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Association Between Serum Lipids and Survival in Patients With Amyotrophic Lateral Sclerosis

A Meta-analysis and Population-Based Study

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Study Question

What is the association between lipids, polygenic profile scores (PPS) for biomarkers of lipid metabolism, markers of disease severity, and survival in patients with amyotrophic lateral sclerosis (ALS)?

What Is Known and What This Paper Adds

In some studies, high lipid levels have been associated with an increased metabolic stress and a more aggressive disease course in patients with ALS. Other studies, however, suggest that abnormal lipid levels may be beneficial to the patients' prognosis. As such, the interplay between clinical phenotype and lipid metabolism remains unclear, and elucidating its relationship may guide future therapeutic strategies. This study's results show that only HDL-cholesterol had additional prognostic value for predicting survival after diagnosis in patients with ALS. Changes in components of the lipid profile were primarily related to disease severity. Moreover, there were no immediate associations between lipid-based PPS and overall survival, indicating that changes in the lipid profile may be primarily a consequence of disease.

Methods

This observational study included 1,324 consecutive patients diagnosed in the primary ALS referral center in The Netherlands with possible, probable laboratory-supported, probable, or definite ALS between January 1, 2012, and December 31, 2017 (mean age 66 years [SD 11], 44% women). Survival information was updated at quarterly intervals by cross-referencing with the municipal population register, whereas blood samples were collected on the day of diagnosis. Data were enriched by extracting clinical information from our population-based registry and a genome-wide association study (GWAS) to estimate PPS. PPS were calculated by estimating a weight for each single-nucleotide variation for each lipid using a large reference cohort of 50,000 unrelated individuals of inferred European ancestries included in the UK Biobank. The Cox proportional hazard model was used to assess the association between survival, lipids, and their PPS.

Table Hazard Ratios for Biomarkers of Lipid Metabolism

Lipid	Hazard ratio	95% CI
Total cholesterol	1.04	0.99–1.09
LDL-C	1.03	0.98–1.09
HDL-C	1.33	1.14–1.55
Triglyceride	0.91	0.80–1.03

