Opposite associations between alanine aminotransferase and γ-glutamyl transferase levels and all-cause mortality in type 2 diabetes: analysis of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

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Abstract

Aims

Reported associations between liver enzymes and mortality may not hold true in type 2 diabetes, owing to a high prevalence of non-alcoholic fatty liver disease, which has been linked to cardiovascular disease and mortality in its own right. Our study aimed to determine whether alanine aminotransferase (ALT) or γ-glutamyl transferase (GGT) levels predict mortality in type 2 diabetes, and to examine possible mechanisms.

Methods

Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study were analysed to examine the relationship between liver enzymes and all-cause and cause-specific mortality over 5 years.

Results

Over 5 years, 679 (6.9%) individuals died. After adjustment, for every standard deviation increase in ALT (13.2U/L), the HR for death on study was 0.85 (95% CI 0.78-0.93), $p<0.001$. Conversely, GGT >70 U/L, compared with GGT ≤70 U/L, had HR 1.82 (1.48−2.24), $p<0.001$. For cause-specific mortality, lower ALT was associated with a higher risk of cardiovascular death only, whereas GGT >70 U/L was associated with higher risks of death due to cardiovascular disease, cancer and non-cancer/non-cardiovascular causes. The relationship for ALT persisted after adjustment for indirect measures of frailty but was attenuated by elevated hsCRP.

Conclusions

As in the general population, ALT has a negative, and GGT a positive, correlation with mortality in type 2 diabetes when ALT is less than two times the upper limit of normal. The relationship

for ALT appears specific for death due to cardiovascular disease. Links of low ALT with frailty, as a potential mechanism for relationships seen, were neither supported nor conclusively refuted by our analysis and other factors are also likely to be important in those with type 2 diabetes.

Abbreviations

ALT   alanine aminotransferase

BMI   body mass index

CI   confidence interval

CV   coefficient of variation

eGFR   estimated glomerular filtration rate

ELISA   enzyme-linked immunosorbent assay

GGT   γ-glutamyl transferase

HDL-c   high-density lipoprotein cholesterol

HOMA IR   homeostatic model of insulin resistance

HR   hazard ratio

hsCRP   highly sensitive C reactive protein

IQR   interquartile range

LDL-c   low-density lipoprotein cholesterol

NAFLD   non-alcoholic fatty liver disease

SD   standard deviation

sICAM   soluble intercellular cell adhesion molecule

sVCAM   soluble vascular cell adhesion molecule

WHR   waist-hip ratio

1. Introduction

The enzymes alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) are found within many tissues. Blood elevations of ALT and GGT are widely used in clinical practice as markers of hepatic dysfunction [1]. GGT, found in hepatocytes and biliary epithelial cells, is a sensitive marker of hepatobiliary disease, while blood ALT levels increase when the hepatocyte membrane is damaged, as an indicator of hepatocellular injury. Both ALT and GGT are recognised as surrogate markers of the metabolic syndrome, fatty liver and cardiovascular disease risk, while GGT is also a marker of oxidative stress and systemic inflammation [1-4]. Several recent publications report an inverse association between ALT and mortality [5, 6]. While this would seem counterintuitive if lower ALT is to be considered a marker of liver health, this observation has been repeatedly noted in different populations, including in the elderly, the middle-aged and those with HIV infection [5-9]. Intriguingly, the relationship is opposite to that for GGT, which has a positive association with mortality [4, 9-11].

While the mechanisms behind the positive association between GGT and mortality can easily be discerned through the known correlations of GGT with liver disease, oxidative stress, inflammation and comorbidities [1, 12], those explaining the inverse relationship between ALT and mortality are elusive. Possible links between low ALT and sarcopenia, biological frailty and chronological age have been postulated [6, 7].

This study aimed to determine whether the relationships between blood levels of ALT and GGT and mortality observed in the general population were similar in a community dwelling cohort with type 2 diabetes. We surmised that such relationships may not exist in type 2 diabetes as it is a condition associated with higher ALT and GGT, largely owing to the presence of non-alcoholic fatty liver disease (NAFLD), which is also associated with increased cardiovascular disease and mortality [13-15]. A secondary aim was to explore potential mechanisms behind any relationships found between ALT and GGT and mortality.

2. Patients and methods

The study was a subsidiary analysis of the FIELD study—a double-blind, placebo-controlled trial done in 63 centres in Australia, New Zealand, and Finland [16]. In brief, 9795 participants aged 50–75 years with type 2 diabetes according to WHO criteria [17] were randomly allocated between 1998 and 2000 to once-daily micronized fenofibrate or placebo. Participants had an initial total-cholesterol concentration 3.0–6.5 mmol/L, plus either total-cholesterol/HDL-c ratio $\geq$ 4.0 or plasma triglyceride concentration 1.0–5.0 mmol/L, and were not on lipid-modifying therapy at study entry. Exclusion criteria included: blood creatinine >130 μmol/L, history of chronic liver disease, as determined by patient or doctor report, a cardiovascular event within 3 months of recruitment, ALT > two times the upper limit of normal (> 100 U/L) and a recent history of alcohol abuse, as defined by the medical history or at the discretion of the investigators. All deaths were adjudicated by an outcomes assessment committee. Total mortality and cause-specific mortality were predefined secondary outcomes [16].

