

Methodological Limitations in Global Burden of Disease Alcohol Models: A Hepatology-oriented Perspective

Global Hastalık Yüğü Alkol Modellerinde Metodolojik Sınırlılıklar: Hepatoloji Odaklı Bir Değerlendirme

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ABSTRACT

To critically evaluate the methodological limitations of global burden of disease (GBD) alcohol models from a hepatology-oriented perspective and to highlight the inadequate representation of liver-specific outcomes in current risk frameworks. This review analyzes the GBD alcohol studies from 2016, 2018, and 2022, examining their interpretive inconsistencies, methodological approaches, and the underrepresentation of alcohol-attributable liver diseases. Key concepts such as theoretical minimum risk exposure level (TMREL) and non-drinker equivalence (NDE) are critically assessed for their clinical applicability in hepatology. Despite relying on similar datasets, GBD studies have presented conflicting conclusions regarding safe alcohol consumption thresholds. The 2016 analysis suggested cardiovascular benefits from low-to-moderate intake, while the 2018 report—without new data—concluded all alcohol levels are harmful. The 2022 models introduced TMREL and NDE but failed to adequately account for hepatotoxic effects such as alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma. Current frameworks overlook beverage type differences, consumption patterns, and comorbid liver conditions such as metabolic dysfunction-associated steatotic liver disease. Existing GBD alcohol models have significant methodological shortcomings that compromise their clinical applicability in hepatology. Future risk frameworks must integrate liver-centered endpoints, differentiate between beverage types,

Öz

Hepatoloji odaklı bir bakış açısıyla küresel hastalık yükü (GBD) alkol modellerinin metodolojik sınırlılıklarını eleştirel bir şekilde değerlendirmek ve mevcut risk çerçevelerinde karaciğere özgü sonuçların yetersiz temsilini vurgulamak. Bu derleme, 2016, 2018 ve 2022 yıllarına ait GBD alkol çalışmalarını analiz ederek, yorumlamadaki tutarsızlıkları, metodolojik yaklaşımları ve alkole bağlı karaciğer hastalıklarının yetersiz temsilini incelemektedir. Teorik minimum risk maruziyet düzeyi (TMREL) ve alkol kullanmayan eşdeğeri (NDE) gibi temel kavramlar, hepatolojideki klinik uygulanabilirlikleri açısından eleştirel olarak değerlendirilmektedir. Benzer veri kümelerine dayanmalarına rağmen, GBD çalışmaları güvenli alkol tüketim eşikleri konusunda çelişkili sonuçlar ortaya koymuştur. 2016 analizi, düşük ila orta düzeyde alımın kardiyovasküler faydalar sağladığını öne sürerken, 2018 raporu—yeni veriler olmaksızın—tüm alkol seviyelerinin zararlı olduğu sonucuna varmıştır. 2022 modelleri TMREL ve NDE'yi tanıtmıştır ancak alkolik hepatit, siroz ve hepatoselüler karsinom gibi hepatotoksik etkileri yeterince hesaba katmamıştır. Mevcut çerçeveler, içecek türü farklılıklarını, tüketim modellerini ve metabolik disfonksiyonla ilişkili steatotik karaciğer hastalığı gibi eşlik eden karaciğer rahatsızlıklarını göz ardı etmektedir. Mevcut GBD alkol modelleri, hepatolojideki klinik uygulanabilirliklerini tehlikeye atan önemli metodolojik eksikliklere sahiptir. Gelecekteki risk çerçeveleri, karaciğer merkezli sonlanım noktalarını entegre etmeli, içecek türleri

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ABSTRACT

and stratify risk by comorbidities. Evidence-based guidelines anchored in randomized controlled trials, systematic reviews, and meta-analyses are essential to provide clinically meaningful and organ-specific public health recommendations.

