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***Retrospective Study*****Sex and racial disparities in non-alcoholic fatty liver disease-related cardiovascular events: National inpatient sample analysis (2019)**

Desai R *et al.* NAFLD-related cardiovascular events

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**Abstract****BACKGROUND**

Non-alcoholic fatty liver disease (NAFLD) increases cardiovascular disease (CVD) risk irrespective of other risk factors. However, large-scale cardiovascular sex and race differences are poorly understood.

**AIM**

To investigate the relationship between NAFLD and major cardiovascular and cerebrovascular events (MACCE) in subgroups using a nationally representative US inpatient sample.

**METHODS**

We examined National Inpatient Sample (2019) to identify adult hospitalizations with NAFLD by age, sex, and race using ICD-10-CM codes. Clinical and demographic characteristics, comorbidities, and MACCE-related mortality, acute myocardial infarction (AMI), cardiac arrest, and stroke were compared in NAFLD cohorts by sex

and race. Multivariable regression analyses were adjusted for sociodemographic characteristics, hospitalization features, and comorbidities.

## RESULTS

We examined 409130 hospitalizations [median 55 (IQR 43-66) years] with NFALD. NAFLD was more common in females (1.2%), Hispanics (2%), and Native Americans (1.9%) than whites. Females often reported non-elective admissions, Medicare enrolment, the median age of 55 (IQR 42-67), and poor income. Females had higher obesity and uncomplicated diabetes but lower hypertension, hyperlipidemia, and complicated diabetes than males. Hispanics had a median age of 48 (IQR 37-60), were Medicaid enrollees, and had non-elective admissions. Hispanics had greater diabetes and obesity rates than whites but lower hypertension and hyperlipidemia. MACCE, all-cause mortality, AMI, cardiac arrest, and stroke were all greater in elderly individuals ( $P < 0.001$ ). MACCE, AMI, and cardiac arrest were more common in men ( $P < 0.001$ ). Native Americans (aOR 1.64) and Asian Pacific Islanders (aOR 1.18) had higher all-cause death risks than whites.

## CONCLUSION

Increasing age and male sex link NAFLD with adverse MACCE outcomes; Native Americans and Asian Pacific Islanders face higher mortality, highlighting a need for tailored interventions and care.

**Key Words:** Non-alcoholic fatty liver disease; Cardiovascular disease; Major cardiovascular and cerebrovascular events; Sex/gender disparities; Mortality

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**Core Tip:** Non-alcoholic fatty liver disease is associated with adverse major cardiovascular and cerebrovascular events, especially with increasing age and male sex. Native Americans and Asian Pacific Islanders had higher all-cause mortality.

## **INTRODUCTION**

With the global rise in <sup>8</sup>obesity and metabolic diseases, non-alcoholic fatty liver disease (NAFLD) has become a prevalent condition. It is now widely recognized that NAFLD has numerous extrahepatic consequences<sup>[1]</sup> including <sup>3</sup>an increased risk of cardiovascular disease (CVD) independent of traditional cardiovascular risk factors<sup>[2,3]</sup>. Understanding NAFLD and its impact on patient outcomes is of utmost importance, given its intricate underlying mechanisms. This is particularly significant because various modifiable behavioral factors play a role in the development and progression of the condition. Therefore, gaining insight into NAFLD and exploring the potential effects of lifestyle interventions can significantly enhance patient outcomes<sup>[4]</sup>. Risk factors for NAFLD are well-established and can be categorized as modifiable, such as smoking, sedentary lifestyle, poor nutrition habits, and physical inactivity, or non-modifiable, including genetic background, fat metabolism, and age<sup>[5]</sup>. The exploration of sex and racial disparities in cardiovascular outcomes related to NAFLD is an area that has received limited attention and remains largely unexplored on a broader scale. The current body of evidence in this regard is lacking, highlighting the need for further research to address these gaps in knowledge<sup>[6]</sup>. Therefore, this study was conducted to investigate <sup>1</sup>the association between NAFLD and major cardiovascular and cerebrovascular events (MACCE) using a nationally representative sample in the United States.