2.1 Baseline characteristics

A full clinical assessment was performed at baseline. A history of cardiovascular disease was defined as any self-reported history of myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, claudication, peripheral vascular disease, or peripheral revascularisation. Dyslipidaemia was defined as low HDL-c (<1.03 mmol/L in men, <1.29 mmol/L in women) and high triglyceride concentration (>1.70 mmol/L). Nephropathy was defined as the presence of albuminuria [16]. Alcohol consumption was classified as none, infrequent (special occasion to once/week) or regular ($\geq$ 2 times/week); data were lacking for grams taken per week. Grade of current exercise capacity using routine daily activities (very light, light, moderate, heavy and very heavy; see eTable 1 for more detail), in addition to the highest level of education obtained (primary school, some high school, completed

high school, some university, completed university) and employment status (full-time, part-time and not working) were recorded on all participants at baseline [16].

A subset of individuals (*n*=1956) were randomly allocated to a quality-of-life and economic evaluation substudy. As part of this, they were asked to complete the SF-36 questionnaire at baseline as a comprehensive and extensively validated, generic, quality-of-life assessment [18].

2.2 Laboratory parameters

During the study, all samples were analysed at one of two laboratories: SA Pathology, Adelaide, Australia, or the laboratory of the National Public Health Institute, Helsinki, Finland. Both laboratories participated in national quality assurance schemes. ALT and GGT were measured 16 weeks and ALT again 6 weeks before randomisation. The average of the two ALT measurements was used for analysis. All specimens were stored immediately at -20°C and shipped within 7 days for processing. ALT and GGT assays used standard colorimetric techniques consistent with the guidelines of the International Foundation of Clinical Chemistry (IFCC) [19, 20]. Vascular cell adhesion molecules were analysed in the laboratory of AJJ and ASJ in the University of Melbourne, Department of Medicine using ELISAs (R&D Systems, Minneapolis, MN, USA). The intra-assay and inter-assay CVs for sVCAM, sICAM and sE-selectin were 2.07% and 9.37%, 2.71% and 7.77% and 4.15% and 10.98%, respectively.

2.3 Statistical analysis

Analyses were by intention-to-treat using SPSS v22 and ACCORD v2.0.5, confirmed on SAS v9.3. Owing to the non-normal distributions of ALT and GGT, their relationship with baseline characteristics was determined using Spearman's correlation for continuous variables and the Wilcoxon rank–sum or Kruskal–Wallis test for categorical variables. To assess the relationship between baseline ALT and GGT and total mortality, Cox proportional-hazards regression was used to compute HRs and 95% CIs. Examined by deciles, the data were consistent with a linear

relationship between ALT and cardiovascular events (Fig. 1A and 1B), and so continuous ALT (per one SD) was used in predictive models. With similar techniques, GGT had a non-linear relationship with time to all-cause mortality (Fig. 1C and 1D), and so analysis was conducted using the top decile (GGT > 70 U/L) versus the rest of the cohort. All models were adjusted for assignment to fenofibrate, despite fenofibrate use having no association with mortality [16], and the following pre-specified baseline variables: age, sex, diabetes duration, hypertension, dyslipidaemia, nephropathy, cardiovascular disease, current-smoker status, WHR, HbA1$_c$, and LDL-c. Models were tested for appropriateness using co-linearity diagnostics and Harrell Lee statistical testing. With identical variables, cause-specific mortality, defined as death due to total cardiovascular events, cancer and non-cancer/non-cardiovascular causes, was examined using competing risks analysis (Fine and Gray method [21]).

For all-cause mortality, in post hoc analysis, the multivariable model was further individually adjusted for laboratory used, alcohol consumption pattern, level of education, hsCRP, continuous HDL-c and triglycerides (to replace dyslipidaemia), body-mass index (BMI, to replace WHR), systolic and diastolic blood pressure (to replace the binary variable of hypertension), past and present smoking (to replace current smoking), or C-peptide, fasting glucose (to replace HbA1c), and diabetes treatment category (diet, oral antidiabetic therapy or insulin±oral therapy), and also ALT or GGT, as appropriate. Penalised Cox modelling, with an estimate of treatment effect, was then used to adjust for statin therapy use on study [22]. To explore whether ALT might be acting as a marker of systemic frailty, the model was individually adjusted for grade of current exercise capacity, employment status, eGFR, resting heart rate, and also weight loss over the first 12 months after exclusion of events in the first 12 months of study in a landmark analysis [23]. Analysis was also done after excluding events at one and two years after randomisation.

In exploratory analysis, interactions among all predefined baseline variables, in addition to variables used for further adjustment, were tested to identify any differential effect of ALT or GGT between various categories, with $p<0.05$ considered significant. If positive interactions were found, appropriate sub-analysis was performed, after inspection of data graphically by scatter-dot, and also by decile analysis in the case of a continuous variable.

To further explore the associations between ALT and GGT and surrogate measures of frailty, scores out of 100 for each of the eight domains (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional wellbeing, social functioning, pain and general health) from the SF-36 were calculated using standard techniques in those with available data [24-26]. In this way, a higher score was consistent with higher physical and/or emotional function. Given an apparent non-linear relationship between domain scores and ALT and GGT, and also a score limit of 100, the cohort was divided into four groups by each of the eight domain scores using cut-off values of 0–25, 26–50, 51–75 and 76–100. The median (interquartile range (IQR)) ALT and GGT was obtained for each of the four groups in each domain of the SF-36 and statistical differences were determined using Kruskal-Wallis test. The primary model was not adjusted for SF-36 scores given that these data were only available in 16% of the total cohort.

