Determination of serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] was first introduced in 1955 as a means of diagnosing viral hepatitis and other liver diseases, with gamma glutamyltranspeptidase (GGT) introduced into clinical laboratories some 10 years later. Liver function tests [including alkaline phosphatase (ALP)], as they are commonly and somewhat misleadingly known, are increasingly performed in primary care settings in the UK as part of general health checks as well as in the investigation of potential liver, pancreas, bone and gallbladder disease, alcohol misuse and for monitoring of drug effects. With the growing interest in the epidemiology of non-alcoholic fatty liver disease, liver enzymes—ALT and GGT in particular—also have been increasingly studied in recent years as they are relatively easy to measure in large-scale general population studies.

In this issue of IJE, Kunutsor et al. report results of a sound systematic review and meta-analysis of prospective cohorts that examined associations between these enzymes and all-cause mortality over a median follow-up time of 10 years in general populations. In pooled analyses, they found a 60% (95% confidence interval (CI): 42%, 80%; 11 studies) increased mortality risk in the top third of the GGT distribution compared with the bottom third, an equivalent 38% increase (95% CI: 17%, 63%; four studies) for ALP and no strong evidence of overall associations of the transaminases with mortality (eight and four studies of ALT and AST, respectively). They also report: positive linear associations of GGT and ALP with mortality, with a 7% (95% CI: 4%, 10%) and 3% (95% CI: 1%, 6%) increase in risk per 5 U/l, respectively; non-linear associations of ALT and AST with mortality, with sharp increases in risk observed from 20 U/l of ALT and 15 U/l of AST; and marked heterogeneity in associations in Asian (ALT positively associated with mortality) vs American and European (inverse association) populations.

Kunutsor et al. acknowledge the low specificities of liver enzymes but argue that they are sensitive, well standardized, simple, inexpensive and common laboratory tests, and hence the need to assess their associations with all-cause mortality. And indeed their rigorous systematic review and meta-analysis does just that. But where do we go from here?

The pathophysiological processes that determine serum liver enzymes levels are not well understood, and this is particularly true with regard to non-extreme levels. Hence the mechanisms and pathways underlying the observed associations of liver enzymes across their distributions with all-cause mortality are not obvious. Kunutsor et al. provide a clear and insightful discussion of potential mechanisms driving the reported associations of liver enzymes with mortality, but they too acknowledge that some are ‘hypothesical’ and ‘may be more complex than generally appreciated’.

From an aetiological perspective, the lack of clarity with regard to the pathophysiological mechanisms that determine liver enzyme levels is compounded by the outcome examined, namely all-cause mortality. As opposed to associations with cause-specific mortality that could potentially suggest specific disease processes resulting in variation in liver enzymes’ levels and ultimately in death, all-cause mortality is not informative in this respect.

In light of the above, the implications and utility of the association between liver enzyme levels and all-cause mortality, as accurately estimated as it may be, remain at this point somewhat elusive. Granted, understanding disease aetiology is not the only goal of epidemiological research. Risk prediction is important for early detection of potential existing and future adverse health, allowing for early intervention aimed at reducing subsequent morbidity and mortality. As Kunutsor et al. themselves conclude, their work highlights the need for further clinical evaluation of even mildly elevated liver enzymes or
at least of additional investigation into the determinants of variation in liver enzyme levels across their entire distributions.

**Funding**

A.F. is funded by a UK MRC research fellowship (0701594) and works in a unit that receives infrastructure funding from UK Medical Research Council (MC_UU_12013/5).

**Conflict of interest:** None declared.

**References**


