Wang *et al. Metab Target Organ Damage* 2023;3:14
DOI: 10.20517/mtod.2023.23

Metabolism and Target Organ Damage

Commentary

Open Access

Check for updates

Commentary: Of women, liver, and heart

Jun Wang[1], **Amedeo Lonardo**[2]

[1]Molecular Epidemiology at Department of Biomarker Sciences, Gilead Sciences, Inc. Foster City, CA 94404, USA.
[2]Department of Internal Medicine, Azienda Ospedaliero-Universitaria, Modena 41026, Italy.

Correspondence to: Prof. Amedeo Lonardo, M.D. Department of Internal Medicine, Azienda Ospedaliero-Universitaria, 1135 Via Giardini, Modena 41100, Italy. E-mail: a.lonardo@libero.it

How to cite this article: Wang J, Lonardo A. Commentary: Of women, liver, and heart. *Metab Target Organ Damage* 2023;3:14. https://dx.doi.org/10.20517/mtod.2023.23

Received: 8 Jul 2023 **First Decision:** 29 Aug 2023 **Revised:** 31 Aug 2023 **Accepted:** 4 Sep 2023 **Published:** 7 Sep 2023

Academic Editor: Mariana Machado **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

This commentary is devoted to a recent study by Ren and Zheng (Nutr Metab Cardiovasc Dis. 2023;33:1349-1357). These authors analyzed sex-stratified long-term outcomes relevant to all-cause and cardiovascular field outcomes among 2,627 nonalcoholic fatty liver disease (NAFLD) adults enrolled in the 2000-2014 National Health and Nutrition Examination Surveys and identified with United States Fatty Liver Index (US FLI) score. Data have shown that, compared to women, men were exposed to a significantly higher all-cause mortality and the maximal risk was seen among those who had obesity and type 2 diabetes. However, women aged ≤ 60 years had a higher risk of death owing to cardiovascular disease (CVD). Conversely, no significantly increased risk of death from CVD was observed among women over 60 years compared to men of the same age group. The study by Ren and Zheng further fosters our understanding of cardiometabolic risk factors, illustrating sex differences present in NAFLD. The distinct impact of NAFLD on CVD by sex and age suggests that cardiometabolic comorbidities may be particularly underestimated among young and middle-aged women with NAFLD. The research by Ren and Zhang may stimulate future investigations exploring the molecular and cellular grounds underlying these findings, notably including the role of fibrosing NAFLD as a strong risk modifier of CVD. In conclusion, an improved understanding of sex-specific regulation of human metabolism in the liver and other key metabolic organs is a research priority finalized for implementing precision medicine approaches in NAFLD arena.

Keywords: Cardiovascular risk, nonalcoholic fatty liver disease, sex differences

BACKGROUND

Definitions and burden

While playing a major role in different physiological processes, at variance with the adipose tissue, the liver is not involved in the storage of fatty substrates under normal conditions[1]. Intrahepatic accumulation of even minimal amounts of fat is indeed associated with insulin resistance, hepatic metaflammation, and the ensuing risk of fibrosis progression in a subset of individuals[1,2]. These notions explain why steatosis (i.e., intrahepatic accumulation of fat which occurs in the absence of alcohol, drugs, viral infections, autoimmunity, or specific genetic disorders of metabolism (hence "nonalcoholic") is a true disease [namely "nonalcoholic fatty liver disease" (NAFLD)] rather than an irrelevant variation from normality[3,4]. Although displaying a mutual and bi-directional relationship with the metabolic syndrome (MetS), NAFLD is not comprised in the definition of the MetS, which embraces a cluster of factors including expanded visceral adiposity, impaired glucose metabolism, arterial hypertension, and dyslipidemia[5,6]. However, studies have shown that adding NAFLD to the definition of MetS allows the identification of more severe oxidative stress and endothelial dysfunction and also helps in identifying a larger fraction of the population at metabolic risk[7,8].