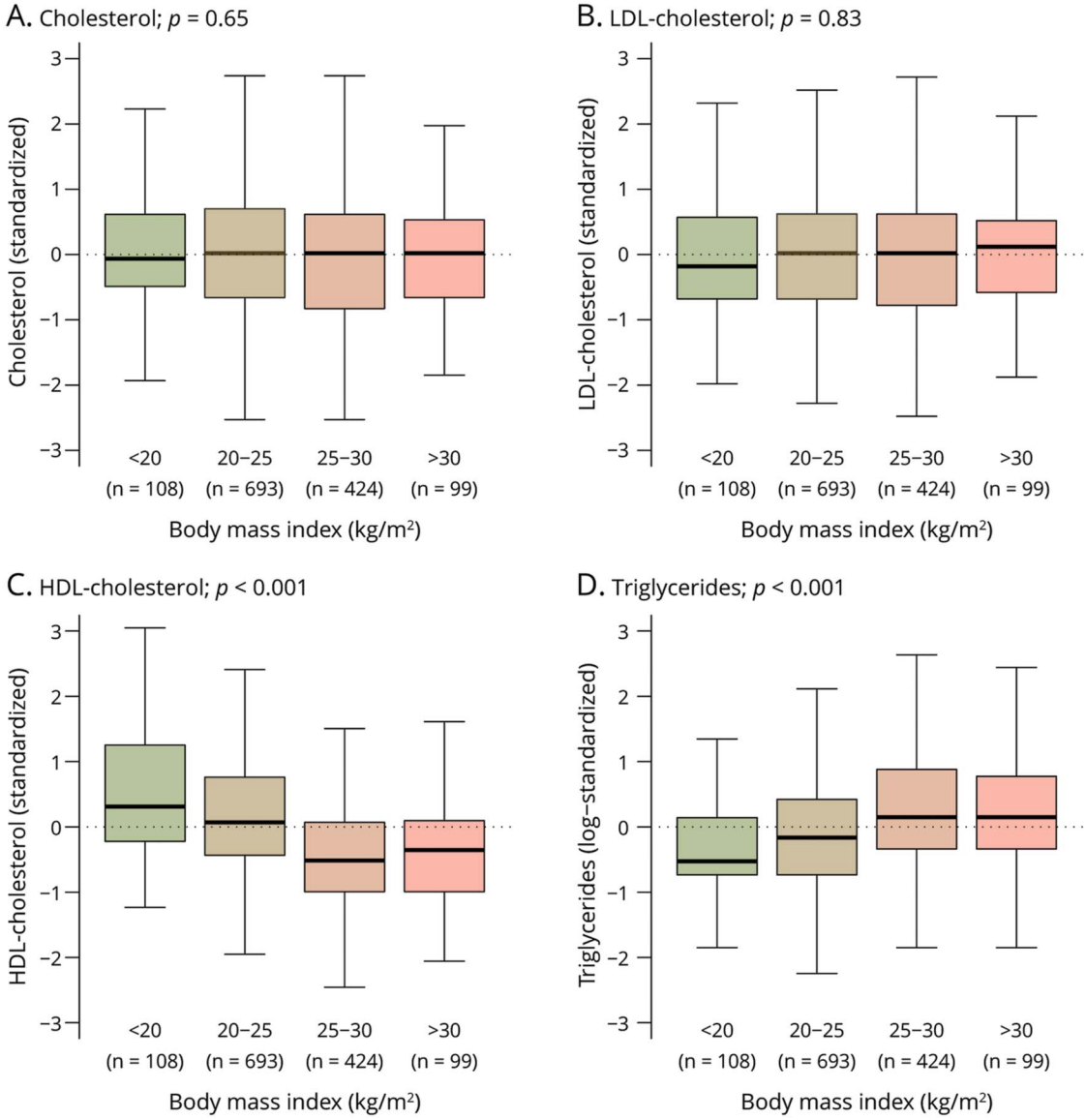
Hazard ratios are determined with a Cox proportional hazards model adjusted for age, site of onset, diagnostic delay, prediagnostic progression rate (ΔFRS), vital capacity, presence of FTD, *C9orf72* repeat expansion, and El Escorial classification.

Results and Study Limitations

We found that with every 1 mmol/L increase of HDL-cholesterol, the hazard for death increased by 33%, where higher levels were associated with a poorer survival (HR of 1.33 [95% CI 1.14 to 1.55, $p < 0.001$]). Other biomarkers of the lipid profile were not associated with survival (Table). Both HDL-C (Pearson's r −0.26, 95% CI −0.32 to −0.20) and TG (Pearson's r 0.18, 95% CI 0.12–0.24) were associated with BMI at diagnosis, as shown in Figure. Lipid-based PPS for biomarkers of lipid metabolism explained 1.2%–13.1% of their variance at diagnosis. None of the PPS were significantly associated with survival (for TC: an HR of 1.02 [95% CI 0.95–1.11], for LDL-C: 1.01 [95% CI 0.93–1.09], for HDL-C: 0.98 [95% CI 0.90–1.06], and for TG: 1.02 [95% CI 0.94–1.10]).

Limitations of this study include the lack of repeated blood samples after diagnosis and information on potential confounding variables such as smoking, diet, or the use of cholesterol-lowering drugs. Longitudinal data would provide definite evidence whether a change in clinical progression

Figure Biomarkers of Lipid Metabolism Stratified by BMI



Boxplots summarizing the cross-sectional concentrations of the lipids linked to BMI at diagnosis. *p* Values are based on the likelihood ratio test. BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

precedes a change in lipid levels. It would be key to carefully collect and adjust for other parameters that influence lipids and preferably assess serum concentration in a fasting state to minimize variability.

Study Funding and Competing Interests

This study was funded by the Netherlands ALS Foundation. The authors report no competing interests. Go to Neurology.org/N for full disclosures.

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