Commentary | Open Access

Metabolism and Target Organ Damage

Gofton *et al. Metab Target Organ Damage.* 2026;6:48 **DOI:**10.20517/mtod.2026.122

Multimorbidity comes to roost: insights from the LiverScreen project on the future burden of metabolic liver disease

Cameron Gofton[1,2,3], Jacob George[3,4]

Citation: Gofton C, George J. Multimorbidity comes to roost: insights from the LiverScreen project on the future burden of metabolic liver disease. *Metab Target Organ Damage.* 2026;6:48. https://dx.doi.org/10.20517/mtod.2026.122

Received: 2 Jun 2026
First Decision: 3 Jul 2026
Revised: 10 Aug 2026
Accepted: 11 Aug 2026
Published: 18 Aug 2026

Academic Editor: Juan Pablo Arab
Copy Editor: Ting-Ting Hu
Production Editor: Ting-Ting Hu

COMMENTARY

Chronic liver disease, for the most part, is minimally symptomatic until the complications of advanced fibrosis and cirrhosis supervene, such as the development of ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal bleeding[1]. Hepatocellular carcinoma, on the other hand, while typically developing in the context of cirrhosis, can also arise at earlier stages. The window to effectively intervene and reverse or prevent adverse liver outcomes is usually wide in the absence of cirrhosis, while these opportunities rapidly dwindle and therapy is less effective with the advent of cirrhosis[1]. Against this dynamic, determining a suitable screening program and the institution of appropriate therapy offers the best hope to prevent long-term adverse liver outcomes, akin to what is done for cardiovascular disease prevention. The starting point of any such strategy is to first understand the prevalence of the condition, i.e., liver fibrosis in this instance, in the general population.

The LiverScreen project[2] sought to answer this question by providing population-level insights on the prevalence of liver fibrosis across 9 European countries and > 30,000 participants who volunteered to take part. Patients who demonstrated a vibration-controlled transient elastography (VCTE) ≥ 8 kPa or elevated alanine aminotransferase (ALT) > 1.5 upper limit of normal were referred for specialist hepatology consultation and repeat fibrosis assessment[3]. Of 2,457 patients who met criteria for specialist referral, either by meeting the above criteria or failing VCTE (342 patients) or investigator oversight (40 patients), 1,491 patients attended a consultation, of whom 32% had chronic liver disease with fibrosis, yielding an overall estimated prevalence of fibrosis of 1.6% (477 of 30,199). In the general population sample, metabolic risk factors were present in over two thirds of participants (70%),

[1]Northern Clinical School, University of Sydney, Sydney 2065, Australia.
[2]Royal North Shore Hospital, Sydney 2065, Australia.
[3]Storr Liver Centre, Westmead Hospital, WSLHD, Westmead Institute for Medical Research and University of Sydney, Westmead 2145, Australia.
[4]Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney 2145, Australia.

Correspondence to: Prof. Jacob George, Storr Liver Centre, Westmead Hospital, WSLHD, Westmead Institute for Medical Research and University of Sydney, Westmead 2145, Australia. E-mail: Jacob.George@sydney.edu.au

while 59% (15,107 of 25,488) reported alcohol use, with 6.1% reporting harmful (current consumption of standard drink units of 14 units or more per week for women and 21 units or more per week for men) consumption. Notably, the prevalence of liver stiffness measurement (LSM) ≥ 8 kPa was 4.6% in the population, and as expected, was strongly associated with obesity, type 2 diabetes, and harmful alcohol use.

So, what are the implications of this study? Clearly, if you undertake population-level screening, chronic liver disease with suspected significant fibrosis (LSM ≥ 8 kPa) in those 40 years of age or older is about 1 in 20 persons. While as clinicians, the institution of early treatment is important, we must also be cognizant that the absolute risk of adverse liver outcomes is not large, especially when faced with competing health priorities. To highlight this issue, Allen *et al*. (2022) evaluated the course of non-alcoholic fatty liver disease (NAFLD), demonstrating that progression from NAFLD to cirrhosis was just 3% at 15 years, with decompensation occurring at approximately 8% per year in those with cirrhosis[4]. Of note, liver-related mortality was 6% over 15 years, with 94% of deaths occurring from diseases outside the liver. Another study by Vilar-Gomez *et al*. (2018) also highlighted the complication rates associated with NAFLD[5]. In that study, individuals with F3 fibrosis were more likely to have non-hepatic complications such as extrahepatic cancer and vascular events. Perhaps the goal in primary care is to identify and treat cardiovascular risk factors and undertake guideline-recommended cancer surveillance. For the Hepatologist, particularly if drugs that treat F2/3 fibrosis such as resmetirom or glucagon-like peptide-1 (GLP1) receptor agonists improve long-term liver-related outcomes rather than the histological outcomes that are currently reported, screening for those who would benefit from treatment, perhaps those with VCTE LSM ≥ 10 kPa as the current international guidelines recommend, is justified[6].