## **MATERIALS AND METHODS**

### ***Source of data***

The 2019 National Inpatient Sample (NIS) database of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and

Quality was examined. The NIS is the largest all-payer inpatient healthcare dataset accessible to the public in the United States. With an annual average of 7 million unweighted discharges (and about 35 million weighted nationwide discharges), the dataset comprises around 20% of US hospitalizations across 50 states. For each inpatient admission, the NIS includes one primary diagnosis and up to 24 sary discharge diagnoses. Due to the de-identified nature of NIS data, permission from the IRB is not mandatory. The HCUP website provides additional information regarding the database<sup>[7]</sup>.

### *Study population*

We identified all hospitalizations with NAFLD in the 2019 NIS database using the K76.0 ICD-10-CM code. We included hospitalizations of adults (18 years and older) with a primary or secondary diagnosis of NAFLD. The latter code has been demonstrated to have a positive predictive value of over 91% for identifying NAFLD and has been previously recommended for use by an expert panel consensus statement for identifying NAFLD in administrative health databases or electronic health records, allowing researchers to ensure accurate identification and classification of NAFLD cases<sup>[8,9]</sup>.

### *Study outcomes*

The primary outcome of interest was to identify gender and racial disparities in NAFLD- related MACCE, including all-cause mortality, acute myocardial infarction (AMI), cardiac arrest, and stroke. Secondary outcomes included clinical, demographic, and hospital-level characteristics, and comorbidities associated with NAFLD hospitalizations by ethnicity and gender. Last, we evaluated and compared across subgroups of gender and race the median duration of hospital stay (in days) and total hospital charges (in USD) due to NAFLD-related MACCE in NAFLD hospitalizations.

### *Statistical analyses*

The prevalence of NAFLD was calculated per sex and race categories. Using Pearson's Chi-square test for categorical variables and the Mann Whitney *U* test for continuous variables, we compared the clinical, demographic and hospital-level characteristics of NAFLD hospitalizations between subgroups of interest: sex and race. Discharge records with missing data for sex or race (< 5% of data) were excluded from analysis. The continuous and categorical variables were expressed as medians and percentages, respectively. To determine statistical significance, a two-tailed alpha level of less than 0.05 was used. The NIS database discharge weight (DISCWT) was utilized to derive national estimates and complex survey modules were used to perform analyses. Multivariate logistic regression analyses were performed to evaluate the independent associations of sex and race with NAFLD-related MACCE, while adjusting for social-demographic and hospitalization characteristics and comorbidities: age, sex, race, household income quartile, payer status, type of admission, hospital bed size, location/teaching status, region, comorbidities including hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking, peripheral vascular disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft (CABG), drug abuse, prior stroke or transient ischemic attack, and prior venous thromboembolism (VTE). The results of logistic regressions were reported using adjusted odds ratios (aOR), 95%CI, and *P*-values. The SPSS statistics 25.0 software package (IBM Corp, Armonk, New York, United States) was used for all statistical analyses.

## **RESULTS**

### ***Participant characteristics***

Our study included 409130 NAFLD hospitalizations [median age = 55 years (IQR = 43-66)]. Social-demographic and clinical characteristics, comorbidities and outcomes were stratified based on sex and race independently.

### ***Prevalence of NAFLD***

The prevalence of NAFLD was higher in males compared to females (1.5% *vs* 1.2%). Among races, the prevalence of NAFLD was highest in Hispanic (2.0%) and Native American (1.9%) patients, compared to White (1.3%), Black (1.0%), Asian-Pacific Islander (1.2) and Other (1.5%). Blacks had the lowest prevalence of NAFLD (all  $P < 0.001$ , Table 1).