2.4 Ethics

All participants provided written informed consent. The study protocol was approved by local and national ethics committees and was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The original trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) 64783481.

3. Results

3.1 Basic demographics

The average age of the cohort was 62±7 years. Median (IQR) diabetes duration was 5 (2–10) years, HbA1$_c$ was 52 (43-62) mmol/mol (6.9 (6.1–7.8) %), and BMI was 29.8 (26.8–33.5) kg/m^2. At baseline, 2608 (27%) were treated with diet, 5841 (59%) oral anti-diabetic therapy only, and 1346 (14%) insulin ± oral therapy.

There were 679 (6.9%) deaths during the study: 316 (3.2%) due to cancer, 267 (2.7%) cardiovascular disease and 96 (1.0%) related to non-cancer/non-cardiovascular causes (see eTable 2 for more detail). Table 1 details the basic characteristics of those who died compared with those who did not. As previously described, 9 (4 in the fenofibrate group) withdrew consent and 22 (12 in the fenofibrate group) were lost to follow up [16].

3.2 ALT, GGT and their clinical and biochemical associations

The median baseline ALT was 24 (IQR 18–33) U/L and GGT 29 (IQR 21–44) U/L. The univariate relationships between ALT and GGT and baseline variables are detailed in Tables 2a and 2b and eTable 3.

3.3 ALT and all-cause mortality

In a Cox model, per one SD (13.2 U/L) increase in ALT, there was a 19% lower risk for death (95% CI 12-26%), $p < 0.001$. This remained significant after adjustment for assignment to fenofibrate, age, sex, diabetes duration, current smoker status, hypertension, dyslipidaemia, nephropathy, prior cardiovascular disease, WHR, LDL-c and HbA1c, with a 15% (95% CI 7-22%) lower risk of death on study, $p < 0.001$. Substituting continuous HDL-c and triglycerides for dyslipidaemia, BMI for WHR, past and present smokers for current smokers, or systolic and diastolic blood pressure for hypertension into the primary model had no significant effect on relationships seen. When ranked by WALD score, obtained from the adjusted model, ALT was

listed 6th, behind age, current smoker status, history of cardiovascular disease, nephropathy and HbA1c.

3.4 GGT and all-cause mortality

Using Cox-modelling, those with a GGT > 70U/L, when compared to those with GGT ≤ 70 U/L, had a HR for death of 1.88 (95% CI 1.53-2.30), $p< 0.001$. After adjustment for assignment to fenofibrate, age, gender, diabetes duration, current smoker status, hypertension, dyslipidaemia, nephropathy, history of cardiovascular disease, WHR, LDL-c and HbA1c, this remained significant, with a HR for death on study of 1.82 (95% CI 1.48-2.24), $p< 0.001$. Substituting continuous HDL-c and triglycerides for dyslipidaemia, BMI for WHR, past and present smokers for current smokers, or systolic and diastolic blood pressure for hypertension into the primary model had no significant effect on relationships seen. When variables were ranked by WALD score, obtained from the adjusted model, GGT > 70U/L was listed fourth, behind age, current smoker status and prior CVD.

3.5 ALT and GGT and cause-specific mortality

The HRs for death due to cancer, cardiovascular or non-cancer/non-cardiovascular causes were calculated in univariable and multivariable models and are listed in Table 3. To illustrate the qualitative nature of the relationships for each cause of death, the data are displayed graphically in Fig. 2 using ALT and GGT deciles.

3.6 Exploring mechanisms for the relationships between ALT and GGT and total mortality

Minimal effect was observed for relationships between ALT and GGT with total mortality when multivariable models were further individually adjusted for additional pre-specified variables to examine for effects of frailty, co-morbidity, insulin resistance, diabetes treatment, statin treatment, alcohol consumption and country of recruitment. Adjustment for hsCRP had no significant effect on relationships seen, although adjustment for the circulating soluble forms of

vascular inflammation markers, sICAM, sVCAM and sE-Selectin, strengthened associations for ALT and weakened associations for GGT (eTable 4 and eTable 5). Of note, grade of current exercise capacity had a significant ($p<0.001$), inverse, stepwise relationship with mortality in its own right (data not shown) and was also positively associated with ALT on univariate analysis (eTable 3). In addition, relationships persisted, and remained similar in strength, for both ALT and GGT when events in the first 1 or 2 years were excluded (eTable 4 and eTable 5).

When ALT and GGT were adjusted for each other within primary models, relationships with mortality were strengthened. When ALT was adjusted for GGT as a linear variable, a 23% (95% CI 15–30%) lower risk per one SD increase in ALT was observed, $p< 0.001$. Similarly, if individuals with GGT > 70 U/L were excluded, there was a 26% (95% CI 17–35%) lower risk of death per one SD increase in ALT, $p< 0.001$. For those with GGT > 70 U/L, after adjustment for ALT as a continuous variable, the HR for death when compared to those with GGT ≤ 70 IU/L was higher, at 2.26 (95% CI 1.82–2.81), $p< 0.001$.

There was a statistically significant interaction noted for hsCRP, as a continuous variable and for a value > 6.0 mg/L, in the relationship between ALT and total mortality. There was also a significant interaction for education level obtained individually and primary school education versus the rest of the cohort. Statistically significant interactions were noted between GGT and hypertension, diabetes treatment type, hsCRP (as a continuous variable and when > 6.0 mg/L) and alcohol consumption pattern. Relevant sub-analyses of the cohort divided by these variables is listed in Table 4.

