Original research

Higher blood high density lipoprotein and apolipoprotein A1 levels are associated with reduced risk of developing amyotrophic lateral sclerosis

Alexander G Thompson, Kevin Talbot, Martin R Turner

ABSTRACT

Background Premorbid body mass index, physical activity, diabetes and cardiovascular disease have been associated with an altered risk of developing amyotrophic lateral sclerosis (ALS). There is evidence of shared genetic risk between ALS and lipid metabolism. A very large prospective longitudinal population cohort permits the study of a range of metabolic parameters and the risk of subsequent diagnosis of ALS.

Methods The risk of subsequent ALS diagnosis in those enrolled prospectively to the UK Biobank (n=502409) was examined in relation to baseline levels of blood high and low density lipoprotein (HDL, LDL), total cholesterol, total cholesterol:HDL ratio, apolipoproteins A1 and B (apoA1, apoB), triglycerides, glycated haemoglobin A1c (HbA1c) and creatinine, plus self-reported exercise and body mass index.

Results Controlling for age and sex, higher HDL (HR 0.84, 95% CI 0.73 to 0.96, p=0.010) and apoA1 (HR 0.83, 95% CI 0.72 to 0.94, p=0.005) were associated with a reduced risk of ALS. Higher total cholesterol:HDL was associated with an increased risk of ALS (HR 1.17, 95% CI 1.05 to 1.31, p=0.006). In models incorporating multiple metabolic markers, higher LDL or apoB was associated with an increased risk of ALS, in addition to a lower risk with higher HDL or apoA. Coronary artery disease, cerebrovascular disease and increasing age were also associated with an increased risk of ALS.

Conclusions The association of HDL, apoA1 and LDL levels with risk of ALS contributes to an increasing body of evidence that the premorbid metabolic landscape may play a role in pathogenesis. Understanding the molecular basis for these changes will inform presymptomatic biomarker development and therapeutic targeting.

INTRODUCTION

Beyond the few monogenetic variants that account for less than 15% of cases, the precise factors underpinning the development of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS) remain unclear.1 2 ALS has a consistent incidence of ∼2/100 000/year across Europe3 and involves a relatively selective degeneration of motor system function, extending to wider cerebral networks in a clinicopathological spectrum with frontotemporal dementia.4 Numerous epidemiological studies have considered the role of metabolic factors in the development of ALS. Relative cardiovascular health and lower premorbid body mass index (BMI) have been associated with an increased risk of developing ALS.3–8 Physical activity has been inconsistently associated with an increased risk of developing ALS, with a suggestion that strenuous exercise is more specific and may be causally related to susceptibility to ALS.9–11 Diabetes appears to modulate the risk of developing ALS in a relationship that varies with age.12–14 Higher levels of low density lipoprotein cholesterol (LDL) and apolipoprotein B:A1 have been associated with an increased risk of subsequent ALS, with temporal changes in the lipid biomarker profile observed in the decade prior to diagnosis.15 Mendelian randomisation studies have also provided evidence of a causal link for some lipid biomarker levels and ALS.16–17

Much of the epidemiological research in ALS has been based on case–control studies, which carry inherent risks of referral, selection and recall bias, issues which can in part be circumvented by prospective cohort studies.18 This study sought to examine the relationship between previously highlighted metabolic factors, including blood markers of lipid and carbohydrate metabolism, physical exercise and BMI, with the risk of subsequent development of ALS using data from a very large prospective longitudinal population cohort.

METHODS

Participants and consent

The UK Biobank is a prospective cohort study of over 500 000 people aged between 39 and 72 years (www.ukbiobank.ac.uk). All people within the specified age range registered with the National Health Service and living within approximately 25 miles of one of the 22 assessment centres distributed around the UK were invited to take part.19 Participants underwent initial assessment between March 2006 and October 2010 and were followed for a median of 11.9 years (11.1–12.6 years; table 1). Ethical approval was granted by the Health Research Authority (North West – Haydock Research Ethics Committee reference 16/NW/0274). All participants provided informed electronic consent.