Keywords: Alcohol, liver cirrhosis, global burden of disease, risk modeling, MASLD

Öz

arasında ayırım yapmalı ve riski eşlik eden hastalıklara göre sınıflandırmalıdır. Klinik olarak anlamlı ve organa özgü halk sağlığı önerileri sunmak için randomize kontrollü çalışmalar, sistematik incelemeler ve meta-analizlere dayanan kanıta dayalı kılavuzlar şarttır.

Anahtar Kelimeler: Alkol, karaciğer sirozu, küresel hastalık yükü, risk modellemesi, MASLD

Introduction

The global burden of disease (GBD) alcohol studies from 2016, 2018, and 2022, though based on overlapping datasets, have generated contradictory conclusions. The 2016 analysis suggested a modest cardioprotective effect of low-to-moderate alcohol consumption, while the 2018 editorial—without new data—claimed that no amount of alcohol is safe, and the 2022 update introduced theoretical minimum risk exposure level (TMREL) and non-drinker equivalence (NDE) metrics recommending zero alcohol intake for those under 40, but permitting up to 1.87 drinks per day for older adults (1-4). These shifting thresholds illustrate the interpretive instability of observational models and the need for greater methodological consistency in population-level alcohol research.

Importantly, these models have consistently underrepresented liver-specific outcomes. Despite the liver being the primary site of alcohol-induced toxicity, GBD frameworks have prioritized cardiovascular metrics, neglecting alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma—conditions with high global burden and direct mechanistic links to alcohol metabolism (1,4). Furthermore, GBD models fail to distinguish between beverage types, overlooking the metabolic and toxicological variability across beer, wine, and distilled spirits, including differential effects on oxidative stress and hepatic inflammation (5,6).

Notably, this underrepresentation persists despite liver-related mortality accounting for a significant and growing proportion of alcohol-attributable deaths, particularly in regions with rising [metabolic dysfunction-associated steatotic liver disease (MASLD); previously known as non-alcoholic fatty liver disease (NAFLD)] prevalence and region-specific liver mortality trends (7,8).

Future alcohol policy models must integrate liver-centered endpoints and stratify risk by alcohol type, dose, and comorbidities such as MASLD. Transparent, evidence-based frameworks—grounded in randomized trials and meta-analyses—are essential to improve the clinical applicability and public credibility of future guidelines (9,10). These concerns echo the hepatology-centered orientation of recent discourse in the Journal of Hepatology and underscore the importance of specialty-driven modeling. Clearer communication of age-specific and organ-specific risks will enhance hepatology’s role in shaping alcohol-related health policy (Table 1) (1,11).

Interpretive Inconsistencies and Methodological Limitations

The GBD 2016 study, a comprehensive systematic analysis covering 195 countries, concluded that low-to-moderate alcohol consumption (e.g., 1-2 standard drinks per day) could provide some cardiovascular benefits (2). However, the 2018 editorial commentary, which did not introduce

Table 1. Comparative summary of GBD alcohol modeling studies (2016-2022) and hepatology-focused critique					
Study	Design	Methodology	Main findings	Limitations	Reference
GBD 2016	Systematic analysis (195 countries)	Observational cohort data	Low-to-moderate alcohol intake may have cardioprotective effects	Residual confounding, underreporting, no liver-specific stratification	(2)
GBD 2018	Editorial commentary	Narrative reinterpretation of 2016 data	No safe level of alcohol consumption	No new data, interpretative overreach, inconsistency with prior GBD	(3)
GBD 2022	Statistical modeling update	Statistical modeling using TMREL and NDE metrics by demographic strata	Risk varies by demographic group; zero alcohol recommended for <40 years	Complex metrics, limited clinical applicability, ambiguous guidance	(4)
Musto et al. (1)	Expert commentary (hepatology-oriented)	Critical review of GBD frameworks	Oversimplified messaging; lack of liver-specific indicators; need for hepatology-centered risk models	Highlights gap between population data and liver disease burden	(1)