3.7 Relationships between ALT and GGT and the SF-36

Data for the 1614 randomly selected participants who had a complete data set for the SF-36 at baseline were used in a sub-analysis to look at relationships between ALT and GGT and the 8 separate domains of the SF-36 (eTable 6). The average age of the sub-cohort was 62.3 ± 6.9

years and 37% (*n*=603) were female. Of the 1614, 5.7% (*n*=92) died on study, 2.3% (*n*=37) due to cardiovascular disease. GGT had inverse associations with seven of the eight domains measured in the SF-36, while no significant associations were found for ALT (eTable 6).

4. Discussion

Similar to findings in the general population, there is an inverse association between ALT and mortality in those with type 2 diabetes and ALT less than two times the upper limit of normal. The paradoxical but more intuitive relationship between higher GGT and subsequent mortality was also seen in this subject group, although only at levels > 70 U/L. Of note, the HRs for ALT (per SD) and GGT (>70 U/L) as predictors of mortality, are similar to those of several established biomarkers, including hsCRP and homocysteine [27]. After adjustment, ALT was significantly associated with cardiovascular death only, whereas GGT was associated with death due to cardiovascular disease, cancer and non-cancer/non-cardiovascular causes (Table 3).

To propose possible factors contributing to the association between lower ALT and mortality is challenging given that, similar to our findings (Table 2), increasing ALT has been directly linked to components of the metabolic syndrome and to markers of insulin resistance and systemic inflammation [1, 3, 6, 9]. The most widely accepted theory in current literature behind the association, is that low ALT is correlated with both frailty and sarcopenia, each associated with mortality in their own right [6, 7]. However, our analysis, while using surrogate techniques to adjust for frailty, did not support it as the principal mechanism involved. Indeed, if lower ALT was acting as a frailty marker alone to predict mortality, it would be expected to relate to all cause-specific categories of mortality (Table 3). In addition, we found exclusion of events at one and two years had no effect on the size of the risk. Similarly, no effect was seen after adjustment for proxy associations with frailty/co-morbidity including grade of current exercise capacity, employment status, eGFR, hsCRP, resting heart rate or weight loss within the first 12 months of the study (with greater weight loss presumed to be associated with frailty) [28] and associations

were strengthened when adjusted for sICAM, sVCAM and sE-Selectin. In addition, no clear relationship could be found between ALT and serum creatinine, an indirect marker of muscle mass (Table 2), or the individual scores for each domain of the SF-36 (eTable 6). These collective findings are not consistent with frailty as the primary contributor to the relationship seen [23, 25, 29].

Another possible cause of low ALT, and thus a potential contributor to its relationship with mortality, is a low liver reserve, as can be seen with aging [30-32] and cirrhosis, including that secondary to 'burnt out' NAFLD/NASH [13]. Indeed, the severity of fibrosis in NAFLD is thought to be the most important histological variable for predicting mortality [33, 34], including cardiovascular mortality [35]. It has also been linked to increased epicardial fat thickness, and abnormal cardiac geometry and function [36] and markers of subclinical atherosclerosis [37, 38]. Moreover, simple steatosis per se, may have no association with overall, or cardiovascular, mortality [35], particularly in the absence of other features of the metabolic syndrome [39]. Of note, adjusting for GGT, or excluding those with GGT > 70 U/L, increased rather than decreased the strength of the relationship between ALT and mortality. Of interest, the relationship was accentuated after adjustment for sICAM, sVCAM and sE-Selectin (eTable 4) and attenuated in those with an elevated hsCRP (Table 4), which would support the concept that a pro-inflammatory state is not the primary driver of the inverse relationship seen. Those with high CRP are also more likely to have necroinflammation (NASH) [40], which may explain why those with higher ALT, presumed to represent NAFLD, and high CRP, are not relatively protected from death [41].

Alternative causes for the relationship between low ALT and mortality could include associations of low ALT with pyridoxine deficiency [9, 42], low levels of sex hormones [32, 43], higher N-terminal pro-Brain natriuretic peptide (BNP, secreted by ventricular myocytes in response to

increased wall stress and ventricular filling pressure) [44] or genetic factors [1]. Given that higher ALT has been associated with markers of insulin resistance and higher BMI [45], low ALT may also be a sign of a more complex diabetes phenotype with greater absolute insulin deficiency, rather than insulin resistance, as a cause of hyperglycaemia [46, 47]. The stronger association of ALT with mortality in those with primary school education only is of interest (Table 4). This may reflect certain adverse environmental factors, to include diet and lifestyle, and unadjusted age related factors (with older subjects presumed to be less likely to have higher education) of importance but not defined in our data set [32].

The finding of a positive association between GGT and mortality would be consistent with its known function as a sensitive but non-specific marker of liver injury, alcohol intake, oxidative stress, vascular disease and other co-morbidities, through primary pathology and also through enzyme induction from medications [1, 2, 4, 9-11, 48]. Indeed, this fact is supported by our finding that GGT >70 U/L associated with mortality in all three categories (cardiovascular, cancer and non-cardiovascular/non-cancer; Table 3). We found, as expected, clear associations between increasing GGT and several inflammatory markers and measures of insulin resistance and the relationship with GGT and mortality, while remaining significant, was weakened by adjustment for sVCAM, sICAM and sE-selectin (eTable 5). In addition, we found clear inverse associations between GGT and seven of the eight domains measured in the SF-36 (eTable 6), such that higher GGT was associated with lower physical and emotional function, again supporting an association of higher GGT with biological frailty.