Participants provided demographic and health information alongside donated blood for biochemical analysis performed by the UK Biobank according to standard protocols (https://biobank.ctsu.ox.ac.uk/), which included measurement of blood total cholesterol, high density lipoprotein cholesterol (HDL), LDL, triglycerides, apolipoprotein A1 (apoA1), apolipoprotein B (apoB), HbA1c...
and creatinine. Excess metabolic equivalent task (MET) hours were calculated based on self-reported walking, moderate and vigorous activity per week. Participants reported how many days per week they undertook each category of exercise for more than 10 min. The reported duration of activity on a typical day was then multiplied by the number of reported days per week. Excess MET was calculated by subtracting one unit per day was then multiplied by the number of reported days per week they undertook each category of exercise for more than 10 min. The reported duration of activity on a typical day was then multiplied by the number of reported days per week. Excess MET was calculated by subtracting one unit per

Comparative data were selected as covariates in order to control for confounding from these variables, since they have at times been associated with both metabolic biomarkers and risk of ALS. Models were constructed controlling for age at initial visit and sex. Combined models were also constructed, incorporating demographic variables, cardiovascular and cerebrovascular disease, smoking and statin use along with excess MET and blood biomarkers for all incident ALS cases and, separately, those diagnosed with ALS more than 5 years from enrolment. Separate models were constructed incorporating apoA1 and apoB, and HDL and LDL due to the high degree of correlation of apoA1 with HDL (Spearman’s \( \rho = 0.92 \), \( p < 0.001 \)) and apoB with LDL (\( p = 0.96 \), \( p < 0.001 \)); total cholesterol was excluded due to the high degree of correlation with HDL (Spearman’s \( \rho = 0.96 \), \( p < 0.001 \)).

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### Table 1: Cohort baseline demographic and metabolic data