Affecting 38% of the population globally, NAFLD is the leading cause of chronic liver disease worldwide, and its prevalence is also projected to increase in the future[9]. As a systemic disorder, the spectrum of manifestations of NAFLD is not limited to hepatic manifestations and complications but also includes metabolic disorders, extra-hepatic cancers, and cardiovascular disease (CVD)[1,10]. Of concern, cardiovascular mortality is the first cause of death among NAFLD patients[9,10]. The long-term risk of fatal or non-fatal CVD events is strongly associated with more advanced NAFLD forms that exhibit higher fibrosis stages, supporting the notion that NAFLD is probably an independent risk factor for morbidity and mortality owing to CVD[11].

In 2020, in an attempt to overcome the critiques regarding the limitations and potentially stigmatizing consequences of using the term "NAFLD", a panel of experts from 22 countries proposed the novel metabolic dysfunction-associated fatty liver disease (MAFLD) nomenclature (reviewed in[12]). The MAFLD definition, which has met universal consensus in Latin America, North Africa and the Middle East, indicates that the motivations to abandon the old nosography prevail on the reasons for keeping it[12]. MAFLD is defined by liver steatosis among patients who have either type 2 diabetes or obesity. Interestingly, the presence of at least two, among the criteria belonging to the MetS domain (expanded abdominal adiposity; arterial hypertension; hypertriglyceridemia; low HDL-cholesterol; pre-diabetes; insulin resistance; and subclinical systemic inflammatory state), is considered to be equivalent to either obesity or diabetes[12]. As discussed in this commentary, the above-listed dysmetabolic traits are deeply implicated in the determination of the risk of CVD.

In 2023, a new nomenclature was proposed by a panel of 236 experts from 56 countries to replace MAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD)[13]. Furthermore, consensus was reached regarding changing the definition to include the presence of at least one of five cardiometabolic risk factors in addition to hepatic steatosis, while those with no metabolic parameters were classified as cryptogenic steatotic liver disease. The new nomenclature highlights the close link between MASLD and cardiovascular (CV) risk factors.

Sex differences

Over the last 10 years, in various fields of medical research, there has been an increasing interest in *sex differences* that principally result from sex chromosomes and sex hormones, as opposed to *gender differences*

that are influenced by socio-cultural factors[14]. Given that sex and gender differences bolster variability in disease pathobiology from development to progression, consideration of sex, age, and reproductive status (e.g., menarche and menopause) is presently deemed key in determining precision medicine approaches in NAFLD arena[15]. Like NAFLD, and before sexual dimorphism became apparent in NAFLD arena, a robust line of research has highlighted sexual dimorphism in cardiometabolic disorders[14,16,17].

Aim

In the previously described context, our Commentary is devoted to a recent study by Ren and Zheng[16]. This study aimed at analyzing sex-stratified long-term outcomes relevant to all-cause and CV field outcomes among 2627 NAFLD adult patients (65.4% were men), identified with United States Fatty Liver Index (US FLI) score of ≥ 30, enrolled in the 2000-2014 National Health and Nutrition Examination Surveys. Data have shown that, compared to women, men were exposed to a significantly higher all-cause mortality (crude or unadjusted mortality rate 12.4% *vs.* 7.7%; $P = 0.005$) and the maximal risk was seen among those who had obesity (body mass index > 30 kg/m^2) and diabetes. However, women aged ≤ 60 years had a higher risk of death owing to CVD (compared to women, adjusted HR for men: 0.214, 95%CI: 0.053 - 0.869, $P = 0.031$). On the other hand, no significantly increased risk of death from CVD was observed among women older than 60 years compared to men in the same age category. The authors conclude that mortality owing to CVD is affected by age and sex, with young and middle-aged women being at a higher risk of dying due to CVD[18].

COMMENT

The study by Ren and Zheng seems to be designed in agreement with recent calls for full consideration of sex and reproductive status in NAFLD arena[15]. As such, it contributes to establishing a novel standard of how future investigations on NAFLD epidemiology and natural history should be conducted.