### ***Sex disparities in social-demographic and clinical characteristics, comorbidities and outcomes***

The females had a median age of 55 years (IQR 42-67). Despite a similar length of stay between genders, females were charged higher costs associated with the admission (41695 USD *vs* 40952 USD). Female patients were more often from lowest income quartile, Medicare enrollees, and had non-elective admissions. Compared to males, females demonstrated lower rates of hypertension, hyperlipidemia, complicated diabetes but higher rates of obesity and uncomplicated diabetes (Table 2).

### ***Racial disparities in social-demographic and clinical characteristics, comorbidities and outcomes***

Despite a similar length of stay across all races, the Hispanics [median age: 48 years (IQR 37-60)] and the Asian-Pacific Islanders (median age: 56 years) were charged the highest median costs (48351 USD and 51003 USD). The majority of the Hispanic patients came from the lowest income quartile (37.3%), were Medicaid enrollees (33.5%), and underwent non-elective admissions (85.7%). The Hispanics exhibited lower prevalence rates of hypertension, hyperlipidemia, but higher rates of diabetes and obesity compared to Whites (Tables 3).

### ***Odds of MACCE, all-cause mortality, AMI, cardiac arrest, and stroke***

Males had a greater risk of MACCE (aOR 1.22) ( $P < 0.001$ ), AMI (aOR 1.35) ( $P < 0.001$ ) and Cardiac arrest (aOR 1.54) ( $P < 0.001$ ). Native Americans (aOR 1.64) ( $P < 0.001$ ) followed by Asian Pacific Islanders (aOR 1.18) ( $P < 0.001$ ) had significantly higher odds

of all-cause mortality compared to whites (aOR 1.00) ( $P < 0.001$ ) (Table 4). Older patients had significantly higher odds of MACCE (aOR 3.01) ( $P < 0.001$ ), all-cause mortality (aOR 4.13) ( $P < 0.001$ ), AMI (aOR 2.81) ( $P < 0.001$ ), cardiac arrest (aOR 2.24) ( $P < 0.001$ ) and stroke (aOR 2.58) ( $P < 0.001$ ) (Table 4).

## **DISCUSSION**

NAFLD is associated with obesity and insulin resistance as comorbidities. In obese individuals, the expansion of adipose tissue results in adipocyte dysfunction and increased insulin resistance, thereby leading to lipolysis. This results in elevated levels of circulating free fatty acids and leptin, with decreasing adiponectin levels, ultimately leading to intrahepatic fat accumulation. The situation is exacerbated by a diet high in carbohydrates and fat, which further contributes to fat accumulation in the liver<sup>[10]</sup>. Additionally, the expansion of adipose tissue promotes infiltration of immune cells into both adipocytes and the liver, leading to chronic inflammation. Prolonged inflammation triggers hepatic stellate cells to mediate fibrosis, ultimately resulting in cirrhosis. Obesity is an independent risk factor for cardiovascular events, as it can also contribute to the development of diabetes mellitus, hyperlipidemia, hypertension, and sleep disorders, thereby indirectly exacerbating cardiovascular risks<sup>[11]</sup>.

Strong evidence indicates that NAFLD causes chronic inflammation through the release of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ , CRP), hepatokines (FGF-21, fetuin-A), adhesion molecules, and procoagulant factors from the liver, resulting in endothelial dysfunction with systemic atherosclerosis, which makes the NAFLD an independent risk factor for cardiovascular disease<sup>[12-14]</sup>. Additionally, NAFLD is associated with a higher risk of left ventricular hypertrophy<sup>[15]</sup>, left ventricular diastolic dysfunction<sup>[16]</sup>, and atrial fibrillation<sup>[17]</sup>, all of which contribute to adverse cardiovascular outcomes. It has also been reported that the presence of NAFLD is associated with poor clinical outcomes in STEMI patients and that greater severity of NAFLD is associated with higher mortality rates in such patients<sup>[18]</sup>. We intended to examine the differences in cardiac and cerebrovascular outcomes (MACCE) between different sex and racial



groups of NAFLD patients. This was a large-scale retrospective cross-sectional study comparing NAFLD outcomes by ethnicity and gender.