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>ALS</th>
<th>ALS &gt;5 years from enrolment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>502 409</td>
<td>343</td>
<td>192</td>
<td>–</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>58 (50–63)</td>
<td>62 (57–66)</td>
<td>62 (56.75–66)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Age at ALS diagnosis, median (IQR) (years)</td>
<td>–</td>
<td>67.36 (61.71–70.95)</td>
<td>69.17 (63.37–72.35)</td>
<td>–</td>
</tr>
<tr>
<td>Latency from enrolment to diagnosis, median (IQR) (days)</td>
<td>–</td>
<td>1986 (1203.5–2444)</td>
<td>2390 (2153–2654)</td>
<td>–</td>
</tr>
<tr>
<td>Latency from diagnosis to death, median(95% CI) (days)</td>
<td>–</td>
<td>445 (401 to 542)</td>
<td>508 (401 to 691)</td>
<td>–</td>
</tr>
<tr>
<td>% ALS diagnoses from death certificate (n)</td>
<td>–</td>
<td>10 (35)</td>
<td>14 (26)</td>
<td>–</td>
</tr>
<tr>
<td>Female participants (%)</td>
<td>273 348 (54.4)</td>
<td>149 (43.4)</td>
<td>84 (43.8)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Follow-up, median (IQR) (days)</td>
<td>4234 (4072–4593)</td>
<td>2491 (1705–3452)</td>
<td>2949 (2499–3882)</td>
<td>–</td>
</tr>
<tr>
<td>Total cholesterol, median (IQR) (mmol/L)</td>
<td>5.65 (4.91–6.42)</td>
<td>5.64 (4.85–6.44)</td>
<td>5.81 (4.96–6.53)</td>
<td>0.760†</td>
</tr>
<tr>
<td>LDL cholesterol, median (IQR) (mmol/L)</td>
<td>3.52 (2.94–4.12)</td>
<td>3.54 (2.94–4.08)</td>
<td>3.65 (3.42–4.12)</td>
<td>0.860†</td>
</tr>
<tr>
<td>HDL cholesterol, median (IQR) (mmol/L)</td>
<td>1.40 (1.17–1.67)</td>
<td>1.30 (1.1–1.58)</td>
<td>1.29 (1.12–1.55)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Total cholesterol:HDL ratio, median (IQR)</td>
<td>3.97 (3.3–4.81)</td>
<td>4.09 (3.43–5.05)</td>
<td>4.19 (3.53–5.05)</td>
<td>0.007†</td>
</tr>
<tr>
<td>Apolipoprotein A, median (IQR) (g/L)</td>
<td>1.51 (1.35–1.7)</td>
<td>1.46 (1.29–1.65)</td>
<td>1.46 (1.3–1.63)</td>
<td>0.002†</td>
</tr>
<tr>
<td>Apolipoprotein B, median (IQR) (g/L)</td>
<td>1.02 (0.86–1.18)</td>
<td>1.03 (0.84–1.18)</td>
<td>1.05 (0.89–1.2)</td>
<td>0.902†</td>
</tr>
<tr>
<td>Glycated haemoglobin HbA1c, median (IQR) (mmol/mol)</td>
<td>35.2 (32.8–37.9)</td>
<td>35.7 (33.6–38.5)</td>
<td>35.5 (33.4–37.77)</td>
<td>0.022†</td>
</tr>
<tr>
<td>Triglycerides, median (IQR) (mmol/L)</td>
<td>1.48 (1.05–2.15)</td>
<td>1.67 (1.18–2.27)</td>
<td>1.68 (1.22–2.23)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Serum creatinine, median (IQR) (µmol/L)</td>
<td>70.4 (61.4–80.9)</td>
<td>71.4 (62.6–81.88)</td>
<td>72.4 (63.8–81.58)</td>
<td>0.106</td>
</tr>
<tr>
<td>Excess MET, median (IQR) (hours/week)</td>
<td>23.14 (10.64–46.15)</td>
<td>20.38 (8.45–45.53)</td>
<td>21.46 (10.11–46.25)</td>
<td>0.099†</td>
</tr>
<tr>
<td>BMI, median (IQR) (kg/m²)</td>
<td>26.74 (24.14–29.91)</td>
<td>27.19 (24.64–30.01)</td>
<td>27.01 (24.78–29.66)</td>
<td>0.111†</td>
</tr>
</tbody>
</table>

Median latency from ALS to diagnosis to death calculated from the Kaplan–Meier survival curve, excluding those in whom the diagnosis is based only on death certificate.

P values indicated for all ALS vs all non-ALS.

*Fisher’s exact test.

†Mann–Whitney U test.

ALS, amyotrophic lateral sclerosis; BMI, body mass index; HbA1c, glycated haemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metabolic equivalent task.

## Statistical analysis

### Cohort study

Statistical analysis was performed in R. Only incident ALS cases were included in the analysis—that is, participants diagnosed with ALS following sampling and not reporting a diagnosis of ALS at their baseline study visit, or in whom a diagnosis was identified by medical linkage dated prior to sampling. The primary analysis included data for all incident ALS cases who fulfilled these criteria. Detectable markers of neuronal loss—for example, a rise in neurofilaments and chitinase proteins—have been shown to occur within at least 1 year of the onset of symptoms in carriers of pathogenic genetic variants. With the aim of targeting metabolic changes occurring in the years before this phase of neurodegeneration, secondary analysis was therefore performed using only data from participants linked to an ALS diagnosis more than 5 years after their baseline study visit.

