

**Global Epidemiology of Non-Alcoholic Fatty Liver Disease.
Meta-Analytic Assessment of Prevalence, Incidence and Outcomes**

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To the Editor:

We appreciated Dr Younossi and colleagues' meta-analysis of the global prevalence, incidence, progression and outcomes of NAFLD (1). We believe that the topic is important and we appreciate the opportunity to offer some comment and perspective on the concepts implicit in this work.

Rather than being exclusively considered as always "*the hepatic manifestation of the metabolic syndrome*" (MetS), it is conceivable that NAFLD should actually be considered a *precursor* of the MetS (2). Strong evidence indicates that NAFLD exacerbates insulin resistance, predisposes to atherogenic dyslipidemia, and increases the risk of incident MetS (3).

Perhaps more importantly, the authors found that NAFLD was associated with liver-related mortality but not with cardiovascular disease (CVD) mortality (1). To date, clear evidence indicates that CVD is the leading cause of death among NAFLD patients (3). Convincing evidence also substantiates a link between NAFLD and functional and structural cardiac abnormalities (3). Thus, we wonder whether the criteria adopted by the authors for selecting the studies (e.g., exclusion of studies including only patients with obesity or diabetes) may have led to underestimating the impact of NAFLD on overall and CVD mortality.

In this regard, it is unclear why the authors included the same population-based cohort of individuals, i.e., the NHANES-III cohort, many times in their meta-analysis (see supplementary Table H).. By using different selection criteria, other investigators concluded that NAFLD was associated with increased all-cause and CVD mortality (4). These nuances of interpretations of the literature bely the complexity of modifiers of the NAFLD phenotype, such as genotype, lipid metabolism, inflammation, insulin resistance and fibrosis, and whether NAFLD influences CVD risk, diabetes risk or risk of other extra-hepatic complications linked with NAFLD, such as chronic renal disease (2-4).

We appreciate the authors' call for more liberal NAFLD screening policies. Based on recent analyses of epidemiological modifiers of NAFLD and preliminary cost-utility analyses, we reached similar conclusions. Individuals belonging to NAFLD high-risk groups warrant screening for fatty liver disease (5).

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