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Critical Assessment of the Reported Bidirectional Associations Between Gallstone, Non-Alcoholic Fatty Liver, and Kidney Stone Diseases

Jingjing Lu *et al*. Assessing Links: GSD, NAFLD, KSD

Abstract

The recent article by Jiang *et al* published in *World Journal of Gastroenterology* (30(46), 4914-4928) reports substantial bidirectional associations between gallstone disease (GSD), non-alcoholic fatty liver disease (NAFLD), and kidney stone disease (KSD), based on multicenter cross-sectional studies and a systematic review with meta-analysis. While the findings have the potential to significantly impact clinical and preventive strategies, several methodological issues merit closer examination. This letter critiques key aspects of the study, including sample population heterogeneity, potential confounding variables, and the reliance on cross-sectional data that may limit causal inferences. We also discuss the generalizability of these results to broader populations given the study's focus on the Chinese demographic. By addressing these concerns, we suggest a more nuanced interpretation of the associations between GSD, NAFLD, and KSD, advocating for longitudinal studies to validate these findings and enhance their applicability in global health contexts.

Key Words: Gallstone disease; Non-alcoholic fatty liver disease; Kidney stone disease; Bidirectional associations; Meta-analysis

Core Tip: This study by Jiang *et al*. examines the bidirectional associations between gallstone disease (GSD), non-alcoholic fatty liver disease (NAFLD), and kidney stone disease (KSD) through multicenter cross-sectional research and meta-analysis. It highlights critical insights into the interconnected pathophysiology of these prevalent disorders. While promising for integrative medical strategies, the findings also underscore the challenges posed by heterogeneous samples and cross-sectional data limitations. The need for robust, longitudinal research to confirm these associations and extend their relevance to diverse global populations is crucial.

TO THE EDITOR

The recent article by Jiang *et al*[1] presents findings of significant clinical interest, suggesting substantial bidirectional associations among gallstone disease (GSD), non-alcoholic fatty liver disease (NAFLD), and kidney stone disease (KSD) through multicenter cross-sectional studies and a systematic review with meta-analysis. While these findings could have significant impact on clinical practice and preventive health strategies, several methodological issues require closer examination to allow for more nuanced interpretations of the associations between these three conditions.

Exploring the bidirectional associations between GSD, NAFLD, and KSD holds substantial potential significance across multiple dimensions of healthcare and medical science. GSD is a chronic recurrent hepatobiliary condition that ranks as one of the most common gastrointestinal disorders worldwide[2,3]. However, there was significant variability in diagnostic criteria for all three diseases in the study by Jiang *et al*[1], particularly in ultrasonography across different centers. For example, the criteria for diagnosing NAFLD can vary significantly, from the simple presence of fat to more specific criteria involving liver stiffness measurements, which are not universally available[4]. Similarly, the diagnosis of kidney stones often depends on detection method, whether CT, ultrasound, or X-ray, each with varying sensitivities and specificities[5]. This variation can lead to inconsistencies in reported incidences across studies. We propose that future research should strive to standardize diagnostic approaches and criteria to enhance consistency and reliability of data across different clinical settings.

GSD pathogenesis involves impaired metabolism of cholesterol, bilirubin, and bile acids, leading to the formation of gallstones within the hepatic bile duct, common bile duct, or gallbladder. Understanding the interconnections between GSD and other metabolic disorders could provide critical insights into broader metabolic dysfunctions and suggest more integrated approaches for treatment and prevention[6].

NAFLD is another prevalent metabolic disorder characterized by the accumulation of triglycerides in hepatocytes, occurring independently of causes like excessive alcohol consumption, viral or autoimmune hepatitis, or iron overload. Its severity varies,

ranging from benign asymptomatic fatty steatosis to more severe forms like steatohepatitis, which can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma[7,8]. Investigating how NAFLD relates to other prevalent conditions such as GSD and KSD might illuminate shared metabolic pathways and risk factors, enhancing our ability to effectively manage or intervene in these conditions.

Lastly, KSD is one of the oldest recognized medical conditions, yet its underlying metabolic mechanisms and the exact process of stone formation remain elusive. Kidney stones result from complex metabolic changes affecting various substances, suggesting a multifactorial etiology[9].