One of the major findings from LiverScreen was confirmation of what previous studies had suggested, namely that the presence of metabolic multi-morbidity and harmful alcohol use increases the risk of significant fibrosis. In LiverScreen, the prevalence of LSM ≥ 8 kPa increased stepwise from 1.3% to 2.2%, 5.2%, 9.4%, and 20.7% with 0, 1, 2, 3, or 4 metabolic risk factors, and to 37.1% in those with 4 metabolic risk factors and harmful alcohol use[2]. The message is clear: in the era of metabolic multimorbidity, these are the individuals at highest risk not just for liver and cardiometabolic outcomes, but also for hepatic and extrahepatic cancers and for a disproportionate burden of healthcare costs. Intensive case finding and aggressive management from lifestyle intervention, including dietary and exercise changes to pharmacotherapy, is perhaps the singular message.

A finding from LiverScreen was that the rates of VCTE LSM scores decreased on repeated testing. Almost half of the individuals referred to hepatology (48%) due to VCTE ≥ 8 kPa or raised ALT had a repeat VCTE < 8 kPa. While this has been observed in other studies, changes in lifestyle, test-retest variability of VCTE and regression to the mean are important contributors[7]. The need for standardised testing conditions and established VCTE quality criteria, whilst not expressly discussed in this research, should be adhered to in an effort to decrease potential outcome variability. There is a lack of granularity regarding the timing between repeat VCTE, changes in alcohol consumption or lifestyle management in this study to adequately identify the potential underlying causes for this change in the LiverScreen study. Furthermore, regarding the individuals who did follow up, it is uncertain if the non-attenders differed systematically from attenders in terms of metabolic risk, alcohol consumption, or healthcare access. On the positive side, it also suggests that reassessment (without a sense of panic) must be part of the physician's usual armamentarium when it comes to assessing chronic metabolic liver diseases. While clinical researchers like to neatly divide patients into diagnostic categories, patients rarely fit that paradigm. This is particularly the case with alcohol consumption, which is ubiquitous in modern societies, frequently under-reported and highly dynamic across the life course of an individual. This was noteworthy in LiverScreen, in which LSM ≥ 8 kPa varied from country to country approximately threefold, with a range between 2.9%-9.6%. The country with the greatest prevalence of liver fibrosis by VCTE LSM ≥ 8 kPa also had the highest rates of harmful alcohol intake.

While LiverScreen has provided robust population-level data, as always, it is important to recognise its limitations. Many of these are inescapable in a study of this size, including missing data, variability in data acquisition tools, mixed entry criteria that varied from health check-up attendees to true population sampling to those that participated in existing population screening programmes or occupational health checks, and absence of protocolised testing for viral hepatitis. Further, the results are only applicable to adults restricted by the demographic characteristics of the study. Nevertheless, what is evident is that while suspected significant liver fibrosis (> 8 kPa LSM on VCTE) is largely asymptomatic, it affects nearly 5% of the adult population, which is likely of a similar order in most developed and developing countries.

LiverScreen has been a massive undertaking, and the results put numbers to population-level estimates of liver fibrosis as judged by VCTE. More than ever, for the authors of this commentary, the project highlights the adverse effects of metabolic multi-morbidity for human health, and targeted screening in primary care of these individuals will improve the recognition of suspected liver fibrosis in the general community. For hepatology practice, should treatments targeting metabolic liver disease be shown to reduce long-term adverse liver outcomes, the race will be on to identify and treat those most likely to benefit.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Gofton C, George J

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

George J is supported by the Robert W. Storr Bequest to the Sydney Medical Foundation, University of Sydney; a National Health and Medical Research Council of Australia (NHMRC) Program Grant (GNT1053206), Project, Ideas and Investigator grants (GNT2001692, GNT1107178, GNT1108422, GNT1196492 and GNT2032407) and a Cancer Institute, NSW grant (2021/ATRG2028).

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Liu YB, Chen MK. Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions. *World J Gastroenterol.* 2022;28:5910-30. DOI PubMed PMC
2. Graupera I, Thiele M, Castera L, et al. ; LiverScreen Consortium Investigators. Prevalence of liver fibrosis in the general population (the LiverScreen project): a multinational European cohort study. *Lancet.* 2026;407:1448-58. DOI PubMed

3. Graupera I, Thiele M, Ma AT, et al. ; LiverScreen Consortium investigators. LiverScreen project: study protocol for screening for liver fibrosis in the general population in European countries. *BMC Public Health.* 2022;22:1385. DOI PubMed PMC
4. Allen AM, Therneau TM, Ahmed OT, et al. Clinical course of non-alcoholic fatty liver disease and the implications for clinical trial design. *J Hepatol.* 2022;77:1237-45. DOI PubMed PMC
5. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. *Gastroenterology.* 2018;155:443-57.e17. DOI PubMed
6. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol.* 2024;81:492-542. DOI PubMed
7. Ndaa M, Pandya PK, Swensson J, et al. Reliable monitoring of patients with metabolic dysfunction-associated steatotic liver disease using imaging: a systematic literature review and meta-analysis on measurement repeatability. *Endocr Pract.* 2026;32:258-67. DOI PubMed