The social-demographic and clinical characteristics and comorbidities of the patients were compared over groups of sex and race. The comorbidities studied in these groups included hypertension, DM, hyperlipidemia, obesity, PVD, prior MI, prior stroke, prior VTE, chronic pulmonary disease, tobacco use, and drug use. An analysis conducted in 2015 as part of the Framingham Heart Study revealed a strong independent association between hepatic steatosis and subclinical cardiovascular disease outcomes, regardless of other metabolic risk factors<sup>[19]</sup>. Furthermore, In a study using data from NHANES, patients with NAFLD demonstrated to develop increased odds of developing cardiovascular disease<sup>[20]</sup>. Their study lacked to control for conditions like hyperlipidemia or systemic hypertension. However, this limitation was addressed in our study through adjustments for a comprehensive range of comorbid conditions, including hyperlipidemia and hypertension, thereby enhancing the robustness of our findings. Patients with NAFLD often have one or more components of the metabolic syndrome, which is a known risk factor for cardiovascular disease<sup>[21]</sup>. This makes NAFLD independently associated with cardiovascular disease. Moreover, our study revealed that the prevalence of hypertension, diabetes with and without chronic complications, hyperlipidemia, and obesity were significantly higher in all racial groups among NAFLD patients. While the relationship between NAFLD and diabetic complications remains unclear, it is worth noting that individuals with steatosis and type 1 diabetes may be at a heightened risk of developing cardiovascular disease and subsequent cardiovascular complications<sup>[22]</sup>. Therefore, it is of utmost importance to screen high-risk groups for NAFLD-related fibrosis, and the American Association of clinical endocrinology clinical practice guideline for the diagnosis and management of NAFLD strongly recommend screening patients with type 2 diabetes using the Fibrosis (FIB)-4 index<sup>[23]</sup>. Other metrics such as the NAFLD activity score, a validated grading system for disease activity<sup>[24]</sup> and noninvasive assessments of hepatic fibrosis, like the NAFLD fibrosis score, are specific to NAFLD. The NAFLD fibrosis score considers

factors such as age, body mass index, hyperglycemia, aminotransferase levels, platelet count, and albumin<sup>[25]</sup>. Elevated NAFLD fibrosis scores may correlate with heightened cardiovascular disease mortality<sup>[26]</sup>. These assessment tools are essential for stratifying the NAFLD population into distinct grading categories, enabling targeted screening for adverse cardiovascular outcomes. Establishing a causal relationship between NAFLD and cardiovascular disease will be challenging due to the complex interplay of overlapping metabolic disturbances in these individuals, such as obesity, diabetes, hypertension, atherogenic dyslipidemia, and visceral adiposity. Further research is necessary to clarify this mechanistic link. Nevertheless, regardless of causality, it is crucial for endocrinology and primary care clinicians to recognize individuals with NAFLD as being at a heightened risk of cardiovascular complications.

Our findings showed that males had greater risk of MACCE, AMI, and cardiac arrest compared to females. Native Americans, followed by Asian Pacific Islanders, were found to have significantly higher odds of all-cause mortality compared to other racial groups. The literature offers multiple studies demonstrating higher prevalence of NAFLD among males compared to females<sup>[27,28]</sup>, which could be attributable to greater consumption of high-calorie drinks and alcohol, and higher frequency of insulin resistance<sup>[29]</sup>. To improve this poor trend among male population, public health measures should be implemented targeting optimal control of comorbidities among males in the community. The higher prevalence of NAFLD among Hispanics is also consistent with prior studies<sup>[30]</sup>. This could be attributed to a higher prevalence of chronic diseases such diabetes or metabolic syndrome, genetic and lifestyle differences, or access to healthcare among this racial group<sup>[30]</sup>. Regarding genetic factors, one of the most researched genes is the Patatin-like phospholipase domain-containing protein 3 (PNPLA3), which is responsible for encoding a membrane-bound phospholipase protein that regulates the use and storage of energy resources. Hispanics more often have an allele of PNPLA3 (rs738409[G]) that causes an increased hepatic accumulation of fat compared to Blacks, who have a different allele of PNPLA3 (rs6006460[T]) that in turn results in lower hepatic fat accumulation<sup>[31]</sup>. In a striking revelation, a study