Time-to-event analysis for diagnosis of ALS was performed using Cox proportional hazards modelling from study enrolment. Data are presented as hazard ratios (HR) and 95% CI for a 1 SD rise in levels (variables were mean centred and scaled by SD). LDL, HDL, total cholesterol, total cholesterol:HDL ratio, triglycerides and apolipoproteins A1 and B were selected as well-established lipid cardiovascular risk biomarkers, some of which have been found to be associated with ALS risk previously. We included smoking, cardiovascular disease, cerebrovascular disease and statin use in order to control for confounding from these variables, since they have at times been associated with both metabolic biomarkers and risk of ALS. Models were constructed controlling for age at initial visit and sex. Combined models were also constructed, incorporating demographic variables, cardiovascular and cerebrovascular disease, smoking and statin use along with excess MET and blood biomarkers for all incident ALS cases and, separately, those diagnosed with ALS more than 5 years from enrolment. Separate models were constructed incorporating apoA1 and apoB, and HDL and LDL due to the high degree of correlation of apoA1 with HDL (Spearman’s \( \rho = 0.92 \), \( p < 0.001 \)) and apoB with LDL (\( p = 0.96 \), \( p < 0.001 \)); total cholesterol was excluded due to the high degree of correlation with HDL (Spearman’s \( \rho = 0.96 \), \( p < 0.001 \)).

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Models excluding participants diagnosed within 5 years of their initial visit were largely consistent with models incorporating all participants in magnitude and direction of associations, although lipid associations were not significant following correction for multiple comparisons. Higher HDL (HR 0.81, 95% CI 0.73 to 0.90, p=0.010, adjusted p=0.093) and apoA1 (HR 1.11, 95% CI 1.06 to 1.16, p=0.031, adjusted p=0.123) were associated with a reduced risk of ALS (table 2). Higher total cholesterol:HDL (HR 1.19, 95% CI 1.03 to 1.39, p=0.022, adjusted p=0.123) was associated with an increased risk of ALS.

Combined models were constructed incorporating HDL and LDL and, separately, apoA1 and apoB (given the high degree of correlation of HDL and LDL with apoA1 and apoB, respectively), with HbA1c, triglycerides, excess MET, BMI, serum creatinine, sex and age. Given the association of vascular diseases with both ALS risk and blood lipid levels, coronary artery and cerebrovascular disease were added as covariates, along with smoking which has been associated with HDL cholesterol levels and risk of ALS, and statin use, which are used in the treatment of hypercholesterolaemia and have been associated with both higher and lower risk of ALS. Total cholesterol was excluded due to a high degree of correlation with LDL. Higher HDL (HR 0.78, 95% CI 0.64 to 0.96, p=0.017, adjusted p=0.054) and apoA1 (HR 0.82, 95% CI 0.68 to 0.97, p=0.024, adjusted p=0.088) levels were associated with a lower risk of ALS. Excluding those diagnosed within 5 years of their first visit, higher HDL (HR 0.66, 95% CI 0.49 to 0.88, p=0.005, adjusted p=0.020) or apoA1 (HR 0.77, 95% CI 0.61 to 0.98, p=0.034, adjusted p=0.110) levels were associated with a reduced risk of ALS. Higher LDL (HR 1.35, 95% CI 1.09 to 1.68, p=0.007, adjusted p=0.021) or apoB (HR 1.23, 95% CI 1.00 to 1.25, p=0.050, adjusted p=0.129) were associated with an increased risk of ALS. Smoking was not significant in combined models whereas age, cerebrovascular disease and coronary artery disease were associated with higher ALS risk in all models (table 3).

Nested case–control analysis was used to examine the temporal relationship between ALS diagnosis and lipid biomarker levels for HDL and LDL cholesterol, apoA1 and apoB, matching each participant going on to develop ALS with 20 other participants by age at sampling, month of sampling and sex. Linear models identified significant differences in LDL and apoB slope in participants going on to develop ALS compared with healthy controls, with a downward slope observed in patients with ALS (time–ALS relationship for multiple comparisons. Higher HDL (HR 0.81, 95% CI 0.73 to 0.90, p=0.010, adjusted p=0.093) and apoA1 (HR 1.11, 95% CI 1.06 to 1.16, p=0.031, adjusted p=0.123) were associated with a reduced risk of ALS (table 2). Higher total cholesterol:HDL (HR 1.19, 95% CI 1.03 to 1.39, p=0.022, adjusted p=0.123) was associated with an increased risk of ALS.