GBD: Global burden of disease, TMREL: Theoretical minimum risk exposure level, NDE: Non-drinker equivalence

any new statistical analysis, contradicted these findings by claiming that all levels of alcohol consumption are harmful (3). The 2022 publication recalculated alcohol risks based on age, sex, and geographical differences, introducing TMREL and NDE metrics (4). These concepts, though statistically nuanced, are difficult to apply in practice and present challenges for policy development. The TMREL was determined to be zero alcohol for individuals under 40 years of age, while being acceptable at a certain level—up to 1.87 standard drinks—for those over 40. This age-based distinction has caused confusion in public health messaging and limits its applicability in clinical guidelines.

The GBD 2016 study's relative risk curve for all-cause outcomes showed a modest protective effect for low-level alcohol consumption, especially in cardiovascular diseases (2). However, the 2018 commentary dismissed this interpretation and emphasized a zero-risk stance (3). This sharp contrast demonstrates how observational data can be interpreted flexibly and, at times, inconsistently. The risk differential between abstainers and those consuming one drink per day is extremely small—and arguably not clinically significant—yet it formed the basis for a shift in global guidance (2-4). Such variability in interpretation underscores a broader methodological fragility in observational studies. These analyses are prone to biases, including underreporting, social desirability effects, and failure to account for binge drinking or irregular drinking patterns (9,10). For high-stakes decisions in health policy, reliance on observational data alone is insufficient; more robust methodologies such as randomized controlled trials (RCTs) and meta-analyses should be emphasized in future evaluations (10).

The Case for Liver-specific Risk Modeling

One of the fundamental methodological shortcomings identified by Musto et al. (1) is the inadequate representation of alcohol-attributable liver diseases in GBD alcohol models.

Hepatic complications such as alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma, which are associated with high morbidity and mortality, constitute a significant proportion of the global alcohol-related disease burden. The direct toxic processes initiated by alcohol in the liver should be assessed before systemic effects, and the liver must be recognized as the primary target organ of alcohol toxicity (1,7,8).

Therefore, future public health policies and risk prediction models should prioritize liver-specific parameters. Although hepatic consequences—including alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma—are major contributors to morbidity and mortality globally, they receive disproportionately less attention compared to cardiovascular endpoints. In hepatology and gastroenterology practice, hepatic effects are at least as critical as cardiovascular ones and must be adequately

represented in population-level modeling. Moreover, subclinical hepatic inflammation and fibrosis progression may go undetected in individuals consuming “moderate” amounts, especially when risk thresholds are generalized across populations (1,2,4).

Additionally, the term “alcohol” in GBD reports is typically applied generically, neglecting key differences among beverage types. Ethanol-containing drinks such as beer, wine, and distilled spirits differ significantly in polyphenol content, metabolic profiles, and associated toxicities (5). The cardioprotective properties of red wine, attributed to polyphenols such as resveratrol, have been acknowledged in the context of the French paradox (12), and moderate red-wine intake is even integrated into the Mediterranean diet, which is widely regarded as a model for healthy eating (6,12). In conditions such as MASLD/NAFLD, alcohol type, dosage, and comorbidities should be considered for personalized clinical evaluation.

While TMREL and NDE offer statistically sophisticated tools for quantifying alcohol-related harm, their clinical and public-health utility is undermined by key limitations as illustrated in Figure 1 (4).

These metrics fail to account for liver-specific outcomes—despite the liver being the primary organ affected by alcohol toxicity—and present age-stratified risk thresholds that complicate public messaging. The abstraction inherent in these models obscures actionable guidance, particularly in hepatology, where alcohol-induced injury is cumulative, organ-specific, and often irreversible (1,4,7,8,11).