focusing on Native American patients with Medicare in the United States uncovered that nearly half of the patients grappled with severe cardiovascular conditions, while also bearing a heightened load of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia<sup>[32]</sup>. These alarming findings parallel our own study, which demonstrated that Native Americans faced elevated odds of in-hospital mortality. This stark correlation underscores the profound and widespread racial disparities in cardiovascular health across the United States<sup>[33]</sup>. Consequently, there is a pressing need for the implementation of comprehensive multilevel interventions in healthcare, encompassing individual- and community-level factors for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD, to enhance cardiovascular health. This approach must be complemented by strategic investments in communities to tackle the socioeconomic determinants of health, ultimately leading to improved cardiovascular outcomes within these populations.

### *Clinical implications*

It is crucial to understand the implications of NAFLD, the increasing worldwide incidence of hepatic disease caused by NAFLD, aggressive public health measures are needed to target optimal control of comorbidities among the general population. This can be achieved through education on lifestyle modification, exercise, and dietary changes, including low calorie and high glycemic index foods, increased consumption of omega 3 and monounsaturated fatty acids. If lifestyle and dietary changes are unsuccessful, bariatric surgery may be considered<sup>[34]</sup>. Early diagnosis and proper management of NAFLD and related risk factors are essential to prevent atherosclerosis and other cardiovascular outcomes, particularly in high risk and underserved racial and ethnic groups. Furthermore, comprehensive multilevel interventions in healthcare, addressing individual and community level factors, are urgently needed for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD to enhance cardiovascular health and reduce disparities. These efforts must be complemented by strategic investments in communities to address the socioeconomic determinants of

health, ultimately leading to improved cardiovascular outcomes within these populations and promoting health equity.

### *Limitations*

This retrospective cross-sectional study has limitations tied to its reliance on ICD-10 codes for identifying NAFLD hospitalizations, potentially influenced by coding accuracy and completeness. Because it focused solely on hospitalized patients, the findings may not fully capture NAFLD characteristics in the general population. The study's use of a 2019 sample might not be entirely representative of the broader NAFLD patient population over time. The study design doesn't provide insights into causality, and unmeasured confounding variables may impact observed associations. Generalizability is confined to the US population and may not extend to regions with different demographics or healthcare systems. Notably, the study did not consider the severity of NAFLD, including crucial factors such as NAS score, NAFLD fibrosis score, FIB-4 index, and ultrasonography findings. The absence of this information in the NIS database hinders a comprehensive understanding of the disease's nuances. Furthermore, the lack of established screening guidelines for NAFLD exacerbates the issue, as its asymptomatic nature and the absence of a correlation with elevated liver function enzymes make it easily overlooked in clinical settings. Hence, our results are only representative of a small group of patients already diagnosed with NAFLD and may not reflect the actual disease burden<sup>[13,18,35]</sup>. This could be crucial when considering that certain racial groups may not have access to ideal healthcare services and meticulous laboratory evaluation and may not be aware of the severity of their NAFLD, thereby being underrepresented in the included data. Additional potential limitations may include limited availability of thorough clinical data, potential misclassification or underreporting of comorbid conditions, lack of long-term follow-up data, conceivable changes in coding practices over time, and inability to account for lifestyle and behavioral factors that could influence NAFLD and cardiovascular outcomes.

