both sporadic ALS (sALS) and familial ALS (fALS) patients. Although sALS and fALS share similar clinical and neuropathological changes and risk factors, a recent study proposed that the effects of a lifetime accumulation of risk factors on neurodegenerative disorders largely depends on genotypes [48].

CONCLUSIONS

We provided a high level of genetic evidence verifying the positive association between preclinically elevated lipid levels and the risk of developing ALS that had been described in previous genetic and observational studies. Furthermore, we explored the effects of apolipoproteins and lipid-modifying lifestyles on the risk of ALS via an MR-based approach. We also demonstrated a potential mediating role of LDL-C in the pathway from PUFAs to ALS. Therefore, in our opinion, our findings contribute to the understanding of pathogenesis and yield novel potential therapeutic targets in ALS.

AUTHOR CONTRIBUTIONS

Kailin Xia analyzed the data and wrote the manuscript. Veronika Klose validated the data. Veronika Klose and Johannes Dorst revised the draft and data analysis. Josef Högel, Tao Huang, and Linjing Zhang supervised the data analysis. Albert C. Ludolph and Dongsheng Fan designed the study and supervised the work. Albert C. Ludolph and Dongsheng Fan contributed equally to this work.

ACKNOWLEDGMENTS

We would like to thank Prof. Tom G. Richardson for sharing lipid-related GWASs summary data used in this study and the authors for making the GWASs summary data available. We are also grateful to all the participants who contributed to those studies. The support provided by the China Scholarship Council (CSC) during a visit of Kailin Xia to Ulm, Germany is acknowledged. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This research was funded by the National Natural Science Foundation of China (grant numbers 81873784 and 82071426) and the Clinical Cohort Construction Program of Peking University Third Hospital (grant number BYSYDL2019002).

CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article and its supplementary information files.

ETHICAL APPROVAL

There were no patients directly involved in the overall process of our study. Our study is based on publicly available data only. All human studies included in this analysis were conducted according to the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All authors agreed to the publication of this article.

CODE AVAILABILITY

Codes generated or used during the study are available from the corresponding author by request.

ORCID

Johannes Dorst https://orcid.org/0000-0001-6352-0909
Dongsheng Fan https://orcid.org/0000-0002-6679-0864

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Xia K, Klose V, Högel J, et al. Lipids and amyotrophic lateral sclerosis: A two-sample Mendelian randomization study. *Eur J Neurol*. 2023;30:1899-1906. doi:10.1111/ene.15810