Surprisingly, the relationship between GGT and mortality was most clear in those without diagnosed hypertension and in those treated with diet alone (Table 4). These subgroups may include individuals who have less frequent medical contact or whose GGT elevation is due to causes other than medications, such as co-morbidity, alcohol intake or oxidative stress [1, 2, 9-11]. The findings were stronger in those who consumed regular alcohol and were attenuated in

those who were abstinent, suggesting that excessive alcohol consumption is likely to play a significant role in this association [49].

Strengths of our analysis include the use of prospective data from a large, well-defined cohort, with pre-specified outcomes and novel vascular risk biomarkers. In addition, intra-individual variation in ALT was accommodated by using an average of two independent samples. The main weakness of the data set is the exclusion of subjects with ALT more than 2 times the upper limit of normal (>100 U/L), without clear restriction on GGT at study entry. Hence, we are unable to make any comment about higher levels of ALT, where, as in other publications, mortality may increase [50]. This exclusion may also at least partly explain the paradoxical associations between ALT and GGT and mortality observed. Despite this, our data set is consistent with multiple equivalent publications where higher ALT has been excluded in order to avoid the inclusion of individuals with significant liver disease [5, 51, 52]. Other weaknesses of our analysis include the lack of data for alcohol consumption in grams per week, although this is a notoriously difficult measure to quantify accurately [53], and also the possible inadequate period of follow-up to see the effects of an adverse metabolic profile that may be seen at higher levels of ALT. The markers of frailty were indirect and not tested with dual-energy X-ray absorptiometry (DEXA) or other standardised assessment tools. Exercise capacity was self-graded and did not include parameters for frequency and time and SF-36 data were only available in 16% of the cohort and therefore could not be used to adjust primary models. In addition, the FIELD cohort is generally considered to have a relatively 'mild' phenotype of type 2 diabetes, with relatively short diabetes duration, low complication rates and low rates of insulin use [54], although one could argue that it is reflective of a community-based cohort and thus more likely to have relevance to the general population than findings from individuals studied at a tertiary diabetes centre. Finally, while pre-specified, multiple interaction tests were applied to the data set to explore potential mechanisms behind the associations between ALT or GGT and mortality,

increasing the possibility of a chance finding. However, this analysis was subsidiary only and did not affect the main finding of our primary analysis.

In summary, similar to findings in the general population, ALT has an inverse association with mortality in a community-based cohort of individuals with type 2 diabetes and ALT less than two times the upper limit of normal, despite the higher prevalence of NAFLD in this population [13]. This is opposite to the relationship seen for GGT and mortality, and both associations are of similar magnitude to those of biomarkers considered important predictors of mortality in populations with and without diabetes [27]. While GGT was associated with death due to cardiovascular disease, cancer and non-cancer/non-cardiovascular causes, low ALT was specific for death due to cardiovascular disease. The positive association between GGT and mortality would appear intuitive from our understanding of GGT as a marker of liver disease, alcohol intake, oxidative stress and co-morbidity [1, 2, 11]. The association between lower ALT, which is traditionally seen as a marker of liver health, and mortality is more difficult to understand [1, 45]. Mechanisms behind the inverse association between ALT and mortality have been reported by others to include frailty, sarcopenia and reduced liver reserve. However, links with frailty were neither supported nor conclusively refuted by our analysis and other factors are also likely to be important in those with type 2 diabetes [5, 7, 23]. Research into the causes, liver-related or otherwise, behind the association between low ALT and mortality is needed.

5. Funding

6. Disclosure statement

Conflicts of interest: none

7. Author contributions

KHW drafted the paper and DRS performed the first major revision. KHW, ST, ACK contributed to conception and design, data analysis and interpretation, and revised the paper. MD and LB contributed to design, data analysis and interpretation and revised the paper. AJJ, ASJ and ACK suggested, obtained grant funding for and analysed sVCAM, sICAM and sE-Selectin levels. ASJ, GCN, JG, AJJ, VJG, PM, YMT, CE, RO and SY contributed to data interpretation and revised the manuscript. ACK supervised the study. All authors gave final approval of the version to be published. KHW and DRS are responsible for the integrity of the work as a whole.

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9. Tables

Table 1: Clinical and biochemical characteristics of those who survived compared with those who died on the study.

Baseline variable	Survivors	Died on study	*p* value
Fenofibrate use	4539 (50%)	356 (52%)	0.19
Age (years)	62 (56–67)	67 (62–71)	<0.001
Female	3473 (38%)	184 (27%)	<0.001
Residence in Australia or New Zealand	7805 (86%)	597 (88%)	0.10
Diabetes duration (years)	5 (2–10)	7 (3–12)	<0.001
Current smoker	812 (9%)	110 (16%)	<0.001
Hypertension	5113 (56%)	433 (64%)	<0.001
Nephropathy	2228 (24%)	280 (41%)	<0.001
Prior cardiovascular disease	1865 (20%)	275 (41%)	<0.001
Diabetes treatment			
Diet	2483 (27%)	125 (19%)	<0.001
Oral	5425 (60%)	416 (61%)	
Insulin ± oral	1208 (13%)	138 (20%)	
HbA1c (%)	6.9 (6.1–7.8)	7.2 (6.3–8.2)	<0.001
HbA1c (mmol/mol)	52 (43–62)	55 (45–66)	
ALT (U/L)	24 (18–33)	22 (17–29)	<0.001
GGT (U/L)	29 (21–44)	31 (22–50)	<0.001

Data are presented as number (%) or median and interquartile range.