## **CONCLUSION**

The findings from this study indicated that NAFLD is linked to a greater risk of major cardiovascular events, especially among older males, and that Native Americans and Asian Pacific Islanders with NAFLD have higher all-cause mortality. These results emphasize the need for early detection and comprehensive management of cardiovascular risk factors in NAFLD patients, as well as the significance of addressing racial and gender disparities in outcomes. Future research directions may include investigating the mechanisms involved in contributing to the increased cardiovascular risk in individuals with NAFLD, exploring sex- and race-specific risk factors, and assessing the effectiveness of targeted interventions in improving cardiovascular outcomes. Strategies enhancing access to healthcare and addressing the disparities in NAFLD-related outcomes across sexes and racial/ethnic groups may also be a subject of future research.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

This study delves into the impact of non-alcoholic fatty liver disease (NAFLD) on cardiovascular disease (CVD) risk, focusing on the underexplored variances in cardiovascular outcomes across different sexes and races within a large, nationally representative U.S. inpatient sample.

### ***Research motivation***

The motivation for this research was to elucidate the relationship between NAFLD and major cardiovascular and cerebrovascular events (MACCE), particularly investigating the sex and racial disparities, to inform future healthcare strategies and interventions.

### ***Research objectives***

The objective was to examine the association of NAFLD with MACCE across various subgroups by age, sex, and race, aiming to highlight specific population needs and guiding tailored healthcare approaches.

### ***Research methods***

The study utilized a thorough analysis of the National Inpatient Sample, with multivariable regression models adjusted for sociodemographic and clinical factors, to compare MACCE-related outcomes in patients with NAFLD.

### ***Research results***

It found that NAFLD prevalence varies by sex and race, with adverse MACCE outcomes more common in older age groups and males, and higher all-cause mortality observed in Native Americans and Asian Pacific Islanders.

### ***Research conclusions***

The study revealed critical links between NAFLD, MACCE, age, and sex, as well as significant racial disparities in mortality rates, underscoring the necessity for customized care to improve health outcomes.

### ***Research perspectives***

This research paves the way for future studies focused on individualized patient care and highlights the importance of considering demographic variables in medical research and healthcare provision.

## **REFERENCES**

- 1 **Armstrong MJ**, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology* 2014; **59**: 1174-1197 [PMID: 24002776 DOI: 10.1002/hep.26717]

- 2 **Kasper P**, Martin A, Lang S, Kütting F, Goeser T, Demir M, Steffen HM. NAFLD and cardiovascular diseases: a clinical review. *Clin Res Cardiol* 2021; **110**: 921-937 [PMID: 32696080 DOI: 10.1007/s00392-020-01709-7]
- 3 **Targher G**, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010; **363**: 1341-1350 [PMID: 20879883 DOI: 10.1056/NEJMr0912063]
- 4 **Niederseer D**, Wernly B, Aigner E, Stickel F, Datz C. NAFLD and Cardiovascular Diseases: Epidemiological, Mechanistic and Therapeutic Considerations. *J Clin Med* 2021; **10** [PMID: 33530440 DOI: 10.3390/jcm10030467]
- 5 **Miptah HN**, Ramli AS, Mohamad M, Hashim H, Tharek Z. Non-alcoholic fatty liver disease (NAFLD) and the cardiovascular disease (CVD) risk categories in primary care: is there an association? *BMC Fam Pract* 2020; **21**: 238 [PMID: 33218301 DOI: 10.1186/s12875-020-01306-7]
- 6 **Mantovani A**, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, Byrne CD, Targher G. 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**: 903-913 [PMID: 34555346 DOI: 10.1016/S2468-1253(21)00308-3]
- 7 **HCUP Databases**. Healthcare Cost and Utilization Project (HCUP); Agency for Healthcare Research and Quality: Rockville, MD, USA, November 2022. Accessed December 15, 2022. Available from: <https://hcup-us.ahrq.gov/nisoverview.jsp>
- 8 **Hayward KL**, Johnson AL, Horsfall LU, Moser C, Valery PC, Powell EE. Detecting non-alcoholic fatty liver disease and risk factors in health databases: accuracy and limitations of the ICD-10-AM. *BMJ Open Gastroenterol* 2021; **8** [PMID: 33568418 DOI: 10.1136/bmjgast-2020-000572]
- 9 **Hagström H**, Adams LA, Allen AM, Byrne CD, Chang Y, Grønbaek H, Ismail M, Jepsen P, Kanwal F, Kramer J, Lazarus JV, Long MT, Loomba R, Newsome PN, Rowe IA, Ryu S, Schattenberg JM, Serper M, Sheron N, Simon TG, Tapper EB, Wild S, Wong VW, Yilmaz Y, Zelber-Sagi S, Åberg F. Administrative Coding in Electronic Health Care