Sex differences in NAFLD natural course

As for other metabolic diseases, women are seemingly protected from the development of disease. However, once diseases occur, their course tends to be more aggressive. This can result from a variety of explanations, including delayed diagnosis and immunological pathomechanisms. Regarding NAFLD, this point is strongly corroborated by recent data. Balakrishnan *et al.* have published a milestone meta-analytic review of 54 studies totaling 62,239 cases with NAFLD, 5,428 with NASH, and 6,444 with advanced fibrosis[19]. Data have shown that, compared to men, women in the general population were protected from NAFLD [having a 19% lower risk of NAFLD (pooled risk ratio [RR], 0.81; 95%CI: 0.68-0.97; $I^2 = 97.5\%$)] while the odds of NASH were similar to men (RR, 1.00; 95%CI: 0.88-1.14; $I^2 = 85.1\%$), and the risk of advanced fibrosis was 37% higher (RR, 1.37; 95%CI: 1.12-1.68; $I^2 = 74.0\%$). Age of 50, a surrogate index of menopausal status, was a modifier of the effect of sex on disease severity, odds of NASH and advanced fibrosis being substantially higher in women ≥ 50 years (RR, 1.17; 95%CI: 1.01-1.36; and RR, 1.56; 95%CI: 1.36-1.80, respectively) while sex differences in NASH and advanced fibrosis were attenuated, among younger cohorts.

Sex differences in NAFLD pathobiology as related to cardiovascular risk

Physiopathological explanations underlying the findings reported above include sex differences in the supply and utilization of energetic substrates, storage of excess lipids, and mobilization of accumulated lipids in metabolic organs[20,21].

For any given BMI, compared to men, women of fertile age have a more abundant mass of adipose tissue, which is typically located at subcutaneous sites, predominantly in the gluteo-femoral area[22]. Therefore, sexual dimorphism in adipose tissue, skeletal muscle, and liver substrate metabolism accounts for sex differences in tissue-specific insulin sensitivity and lays the foundations for variable risks of target tissue

damage and different profiles of cardiometabolic risk[21]. Women of fertile age are protected from cardiometabolic diseases compared to BMI and age-matched men, although this protective effect wanes post-menopausally: one explanation could be owing to post-menopausal impaired glucose metabolism[21].

However, it is apparent from the study by Ren and Zheng that NAFLD abrogates the natural protection women have from CVD. Results from Ren and Zheng are consistent with an earlier longitudinal study, which also found that the protective effect of female sex on CVD in the general population diminished or no longer existed among women with NAFLD[23]. A recent meta-analysis of over 108,000 people with NAFLD (44% were women) also reported that the female sex was associated with more than doubled risk of cardiovascular events and mortality (odds ratio = 2.12, 95%CI: 1.65-2.73)[24]. However, both prior studies did not find a stronger association (or higher risk) in young and middle-aged women compared to older women as seen in Ren and Zhang's study. Young-onset arterial hypertension could be one of the mechanisms underlying NAFLD's negative influx on cardiovascular health in women. Kim *et al.* investigated the hypothesis that sex might modulate the association between NAFLD and incident hypertension in young adults < 40 years[25]. To this end, a study population of 85,789 women and 67,553 men aged < 40 years who were hypertension-free at the baseline were followed for a median follow-up of 4.5 years to ascertain whether incident hypertension was in relationship with the NAFLD status. Data have shown stronger associations between NAFLD and incident hypertension in women, regardless of obesity/central obesity (all *P*-values for interaction by sex < 0.001), supporting the notion that NAFLD, as a potential risk factor for young-onset hypertension, exerts a proportionally superior impact in women and among those with more severe NAFLD. Alternatively, women who developed NAFLD at a younger age (e.g., during pre-menopausal) may lose the protection from sex-related or hormonal factors while having to bear the metabolic burden of more severe insulin resistance and low-grade chronic inflammation at a younger age, thus rendering them more susceptible to CVD.