By examining the potential bidirectional relationships with GSD and NAFLD, researchers could identify novel metabolic or genetic markers that influence kidney stone formation, potentially leading to innovative preventive and therapeutic strategies. The published article presents a multicenter cross-sectional study, systematic review, and meta-analysis, utilizing data from subjects at Jinshan Hospital of the First Affiliated Hospital of Chongqing Medical University (urban Chongqing), Kaizhou District People's Hospital of Chongqing (rural Chongqing), Beijing Xiaotangshan Hospital, and Tianjin Medical University Cancer Institute and Hospital. It examines pairwise relationships between GSD, NAFLD, and KSD.

Of major concern is the study's reliance on cross-sectional data to infer causality between GSD, NAFLD, and KSD. While the authors provide valuable insights into disease prevalence, cross-sectional studies inherently lack the temporal perspective required to establish directionality and causality of these relationships[10,11]. This limitation is critical, as the bidirectional nature of disease associations suggests a complex interplay that could be better explored through longitudinal research designs. Such studies would allow for the observation of the diseases over time, offering stronger evidence of causality rather than mere association. Such studies should also include a comprehensive set of potential confounding variables including body mass index, dietary habits, genetic predispositions, and socioeconomic status, which could significantly influence disease outcomes.

Another significant issue in the study is the variability in diagnostic criteria across the multiple centers. While ultrasonography is practical, it may not consistently capture the nuanced presentations of NAFLD and KSD across different settings and operators. The potential for diagnostic misclassification is a notable risk that could lead to biased results. We suggest that future studies incorporate more consistent diagnostic standards across multiple centers to reduce variability and improve the reliability of findings. Moreover, the heterogeneity of sample populations, spanning various regions within China, raises questions about the consistency of healthcare practices, access to medical services, and environmental or lifestyle factors that might influence the prevalence and detection of these diseases.

The study's focus on a predominantly Chinese population complicates the generalizability of the findings. The epidemiology of GSD, NAFLD, and KSD can significantly vary across different ethnicities and geographic regions due to genetic, dietary, and lifestyle factors. Thus, while the study presents valuable data, its applicability to other populations remains uncertain. To enhance the relevance of these findings globally, replication studies with diverse demographic settings are necessary. For instance, the genetic factors influencing cholesterol and bile acid metabolism, which are critical in GSD pathogenesis, may significantly differ between populations. Certain genetic polymorphisms associated with GSD in Asian populations may not be as prevalent or may have different effects in Caucasian or African populations. Similarly, dietary factors, such as the high consumption of high-fructose corn syrup in Western diets, have been linked to higher rates of NAFLD in these populations compared to Asian diets, which tend to be lower in fructose.

To validate the findings of Jiang *et al*[1] in non-Chinese populations, it is crucial to perform replication studies that are designed to consider these regional and ethnic variations. By addressing these aspects, future research can enhance the global relevance of the findings and contribute to a more nuanced understanding of how GSD, NAFLD, and KSD are interconnected. This broader understanding is essential for developing targeted prevention and treatment strategies that are effective across

diverse global populations. Additionally, investigation into biomarkers that could help establish causal links between these diseases offers promising directions for future research. Biomarkers such as C-reactive protein for inflammation, liver enzymes for NAFLD, and urinary markers for KSD could provide more definitive evidence of disease mechanisms and progression[6,12,13]. These biomarkers could potentially streamline diagnosis and enable earlier therapeutic intervention, thereby improving patient outcomes.

If the reported bidirectional associations are validated, they could transform current approaches to screening, diagnosing, and managing these common but often compartmentalized diseases. Recognizing interconnected pathways may promote the development of integrated treatment protocols and preventive measures. However, the translation of these findings into clinical practice requires rigorous validation of the results through methodologically sound research, ideally longitudinal in nature, to confirm these preliminary observations[14].

In conclusion, Jiang *et al*[1] provide important preliminary insights into the interconnected nature of GSD, NAFLD, and KSD. However, addressing the concerns of methodological rigor, diagnostic accuracy, and population diversity through well-designed follow-up studies will be crucial for advancing our understanding of these diseases and effectively translating research findings into practice. Therefore, further understanding the bidirectional associations among these diseases is not only a pursuit of academic interest but also a crucial step towards a more holistic understanding of metabolic diseases. This exploration could ultimately lead to breakthroughs in how these common and burdensome diseases are predicted, prevented, and treated, thereby reducing their extensive impact on global health.

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