Record-Based Research of NAFLD: An Expert Panel Consensus Statement. *Hepatology* 2021; **74**: 474-482 [PMID: 33486773 DOI: 10.1002/hep.31726]

10 **Polyzos SA**, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism* 2019; **92**: 82-97 [PMID: 30502373 DOI: 10.1016/j.metabol.2018.11.014]

11 **Powell-Wiley TM**, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 2021; **143**: e984-e1010 [PMID: 33882682 DOI: 10.1161/CIR.0000000000000973]

12 **Tana C**, Ballestri S, Ricci F, Di Vincenzo A, Ticinesi A, Gallina S, Giamberardino MA, Cipollone F, Sutton R, Vettor R, Fedorowski A, Meschi T. Cardiovascular Risk in Non-Alcoholic Fatty Liver Disease: Mechanisms and Therapeutic Implications. *Int J Environ Res Public Health* 2019; **16** [PMID: 31455011 DOI: 10.3390/ijerph16173104]

13 **Adams LA**, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut* 2017; **66**: 1138-1153 [PMID: 28314735 DOI: 10.1136/gutjnl-2017-313884]

14 **Ballestri S**, Lonardo A, Bonapace S, Byrne CD, Loria P, Targher G. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. *World J Gastroenterol* 2014; **20**: 1724-1745 [PMID: 24587651 DOI: 10.3748/wjg.v20.i7.1724]

15 **Mantovani A**, Zoppini G, Targher G, Golia G, Bonora E. Non-alcoholic fatty liver disease is independently associated with left ventricular hypertrophy in hypertensive Type 2 diabetic individuals. *J Endocrinol Invest* 2012; **35**: 215-218 [PMID: 22490991 DOI: 10.1007/BF03345421]

16 **Mantovani A**, Pernigo M, Bergamini C, Bonapace S, Lipari P, Pichiri I, Bertolini L, Valbusa F, Barbieri E, Zoppini G, Bonora E, Targher G. Nonalcoholic Fatty Liver



Disease Is Independently Associated with Early Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes. *PLoS One* 2015; **10**: e0135329 [PMID: 26252899 DOI: 10.1371/journal.pone.0135329]

17 **Wijarnpreecha K**, Boonpheng B, Thongprayoon C, Jaruvongvanich V, Ungprasert P. The association between non-alcoholic fatty liver disease and atrial fibrillation: A meta-analysis. *Clin Res Hepatol Gastroenterol* 2017; **41**: 525-532 [PMID: 28866089 DOI: 10.1016/j.clinre.2017.08.001]

18 **Keskin M**, Hayiroğlu Mİ, Uzun AO, Güvenç TS, Şahin S, Kozan Ö. Effect of Nonalcoholic Fatty Liver Disease on In-Hospital and Long-Term Outcomes in Patients With ST-Segment Elevation Myocardial Infarction. *Am J Cardiol* 2017; **120**: 1720-1726 [PMID: 28867124 DOI: 10.1016/j.amjcard.2017.07.107]