Table 2A and 2B: Clinical and biochemical associations with baseline alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) levels

Table 2A. Clinical associations with baseline ALT and GGT

Baseline clinical characteristic	ALT		GGT	
	Median and IQR (U/L) *or* correlation coefficient	*p* value	Median and IQR (U/L) *or* correlation coefficient	*p* value
Age (years)	–0.21	<0.001	–0.13	<0.001
Sex		<0.001		<0.001
Female (*n*=3657, 37%)	21 (16–29)		26 (19–40)	
Male	25 (19–35)		31 (22–46)	
Country of recruitment		<0.001		<0.001
Australia and New Zealand (*n*=8402, 86%)	23 (18–32)		29 (21–43)	
Finland	26 (19–37)		32 (22–48)	
Waist-hip ratio	0.26	<0.001	0.25	<0.001
Body mass index (kg/m^2)	0.19	<0.001	0.21	<0.001
Diabetes duration (years)	–0.041	<0.001	–0.05	<0.001
Smoking status		<0.001		<0.001
Non-smoker (*n*=3929, 40%)	23 (17–32)		27 (19–40)	
Ex-smoker (*n*=4944, 51%)	25 (19–34)		30 (22–46)	
Current smoker (*n*=922, 9%)	23 (17–31)		31 (22–47)	
Alcohol intake		<0.001		<0.001
None (*n*=2691, 28%)	23 (17–31)		27 (20–40)	
Infrequent (*n*=4604, 47%)	24 (18–32)		28 (20–42)	
Regular (*n*=2494, 25%)	25 (19–35)		34 (24–52)	
Comorbidity				
Hypertension (*n*=5546, 57%)	24 (18–33)	0.34	30 (22–46)	<0.001
No hypertension	24 (18–32)		28 (20–41)	

Baseline clinical characteristic	ALT		GGT	
	Median and IQR (U/L) or correlation coefficient	*p* value	Median and IQR (U/L) or correlation coefficient	*p* value
Systolic blood pressure (mmHg)	0.03	0.02	0.07	<0.001
Diastolic blood pressure (mmHg)	0.15	<0.001	0.13	<0.001
Dyslipidaemia (*n*=3710, 38%)	25 (19–35)	<0.001	31 (23–46)	<0.001
No dyslipidaemia	23 (17–31)		28 (20–42)	
Known cardiovascular disease (*n*=2131, 22%)	23 (18–31)	<0.001	29 (21–45)	0.08
No known cardiovascular disease	24 (18–33)		29 (21–44)	
Nephropathy (*n*=2508, 26%)	24 (18–34)	0.007	32 (23–48)	<0.001
No nephropathy	24 (18–32)		28 (20–42)	
Diabetes treatment		<0.001		<0.001
Diet only (*n*=2608, 26%)	23 (18–31)		28 (20–40)	
Oral antidiabetic therapy (*n*=5841, 60%)	25 (18.0–34)		30 (22–46)	
Insulin ± oral antidiabetic therapy (*n*=1346, 14%)	23 (17.0–30)		28 (19–43)	

Table 2B: Association of laboratory measures with baseline alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT)

Laboratory measure	ALT		GGT	
	Median and IQR (U/L) *or* correlation coefficient	*p* value	Median and IQR (U/L) *or* correlation coefficient	*p* value
HbA1c (% or mmol/mol)	0.12	<0.001	0.12	<0.001
Fasting glucose (mmol/L)	0.16	<0.001	0.14	<0.001
C-peptide (nmol/L)	0.29	<0.001	0.30	<0.001
HDL-c (mmol/L)	–0.15	<0.001	–0.09	<0.001
LDL-c (mmol/L)	–0.09	<0.001	–0.09	<0.001
Triglyceride (mmol/L)	0.15	<0.001	0.21	<0.001
Lipoprotein a (µmol/L)	–0.10	<0.001	–0.10	<0.001
hsCRP (mg/L)	–0.01	0.49	0.18	<0.001
Uric acid (µmol/L)	0.11	<0.001	0.14	<0.001
Serum Creatinine (µmol/L)	0.06	<0.001	0.03	0.002
eGFR (MDRD, ml/min/1.73m^2)	0.09	<0.001	0.08	<0.001
Platelets (x10^9/L)	–0.14	<0.001	–0.09	<0.001
HOMA IR	0.32	<0.001	0.33	<0.001
Homocysteine (µmol/L)	–0.06	<0.001	0.01	0.30
sVCAM (U/L)	0.11	<0.001	0.12	<0.001
sICAM (U/L)	0.19	<0.001	0.26	<0.001
sE-selectin (U/L)	0.36	<0.001	0.33	<0.001
Fibrinogen (µmol/L)	–0.02	0.13	0	0.81
ALT (U/L)	–		0.51	<0.001

Table 3: Relationship between baseline alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) > 70 U/L and all-cause and cause-specific mortality on study.