STRENGTHS AND LIMITATIONS OF THE STUDY

Limitations in the study design include its retrospective design, missing data on menstrual cycle irregularities, polycystic ovary syndrome, use of exogenous hormones (e.g., menopausal hormone therapy or oral contraceptives), serum concentrations of sex hormones, body fat distribution, as well as identification of cases with non-idiopathic, i.e., secondary arterial hypertension[26]. In addition, NAFLD was diagnosed with US FLI which was proposed in 2015 by Ruhl & Everhart[27] as an improvement of the original fatty liver index (FLI) conceived by Bedogni *et al.*[28]. The US FLI includes GGT activity, waist circumference, age, race-ethnicity, fasting insulin and fasting glucose aiming at targeting the multi-ethnic U.S. population. Thus, the inclusion of racial-ethnic identity in the US FLI is an important distinguishing feature from FLI[27]. However, neither of the two indices (US FLI and FLI) incorporates major modifiers of NAFLD epidemiology, such as sex and reproductive status[29]. These limitations pave the way for more research on more accurate non-invasive algorithms in NAFLD field. Furthermore, although not a focus of Ren and Zhang's study, future studies assessing sex differences in cardiovascular incidence and mortality in more advanced NAFLD, such as nonalcoholic steatohepatitis or advanced fibrosis (fibrosis stage F3 or F4), are needed as patients with more progressive forms of NAFLD are usually at higher risk for cardiovascular occurrence[30].

RESEARCH AGENDA AND CONCLUSIONS

The study by Ren and Zheng has met a good reception in as much as it develops further, with specific reference to cardiometabolic risk factors, the robust line of research on sexual dimorphism in NAFLD[26]. In particular, the distinct impact of NAFLD on CVD by sex and age suggests that such cardiometabolic comorbidities may be underestimated in women with NAFLD, especially in young and middle-aged

women. It may forerun additional investigations exploring the molecular and cellular grounds explaining these findings and, importantly, focusing on the role of fibrosis stages of NAFLD as potential risk modifiers of CVD[26,31]. In a broader context, further promoting our understanding of sex-specific regulation of human metabolism in key metabolic organs, notably including the liver, is a research priority to implement precision medicine approaches to prevent and manage cardiometabolic complications in NAFLD patients[21,32].

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Wang J, Lonardo A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Jun Wang, Employment and stock of Gilead Sciences. Amedeo Lonardo, no conflicts of interest to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Lonardo A. Extra-hepatic cancers in metabolic fatty liver syndromes. *Explor Dig Dis* 2023;2:11-7. DOI
2. Petersen KF, Dufour S, Li F, Rothman DL, Shulman GI. Ethnic and sex differences in hepatic lipid content and related cardiometabolic parameters in lean individuals. *JCI Insight* 2022;7:e157906. DOI PubMed PMC
3. Lonardo A, Lombardini S, Ricchi M, Scaglioni F, Loria P. Review article: hepatic steatosis and insulin resistance. *Aliment Pharmacol Ther* 2005;22 Suppl 2:64-70. DOI PubMed
4. Han SK, Baik SK, Kim MY. Correspondence on letter regarding "non-alcoholic fatty liver disease: definition and subtypes". *Clin Mol Hepatol* 2023;29:817-9. DOI PubMed PMC
5. Lonardo A, Leoni S, Alswat KA, Fouad Y. History of nonalcoholic fatty liver disease. *Int J Mol Sci* 2020;21:5888. DOI PubMed PMC
6. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2010;375:181-3. DOI PubMed
7. Musso G, Gambino R, Bo S, et al. Should nonalcoholic fatty liver disease be included in the definition of metabolic syndrome? a cross-sectional comparison with adult treatment panel III criteria in nonobese nondiabetic subjects. *Diabetes Care* 2008;31:562-8. DOI
8. Fu CE, Yong JN, Ng CH, et al. The prognostic value of including non-alcoholic fatty liver disease in the definition of metabolic syndrome. *Aliment Pharmacol Ther* 2023;57:979-87. DOI PubMed
9. Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol* 2023;79:842-52. DOI PubMed
10. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013;10:330-44. DOI PubMed
11. Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:903-13. DOI

