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EDITORIAL

Modifiable risk factors for fatty liver disease: Time to act

Fatty liver disease (FLD) is increasingly prevalent, affecting an estimated 1 in 3 adults globally in 2019.[1] There is paramount evidence illustrating the close relationship between metabolic dysfunction and FLD and the crucial role of lifestyle. However, most studies were cross-sectional and could not provide information on causality. Obtaining information on causality through longitudinal studies is particularly challenging given that it requires accurate data on when FLD occurred, in light of other important risk factors or disease modifiers like diabetes, obesity, and metabolic syndrome. Given that FLD is primarily asymptomatic, especially at the early stages where steatohepatitis and fibrosis are not yet present, it often remains untreated.

We therefore read with great interest the study by Xie et al. that aimed to investigate the associations between 35 modifiable risk factors and FLD.[2] Their findings confirmed that healthy lifestyle modification is the first-line, cornerstone preventative measure for FLD. They used Mendelian randomization (MR), a study method that uses (a combination of) genetic variants as exposure to provide evidence for supposed causal relations between exposure and outcome (FLD). An important benefit of this sophisticated method is that it is less prone to confounding and reverse causation, concepts that often affect the associations between FLD and putative risk factors.[3] In Box 1, we briefly emphasize some important MR concepts and methods used in the study published in the current issue of Hepatology.

Xie et al. demonstrated that genetic predisposition to poor physical condition, peripheral and central obesity, type 2 diabetes, and hypertension were associated with an increased risk of FLD. Most of these findings were consistent in the weighted median and MR pleiotropy residual sum and outlier (PRESSO) sensitivity analysis, illustrating the robustness (in particular, independence of horizontal pleiotropy [HP]) of these outcomes. The findings by Xie et al. align with previous results from a multiethnic cohort study also using MR.[4] However, it is important to note that this previous study had an overlap in exposure and outcome data. It is therefore reassuring that Xie et al. found similar results and validated previous findings after excluding the population from which exposure factors were derived to avoid bias caused by sample overlap.

These two MR studies investigating crucial modifiable risk factors for FLD add body to the evidence for the role of metabolic health and lifestyle in FLD obtained in other conventional studies. It is therefore particularly worrisome that metabolic health is rapidly deteriorating on a global scale.[5] This concern is clearly illustrated by the rapid increase of FLD prevalence (+0.7% each year since 1991) to an estimated prevalence of 37.3% in 2019; obesity prevalence that has tripled between 1975 and 2016; and diabetes prevalence that has almost quadrupled since 1980.[1,6,7]

Fortunately, governments and policy makers have noted these worrisome trends, and several countries have introduced policies to reduce overweight. For example, in The Netherlands, the "National prevention agreement" was introduced in 2018. This program aimed to reduce overweight prevalence from 50% to 38% in 2040 by implementing a sugar tax and an additional soft drinks and beer tax, while reducing taxes on vegetables and fruits. However, during the evaluation of this program in March 2022, none of these measures had yet been implemented, and overweight prevalence remained unchanged. Until the implementation of adequate policies that effectively reduce overweight, metabolic health will be increasingly accountable for impaired quality of life, excess mortality, and substantial health care costs.[8–10]

The study by Xie et al. demonstrated the causal relationship between peripheral and central obesity with FLD. This illustrates that the measures taken by many countries to reduce overweight are likely to be effective in improving liver health. Another interesting finding was the role of alcohol consumption in the risk of FLD. The investigators reported genetically derived alcohol frequency to be a risk factor for FLD, whereas genetically derived alcohol quantity was not associated with FLD. These findings conflict with the study by Yuan et al. that reported a lower risk of FLD for moderate alcohol consumption.[4] These findings warrant further investigation, especially given that the results from both studies were not significant in the weighted median methods and may be explained by HP. There is strong evidence that there is no safe limit of alcohol consumption. Likewise, we demonstrated that

Abbreviations: FLD, fatty liver disease; HP, horizontal pleiotropy; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier.

BOX 1 Important concepts in MR

Horizontal pleiotropy (HP) is a concept that the instrumental variable (in this case, a combination of genetic variants) causes not only FLD through exposure, but also by other factors. This does not affect the estimates for the instrumental variable itself, but hampers translation of the estimate from the instrumental variable (e.g., genetically derived diabetes) to the exposure (e.g., observed diabetes). For example, one could assume overlap in the genetic variants used in the instrumental variable for obesity and diabetes, resulting in an overestimation of the risk attributed to diabetes (the exposure) for NAFLD (the outcome) as illustrated in the example below. Several methods are available to prevent overestimating the effect estimates and were applied by the investigators.

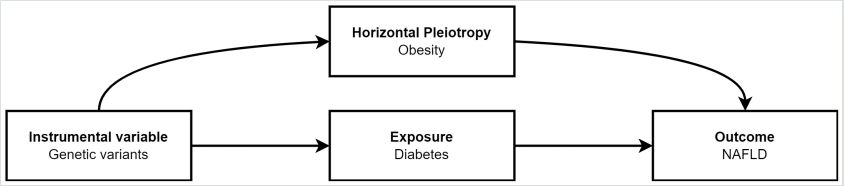

FIGURE Visualization of HP caused by obesity in the MR analysis from genetically derived diabetes risk to NAFLD

Inverse variance weighted method is the standard approach for MR and assumes unbalanced HP. If this is met, it provides the most accurate estimates. Importantly, this method does not account for HP and may result in biased estimates in a real-life setting.

Weighted median method assumes that most genetic variants are valid instrumental variables. This method therefore overcomes the issue of HP, but only in case it does not affect >50% of the components of the instrumental variable.

MR Egger allows all variants to have pleiotropic effects at the cost of losing power and less precise effect estimates. It is similar to the Eggers test used in meta-analysis to rule out small study bias.

MR PRESSO This method assumes that the largest group of candidate instruments in the group are valid instruments. The method tests for pleiotropy by the global test and excludes outliers. After excluding assumed outliers, the inverse variance weighted method is applied. Distortion by the outliers can be assessed by comparing the effect estimates before and after MR PRESSO analysis.

In-depth information regarding MR covering more concepts is available elsewhere.[3,13,14]

even when applying very low thresholds, regular alcohol consumption was associated with all-cause mortality independent of (and simultaneously with) steatosis.[11,12] Altogether, reducing alcohol consumption will likely reduce the risk of FLD and FLD-related adverse outcomes, including mortality.

Fortunately, most FLD patients will not encounter serious symptoms of their disease, and it remains challenging to identify those who are actually at risk for advanced liver disease. Therefore, several groups work on early detection of advanced FLD. It would be interesting whether MR could be the missing link in identifying targets to improve currently available risk-stratification algorithms and point us toward key predictors for steatohepatitis, fibrosis, and liver-related mortality in subjects with FLD.

In conclusion, the overwhelming evidence of metabolic health as a risk factor for FLD and its worrisome global extent demand active countermeasures and enactment of effective policies encouraging lifestyle improvements. Given the ongoing deterioration of metabolic health resulting in hepatic and extrahepatic complications, the time to act is now.

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Conceptualization and writing of the manuscript: LvK. Supervision: RdK. Critical review of the manuscript, approval of final version and approval of submission: LvK and RdK.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

No data has been used in the writing of this manuscript.

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