

# Primary Cardiovascular Event Risk Associated with Nonalcoholic Steatohepatitis Among US Adults, NHANES 2017-2020

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## BACKGROUND

- In nonalcoholic steatohepatitis (NASH), the extent of liver fibrosis is reported to be associated with risk of progression to liver-related morbidity and mortality<sup>1-2</sup>
- In addition, cardiovascular disease (CVD) is recognized to be a leading cause of mortality in patients with NASH<sup>3</sup>
- Despite this, decision-analytic modeling of NASH often does not explicitly incorporate cardiovascular events, formulating progression as transitions between health states defined by liver fibrosis stage

## OBJECTIVES

- To estimate the risk of a primary cardiovascular event associated with NASH as well as assess the variation in risk across liver fibrosis stages and age

## METHODS

- A cross-sectional analysis was conducted using the 2017-March 2020 National Health and Nutrition Examination Survey (NHANES) cycle
- Participants with presumed NASH were identified as those with steatosis (controlled attenuation parameter ≥302 dB/m), without other causes of liver disease (hepatitis B/C, excessive alcohol consumption), and with FibroScan+AST (FAST) score ≥0.48,<sup>4</sup> using liver stiffness and steatosis measurements obtained via vibration-controlled transient elastography
- The 10-year probability of a primary cardiovascular event was estimated by applying the Framingham Heart Study 2008 risk equations<sup>5</sup> for a first coronary heart disease event, cerebrovascular event, peripheral artery disease, or heart failure among participants without history of CVD
- Probabilities were summarized and compared in participants with versus without presumed NASH, by liver fibrosis stage (liver stiffness measurement [LSM] <8.2 kPa for F0-F1, 8.2-13.5 kPa for F2-F3, and ≥13.6 kPa for F4<sup>6</sup>), and age </≥ 65 years

## RESULTS

- Among NHANES participants with complete data for the analysis and aged 30-74 years, N = 122 and N = 4,139 were included with/without presumed NASH
- In participants with presumed NASH, 25.7% (n = 30) had F0-F1 fibrosis and 74.3% (n = 92) had F2-F4 fibrosis

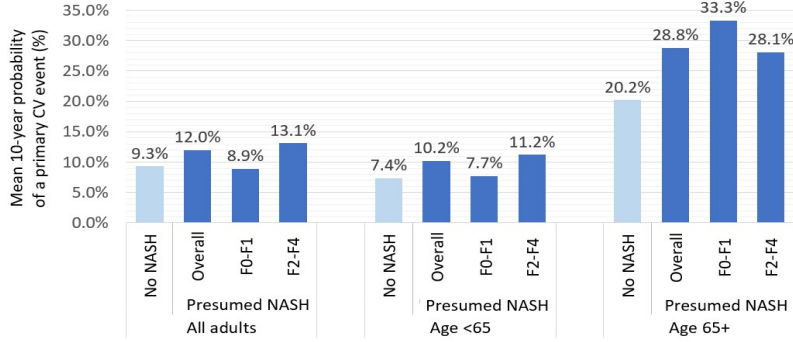
Table 1. Sample characteristics of participants with/without presumed NASH: overall and by age

	Overall		<65 years		≥65 years	
	No NASH	Presumed NASH	No NASH	Presumed NASH	No NASH	Presumed NASH
N	4,139	122	3,453	99	686	23
Cardiovascular risk factors (inputs to Framingham Heart Study 2008 risk equations)						
Age, mean (SE)	50.2 (0.4)	48.1* (1.0)	46.9 (0.3)	45.8 (1.0)	69.0 (0.2)	69.5 (0.7)
Sex, female	51.4%	27.1%*	51.0%	23.6%*	53.7%	59.5%
Diabetes	12.2%	24.1%*	10.6%	18.3%*	21.5%	78.4%*
Current cigarette smoking	17.4%	6.9%*	18.8%	7.4%	9.3%	2.4%
Total cholesterol (mg/dL)						
Mean (SE)	194.0 (1.3)	199.8 (4.9)	194.3 (1.5)	201.1 (5.4)	192.5 (2.7)	187.6 (10.8)
≥200 mg/dL (%)	41.2%	45.3%	40.9%	48.5%	42.8%	14.5%*
HDL-C (mg/dL)						
Mean (SE)	54.3 (0.5)	41.8* (1.3)	54.2 (0.5)	41.3* (1.4)	55.0 (1.0)	46.5* (2.4)
Low (%)	27.0%	56.3%*	27.1%	56.4%*	26.3%	55.4%*
SBP (mmHg)						
Mean (SE)	121.9 (0.4)	126.1* (1.2)	120.5 (0.4)	125.4* (1.3)	129.2 (1.0)	132.3 (4.0)
≥130 mmHg (%)	25.4%	31.2%	22.2%	29.4%	43.1%	47.4%
On medications for SBP	22.8%	31.1%	18.1%	28.1%	49.0%	61.0%
Liver fibrosis stage distribution, % (N)						
F0-F1	92.1% (3,762)	25.7%* (30)	92.5% (3,159)	27.1%* (26)	89.6% (603)	12.9%* (4)
F2-F4	7.9% (377)	74.3%* (92)	7.5% (294)	72.9%* (73)	10.4% (83)	87.1%* (19)

NHANES guidelines recommend sample size of ≥30 for reporting proportions, means, and variances. Asterisks denote statistically significant difference ( $P \leq 0.05$ ) of presumed NASH vs no NASH. Low HDL-C was defined as ≤40 mg/dL for men and ≤50 mg/dL for women.

- Mean (SE) 10-year probability of a primary cardiovascular event was 9.3% (0.2%) without NASH versus 12.0% (1.0%) with presumed NASH ( $P = 0.01$ )
  - The increased probability associated with presumed NASH versus no NASH was driven by higher risk in F2-F4 fibrosis stages at ages <65 years (11.2% vs 7.4%,  $P < 0.01$ ) and in all fibrosis stages at ages ≥65 years
  - However, limited sample size (N=23) challenged the reliability of estimates at ages ≥65 years
- Low HDL-C, diabetes, and male sex (at ages <65 years) were more common ( $P < 0.001$ ) in those with presumed NASH, contributing to elevated predicted primary cardiovascular event risk

Figure 1. Mean predicted 10-year probability of a primary cardiovascular event, presumed NASH vs no NASH



## CONCLUSIONS

- Predicted primary cardiovascular event risk was estimated to be significantly higher among US adults with versus without presumed NASH
- Excess risk of presumed NASH versus no NASH was observed in F2-F4 fibrosis stages at ages <65 years and in all fibrosis stages at ages ≥65 years

## REFERENCES

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## DISCLOSURES

This analysis was sponsored by Madrigal Pharmaceuticals. EB, JJW, and TO are employees of Medicus Economics and CMP is an employee of Pine Mountain Consulting; all received funding from Madrigal Pharmaceuticals in the conduct of this analysis. JF is employed by and owns stock/stock options in Madrigal Pharmaceuticals.