12. Lonardo A. Renaming NAFLD to MAFLD: could the lde system assist in this transition? *J Clin Med* 2021;10:492. DOI PubMed PMC
13. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023;20:S0168-8278(23)00418. DOI PubMed
14. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet* 2020;396:565-82. DOI PubMed PMC
15. Lonardo A, Nascimbeni F, Ballestri S, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. *Hepatology* 2019;70:1457-69. DOI PubMed PMC
16. Regensteiner JG, Reusch JEB. Sex differences in cardiovascular consequences of hypertension, obesity, and diabetes: JACC focus seminar 4/7. *J Am Coll Cardiol* 2022;79:1492-505. DOI PubMed PMC
17. Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. *Diabetologia* 2023;66:986-1002. DOI PubMed PMC
18. Ren R, Zheng Y. Sex differences in cardiovascular and all-cause mortality in nonalcoholic fatty liver disease in the US population. *Nutr Metab Cardiovasc Dis* 2023;33:1349-57. DOI PubMed
19. Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women have a lower risk of nonalcoholic fatty liver disease but a higher risk of progression vs men: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2021;19:61-71.e15. DOI PubMed PMC
20. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a sexual dimorphic disease: role of gender and reproductive status in the development and progression of nonalcoholic fatty liver disease and inherent cardiovascular risk. *Adv Ther* 2017;34:1291-326. DOI PubMed PMC
21. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nat Rev Endocrinol* 2021;17:47-66. DOI PubMed
22. Lonardo A, Suzuki A. Sexual dimorphism of NAFLD in adults. focus on clinical aspects and implications for practice and translational research. *J Clin Med* 2020;9:1278. DOI PubMed PMC
23. Allen AM, Therneau TM, Mara KC, et al. Women with nonalcoholic fatty liver disease lose protection against cardiovascular disease: a longitudinal cohort study. *Am J Gastroenterol* 2019;114:1764-71. DOI PubMed PMC
24. Khalid YS, Dasu NR, Suga H, Dasu KN, Reja D, Shah A, McMahon D, Levine A. Increased cardiovascular events and mortality in females with NAFLD: a meta-analysis. *Am J Cardiovasc Dis* 2020;10:258-271. PubMed PMC
25. Kim Y, Chang Y, Ryu S, et al. Nonalcoholic fatty liver disease and risk of incident young-onset hypertension: effect modification by sex. *Nutr Metab Cardiovasc Dis* 2023;33:1608-16. DOI
26. Ciardullo S. Commentary on Kim et al. Silent threats: how NAFLD and hypertension team up in young adults, and the role of sex. *Nutr Metab Cardiovasc Dis* 2023;33:1617-8. DOI
27. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States national health and nutrition examination survey. *Aliment Pharmacol Ther* 2015;41:65-76. DOI PubMed
28. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006;6:33. DOI PubMed PMC
29. Lonardo A, Ballestri S, Bedogni G, Bellentani S, Tiribelli C. The fatty liver index (FLI) 15 years later: a reappraisal. *Metab Target Organ Damage* 2021;1:10. DOI
30. Kasper P, Martin A, Lang S, et al. NAFLD and cardiovascular diseases: a clinical review. *Clin Res Cardiol* 2021;110:921-37. DOI PubMed PMC
31. Ballestri S, Mantovani A, Di Girolamo M, Baldelli E, Capitelli M, Lonardo A. Liver fibrosis in nonalcoholic fatty liver disease patients: noninvasive evaluation and correlation with cardiovascular disease and mortality. *Metab Target Organ Damage* 2023;3:1. DOI
32. Lonardo A. Precision medicine in nonalcoholic fatty liver disease. *J Gastroenterol Hepatol* 2022;37:1175-8. DOI PubMed