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Table 3 Combined Cox proportional hazards modelling, controlling for age at first study visit and sex

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Excluding ALS within 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td>FDR p value</td>
<td>HR (95% CI) P value</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.97 (0.84 to 1.12)</td>
<td>0.192 0.356 – – –</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.66 (0.49 to 0.88)</td>
<td>0.057 – – –</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>1.07 (0.84 to 1.36)</td>
<td>0.500 0.286 – – –</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>0.97 (0.83 to 1.22)</td>
<td>0.015 0.033 – – –</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.00 (0.99 to 1.01)</td>
<td>0.965 0.411 – – –</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3.25 (1.96 to 5.38)</td>
<td>0.001 0.001 &lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td>Status use</td>
<td>0.68 (0.43 to 1.08)</td>
<td>0.104 0.267 – – –</td>
</tr>
</tbody>
</table>

Four separate models were constructed for HDL and LDL cholesterol and apoA1 and ApoA2, including and excluding participants going on to develop ALS within 5 years of sampling. Hazard ratios indicate for a 1 SD increase in variable level.

Figure 1 Temporal differences in LDL and HDL cholesterol, ApoB and apoA1 and diagnosis of ALS. Participants going on to develop ALS (red) were each matched by age of sampling in years, date of sampling ±60 days and sex to 20 participants not going on to develop ALS (blue). Lines indicate linear model fit for ALS (red) and non-ALS (blue) participants. P values indicate interaction between ALS status and time, indicating difference in temporal trajectory of biomarkers over time. ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ALS, amyotrophic lateral sclerosis; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

DISCUSSION

This study used data from a large, prospectively acquired, longitudinal cohort study to examine the relationship between levels of available lipid and broader metabolic parameters and risk of a subsequent diagnosis of ALS. The key finding is that higher levels of HDL and apoA1, with correspondingly lower total cholesterol:HDL at study enrolment, were associated with a reduced risk of ALS diagnosis during follow-up, independent of age and sex. Excluding participants with a short latency from initial sampling to diagnosis, with the aim of restricting analysis prior to the onset of rapid neurodegeneration in ALS, had no material effect on the results. In combined models, HDL and apoA1 remained independent of other factors, and lower LDL and apoB levels were also associated with a decreased risk of ALS. The persistence of these findings in models controlling for statin use, smoking and vascular disease indicates that the association of lipid levels and ALS is not attributable to a confounding association between lipids, ALS and these factors. Nested case-control analysis also identified temporal variation in LDL and apoB levels, decreasing towards diagnosis in those going on to develop ALS, but stable levels of HDL and apoA1.

The results of this study are usefully compared with a population-based analysis of longitudinal primary care data. The Apolipoprotein-related MOrtality Risk study (AMORIS) identified an association between higher LDL:HDL and increased risk of developing ALS. The increased risk was driven primarily by higher levels of LDL and apoB, whereas in this study the associations mainly reflect relatively lower levels of HDL (or apoA1) measured at enrolment in those subsequently developing ALS, although higher LDL (or apoB) was strongly associated with an
increased risk of ALS in a subset of multivariate models. The temporal changes observed in the nested case-control analysis presented here, suggesting decreasing levels approaching diagnosis, mirror those observed in AMORIS participants, which suggests that the differences between studies with respect to LDL and apoB might well relate to the timing of sampling in relation to ALS diagnosis.