Cause of death	ALT per 13.2U/L				GGT > 70 U/L vs. GGT ≤ 70 U/L			
	Univariable		Multivariable[a]		Univariable		Multivariable[a]	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
All-cause (*n*=679)	0.81 (0.74–0.88)	<0.001	0.85 (0.78–0.93)	<0.001	1.88 (1.53–2.30)	<0.001	1.82 (1.48–2.24)	<0.001
Cancer (*n*=267)	0.88 (0.77–1.00)	0.47	0.93 (0.81–1.07)	0.32	1.82 (1.35–2.44)	0.001	1.81 (1.33–2.47)	<0.001
Cardiovascular (*n*=316)	0.74 (0.64–0.86)	0.001	0.77 (0.67–0.90)	0.001	1.63 (1.16–2.28)	0.005	1.46 (1.03–2.07)	0.03
Non-cancer, non-cardiovascular (*n*=96)	0.78 (0.63–0.97)	0.03	0.85 (0.69–1.05)	0.14	2.58 (1.59–4.19)	<0.001	2.59 (1.57–4.26)	<0.001

a The multivariable model was adjusted for the pre-specified variables of assignment to fenofibrate, age, sex, diabetes duration, current smoker status, hypertension, dyslipidaemia, nephropathy, prior cardiovascular disease, waist-hip ratio, LDL-c and HbA1c.

Table 4: Relationship between baseline alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) >70 U/L and all-cause mortality using subgroup analysis, as defined by variables with a statistically significant interaction with ALT or GGT > 70 U/L.

Variable (deaths/total number of individuals in analysis)	HR (95% CI)	*p* value	Interaction *p* value
ALT per SD (13.2 U/L)			
Subpopulation with hsCRP ≤ 6.0 mg/L (466/7275)	0.81 (0.72–0.90)	<0.001	0.03
Subpopulation with hsCRP > 6.0 mg/L (206/2321)	0.98 (0.85–1.14)	0.82	
Subpopulation with primary school education only (138/1484)	0.67 (0.54–0.85)	0.001	0.03
Subpopulation with high school education or higher (538/8254)	0.89 (0.81–0.99)	0.03	
GGT > 70 U/L			
Subpopulation with hypertension (432/5527)	1.41 (1.07–1.85)	0.01	0.001
Subpopulation with no hypertension (246/4238)	2.74 (2.00–3.75)	<0.001	
Subpopulation on diet control for diabetes (124/2588)	3.06 (1.94–4.81)	<0.001	0.03
Subpopulation on oral antidiabetic therapy (416/5833)	1.69 (1.29–2.20)	<0.001	
Subpopulation on insulin ± oral antidiabetic therapy (138/1344)	1.48 (0.92–2.38)	0.11	
Subpopulation with hsCRP ≤ 6.0 mg/L (466/7275)	1.53 (1.16–2.02)	0.003	0.001
Subpopulation with hsCRP > 6.0 mg/L (206/2321)	2.22 (1.61–3.07)	<0.001	
Subpopulation who consume no alcohol (215/2685)	1.17 (0.74–1.85)	0.50	0.007
Subpopulation who consume infrequent alcohol (303/4591)	1.83 (1.33–2.53)	<0.001	
Subpopulation who consume regular alcohol (160/2483)	2.53 (1.78–3.60)	<0.001	

a All models were adjusted for the pre-specified variables of assignment to fenofibrate, age, sex, diabetes duration, current smoker status, hypertension, dyslipidaemia, nephropathy, prior cardiovascular disease, waist-hip ratio, LDL-c and HbA1c.

10. Figure legends

Figure 1

Graphical depiction of unadjusted natural log of hazard ratios (HR) and 95% confidence intervals for all-cause mortality on study for alanine aminotransferase (ALT) deciles (Panel 1A) and γ-glutamyl transferase (GGT) deciles (Panel 1C) and their associated Kaplan Meier graphs (Panels 1B and 1D) using Cox proportional hazards regression analysis.