19 **Mellinger JL**, Pencina KM, Massaro JM, Hoffmann U, Seshadri S, Fox CS, O'Donnell CJ, Speliotes EK. Hepatic steatosis and cardiovascular disease outcomes: An analysis of the Framingham Heart Study. *J Hepatol* 2015; **63**: 470-476 [PMID: 25776891 DOI: 10.1016/j.jhep.2015.02.045]

20 **Stepanova M**, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin Gastroenterol Hepatol* 2012; **10**: 646-650 [PMID: 22245962 DOI: 10.1016/j.cgh.2011.12.039]

21 **Ma J**, Hwang SJ, Pedley A, Massaro JM, Hoffmann U, Chung RT, Benjamin EJ, Levy D, Fox CS, Long MT. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. *J Hepatol* 2017; **66**: 390-397 [PMID: 27729222 DOI: 10.1016/j.jhep.2016.09.022]

22 **Targher G**, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 599-612 [PMID: 33972770 DOI: 10.1038/s41575-021-00448-y]

23 **Cusi K**, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JL, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical

Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022; **28**: 528-562 [PMID: 35569886 DOI: 10.1016/j.eprac.2022.03.010]

24 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ; Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321 [PMID: 15915461 DOI: 10.1002/hep.20701]

25 **Angulo P**, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; **45**: 846-854 [PMID: 17393509 DOI: 10.1002/hep.21496]

26 **Henson JB**, Simon TG, Kaplan A, Osganian S, Masia R, Corey KE. Advanced fibrosis is associated with incident cardiovascular disease in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2020; **51**: 728-736 [PMID: 32043602 DOI: 10.1111/apt.15660]

27 **Lazo M**, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol* 2013; **178**: 38-45 [PMID: 23703888 DOI: 10.1093/aje/kws448]

28 **Adejumo AC**, Samuel GO, Adegbala OM, Adejumo KL, Ojelabi O, Akanbi O, Ogundipe OA, Pani L. Prevalence, trends, outcomes, and disparities in hospitalizations for nonalcoholic fatty liver disease in the United States. *Ann Gastroenterol* 2019; **32**: 504-513 [PMID: 31474798 DOI: 10.20524/aog.2019.0402]

29 **Pan JJ**, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol* 2014; **6**: 274-283 [PMID: 24868321 DOI: 10.4254/wjh.v6.i5.274]

- 30 **Saab S**, Manne V, Nieto J, Schwimmer JB, Chalasani NP. Nonalcoholic Fatty Liver Disease in Latinos. *Clin Gastroenterol Hepatol* 2016; **14**: 5-12; quiz e9-10 [PMID: 25976180 DOI: 10.1016/j.cgh.2015.05.001]
- 31 **Romeo S**, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]
- 32 **Eberly LA**, Shultz K, Merino M, Brueckner MY, Benally E, Tennison A, Biggs S, Hardie L, Tian Y, Nathan AS, Khatana SAM, Shea JA, Lewis E, Bukhman G, Shin S, Groeneveld PW. Cardiovascular Disease Burden and Outcomes Among American Indian and Alaska Native Medicare Beneficiaries. *JAMA Netw Open* 2023; **6**: e2334923 [PMID: 37738051 DOI: 10.1001/jamanetworkopen.2023.34923]
- 33 **Benjamin EJ**, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019; **139**: e56-e528 [PMID: 30700139 DOI: 10.1161/CIR.0000000000000659]
- 34 **Pouwels S**, Sakran N, Graham Y, Leal A, Pintar T, Yang W, Kassir R, Singhal R, Mahawar K, Ramnarain D. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. *BMC Endocr Disord* 2022; **22**: 63 [PMID: 35287643 DOI: 10.1186/s12902-022-00980-1]

35 **Targher G**, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. *J Hepatol* 2016; **65**: 589-600 [PMID: 27212244 DOI: 10.1016/j.jhep.2016.05.013]

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