A nested case-control analysis combining five cohort studies reported higher levels of HDL as a risk factor for ALS, in contrast to the findings described here. This could also be explained in relation to temporal changes in lipid levels described in the AMORIS study, in which HDL levels are lower in ALS patients 5–15 years prior to diagnosis, although the data presented here indicate stable HDL levels over the years before ALS diagnosis. There might also be differences arising from the timing of ascertainment of ALS diagnosis (the majority being identified from death certification only compared with just 10% of cases in this study), so that a higher proportion of participants were in the early stages of ALS.

The role of lipid metabolism in ALS is complex. In addition to epidemiological studies implicating cholesterol and apolipoprotein biology in the years prior to ALS diagnosis, a body of evidence suggests contrasting effects during the symptomatic phase of the disease. Unlike the association of higher LDL and apoB and lower HDL and apoA1 with a higher risk of ALS in the presymptomatic literature, higher levels of total and LDL cholesterol as well as triglycerides (and in some cases lower HDL) are associated with less rapid disability progression and better respiratory function and survival. Whether this is a protective effect of lipids or a proxy for other factors portending poor prognosis such as lower BMI is not resolved. However, this highlights the need to distinguish the symptomatic and presymptomatic phases of ALS as much as possible.

Observational studies cannot disentangle the causal direction of the association between HDL and the subsequent development of ALS. Evidence from multiple sources supports shared genetic risk between ALS and lipid profiles. This has not been convincingly established for HDL though, with one Mendelian randomisation study not finding a causal relationship and ALS risk, as implicated in recent Mendelian randomisation approaches exploring causality (although there is not complete agreement between studies). This study has not sought to elucidate this question further, but indicates that the associations between lipid biomarkers and ALS identified here are independent of lifetime tobacco exposure as measured in pack-years.

Although these data do not lend support to the previously identified association between exercise and risk of ALS, it should be noted that our use of excess MET as a continuous variable encompassing any activity from walking to vigorous exercise does not address a specific role for frequent vigorous exercise and ALS risk, as implicated in recent Mendelian randomisation analysis of causality.

It is likely that, due to case ascertainment by inpatient record linkage in the UK Biobank, the latency from symptom onset to date of diagnosis will be longer in these data than using outpatient encounters. This is reflected in the older age of onset in ALS cases in the UK Biobank cohort and relatively short latency to death compared with other studies. Our restricted analysis, including only those ALS cases identified more than 5 years after sampling, mitigates that issue.

Limitations relating to the recruitment of participants in the UK Biobank are also recognised and might contribute to the observed differences in relation to previously published data. Participants in the UK Biobank differ from the general population of the UK in indices of lifestyle, ethnicity, health and wealth; it is recognised that this can lead to biased estimates, which cannot be excluded in this or other epidemiological analyses of lipids in ALS. This may have contributed to the apparent older age of ALS diagnosis in the UK Biobank when compared with other studies. The selection of participants by age range could exclude older or younger people developing ALS; this proportion would be expected to be small, however, since most people developing ALS do so between the ages of 40 and 70, and since the follow-up in the UK Biobank (median >11 years, table 1) would capture much of the remainder who develop ALS by 80 years. The incidence of ALS in the UK Biobank is similar to the incidence reported in other countries in Europe and North America, allowing for the age range of participants.

Incorrect identification of ALS cases is still possible within the UK Biobank, due to the reliance on record linkage and the use of ICD10 and ICD9 codes that encompass non-ALS motor
neuron diseases such as primary lateral sclerosis. Validation studies suggest that the positive predictive value of such methodologies is 70–91%, and any diluting effect of rare motor neuron disorders is expected to be small. Additional limitations are the lack of data on common genetic causes of ALS, which might influence lipid biomarkers, and the potential for masked confounding effects.

This study adds to a growing literature documenting differences in the premonbid metabolic profile of those who eventually develop ALS. In addition to providing novel insights into pathogenesis, this emphasises the need to consider a broader set of potential presymptomatic ALS biomarkers. Such markers might help to target population screening for ALS and also build confidence in future trials of preventative therapy.

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