Without integration of beverage type, comorbidities

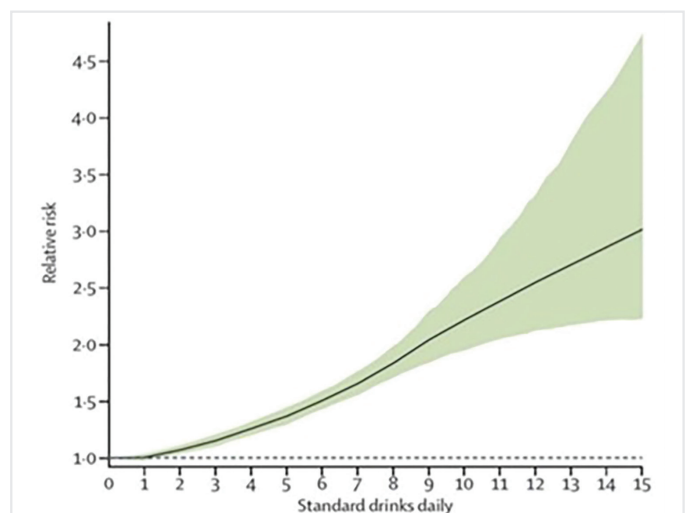


Figure 1. Weighted relative risk of alcohol consumption across all attributable causes by daily standard drink intake, using age-standardized weights determined by the DALY rate in 2016 for both sexes. The dotted line represents the reference point for a relative risk of 1

DALY: Disability-adjusted life-year, Source: Adapted from GBD 2022 (4); created by authors

(e.g., MASLD), and consumption patterns, such models risk oversimplification of complex pathophysiological processes.

In addition, such models rarely consider non-linear hepatotoxic thresholds, where small increases in intake may disproportionately escalate hepatic injury, especially in sensitized populations (1,4,7).

In clinical hepatology, it is frequently observed that individuals reporting what would typically be classified as “moderate” alcohol consumption nonetheless present with elevated transaminase levels, hepatic steatosis on imaging, or even clinical features consistent with alcohol-related liver injury (3,4).

Notably, such presentations often occur at intake levels considered low-risk by population-based models, underscoring a significant disconnect between epidemiological projections and real-world hepatic outcomes. The GBD 2016 analysis (2) visually demonstrates a progressive increase in relative risk for all-cause disease burden with each additional standard drink consumed per day—even within low consumption ranges. These data reinforce the notion that minimal alcohol intake may still pose measurable health risks, particularly to the liver, and call into question the validity of universal “safe” thresholds. This highlights the need for organ-specific, clinically grounded risk-stratification models that better reflect individual vulnerability and hepatotoxic potential (1,4,7,8).

Finally, alcohol use, apart from the liver or cardiovascular system, carries the risk of addiction. Even in moderate use, alcohol can cause dependence in both experimental animals (13) and humans (14), and alcohol addiction remains a significant public-health concern (15,16). The impact of alcohol addiction should be systematically considered when evaluating the full spectrum of alcohol-related health risks. Furthermore, liver and cardiovascular complications progress more rapidly and severely in individuals with alcohol dependence (17,18).

Conclusion

In conclusion, inconsistencies in GBD alcohol studies compromise both the credibility of public messaging and its clinical applicability (1-4). Future guidelines should be anchored in high-certainty evidence—such as RCTs and meta-analyses—and must include hepatology-specific indicators, differentiation by beverage type, and pragmatic risk communication strategies (9,10). Current clinical guidelines such as those jointly issued by EASL, EASD, and EASO, emphasize individual variability in alcohol type, metabolic comorbidities, and drinking patterns; therefore, future GBD updates should align with this multidimensional approach (1,11). Ultimately, risk-stratification models must be organ-specific, evidence-based, and clinically interpretable—reflecting the true complexity of alcohol’s

hepatotoxic potential in populations increasingly affected by MASLD (1,4,7,8,11).

Footnotes

Authorship Contributions

Concept: A.B., Design: A.B., Analysis or Interpretation: A.B., M.U., Literature Search: A.B., M.U., T.U., Writing: A.B., M.U., T.U.

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