Figure 2

Graphical depiction of unadjusted hazard ratios (HR) and 95% confidence intervals for death on study by cause-specific mortality subtype using competing risk analysis (Fine and Gray) for alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) deciles. Abbrev: CVD, cardiovascular.
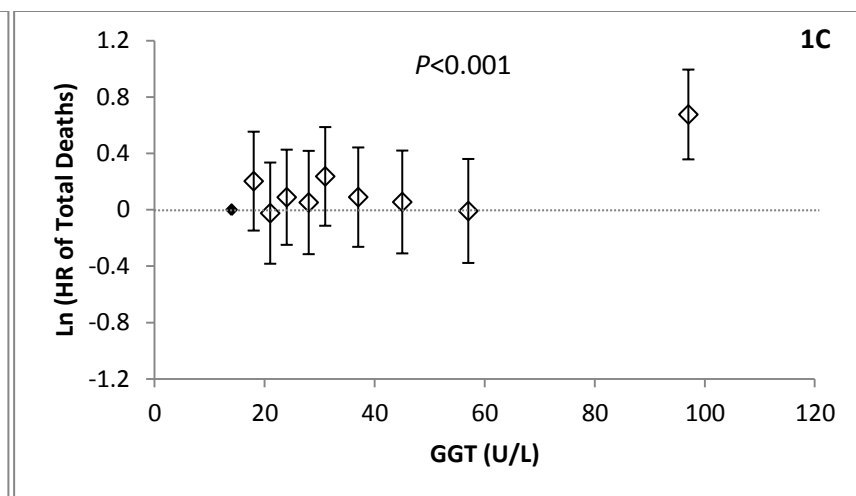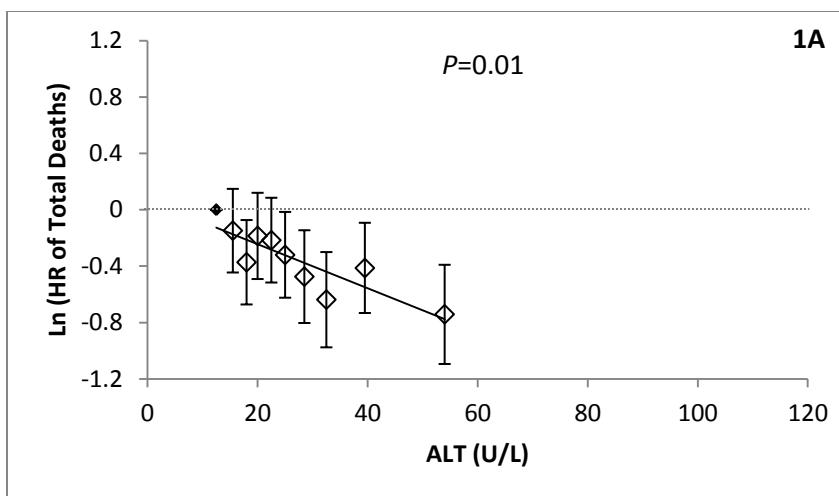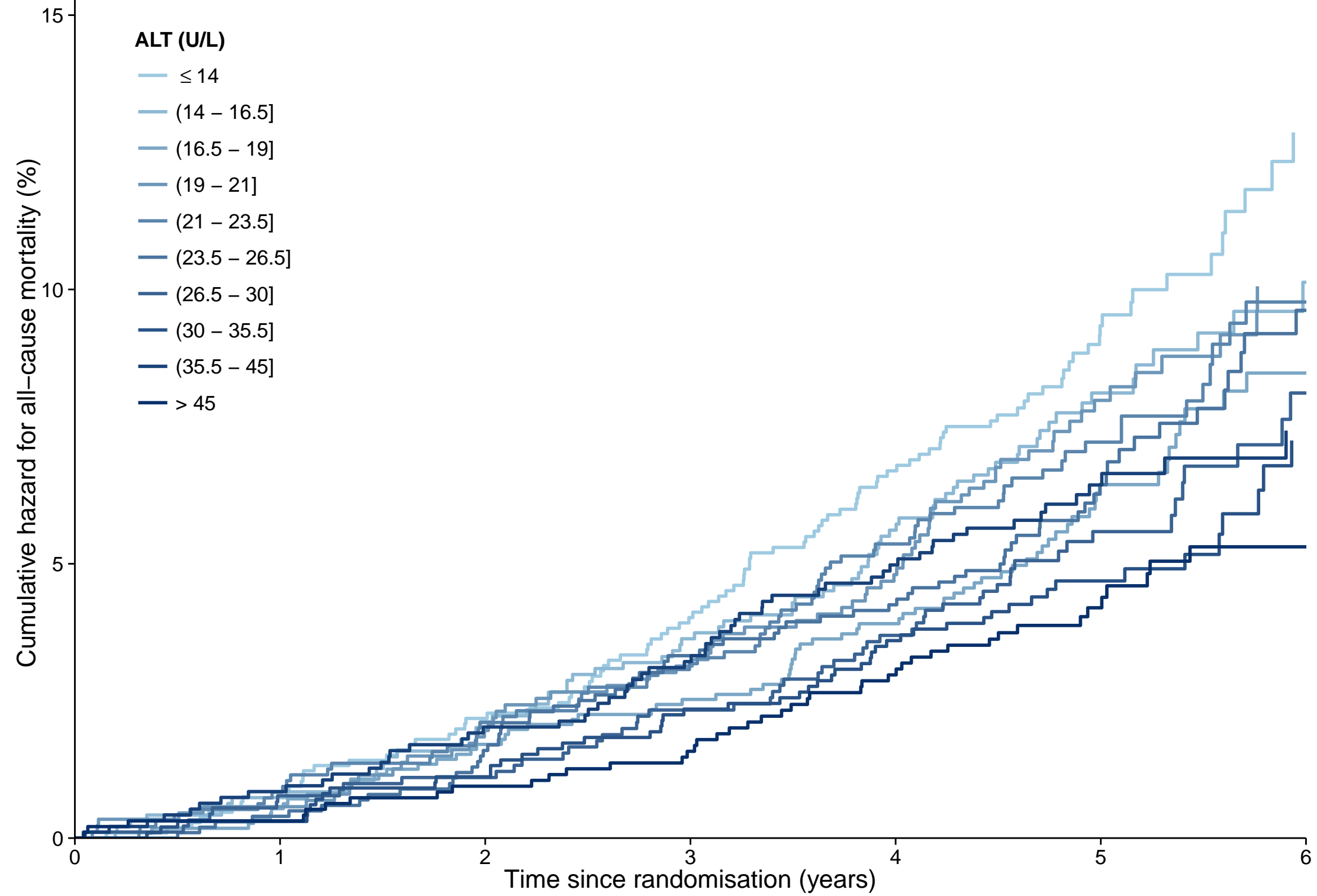
Figure 1 A and C

Figure 1 B

ALT (U/L)

— ≤ 14
— (14 – 16.5]
— (16.5 – 19]
— (19 – 21]
— (21 – 23.5]
— (23.5 – 26.5]
— (26.5 – 30]
— (30 – 35.5]
— (35.5 – 45]
— > 45

Cumulative hazard for all–cause mortality (%)

Time since randomisation (years)

Figure 1 D

Figure 2