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Non-Alcoholic Fatty Liver Disease (NAFLD): Is it really a serious condition?

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Abstract

OBJECTIVE—To evaluate the association between non-alcoholic fatty liver disease and all cause and cause specific mortality in a representative sample of the US general population.

DESIGN—Prospective cohort study.

SETTING—US Third National Health and Nutrition Examination Survey (NHANES III: 1988–94) with follow-up of mortality to 2006.

PARTICIPANTS—11,371 adults aged 20–74 participating in the Third National Health and Nutrition Examination Survey, with assessment of hepatic steatosis.

MAIN OUTCOME MEASURE—Mortality from all causes, cardiovascular disease, cancer, and liver disease (up to 18 years of follow-up).

RESULTS—The prevalence of non-alcoholic fatty liver disease with and without increased levels of liver enzymes in the population was 3.1% and 16.4%, respectively. Compared with participants without steatosis, those with non-alcoholic fatty liver disease but normal liver enzyme levels had multivariate adjusted hazard ratios for deaths from all causes of 0.92 (95% confidence interval 0.78 to 1.09), from cardiovascular disease of 0.86 (0.67 to 1.12), from cancer of 0.92 (0.67 to 1.27), and from liver disease of 0.64 (0.12 to 3.59). Compared with participants without steatosis, those with non-alcoholic fatty liver disease and increased liver enzyme levels had adjusted hazard ratios for deaths from all causes of 0.80 (0.52 to 1.22), from cardiovascular disease of 0.59 (0.29 to 1.20), from cancer of 0.53 (0.26 to 1.10), and from liver disease of 1.17 (0.15 to 8.93).

CONCLUSIONS—Non-alcoholic fatty liver disease was not associated with an increased risk of death from all causes, cardiovascular disease, cancer, or liver disease

BACKGROUND & AIMS—The relative frequency of nonalcoholic steatohepatitis (NASH) as an indication for liver transplantation and comparative outcomes following transplantation are poorly understood.

METHODS—We analyzed the Scientific Registry of Transplant Recipients for primary adult liver transplant recipients from 2001 to 2009.

RESULTS—From 2001 to 2009, 35,781 patients underwent a primary liver transplant, including 1959 for who NASH was the primary or secondary indication. The percentage of patients undergoing a liver transplant for NASH increased from 1.2% in 2001 to 9.7% in 2009. NASH is now the third most common indication for liver transplantation in the United States. No other indication for liver transplantation increased in frequency during the study period. Compared with other indications for liver transplantation, recipients with NASH are older (58.5±8.0 vs 53.0±8.9 years; P<.001), have a larger body mass index (>30 kg/m2) (63% vs 32%; P<.001), are more likely to be female (47% vs 29%; P<.001), and have a lower frequency of hepatocellular carcinoma (12% vs 19%; P<.001). Survival at 1 and 3 years after liver transplantation for NASH

was 84% and 78%, respectively, compared with 87% and 78% for other indications (P=.67). Patient and graft survival for liver recipients with NASH were similar to values for other indications after adjusting for level of creatinine, sex, age, and body mass index.

CONCLUSIONS—NASH is the third most common indication for liver transplantation in the United States and is on a trajectory to become the most common. Outcomes for patients undergoing a liver transplant for NASH are similar to those for other indications

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease ranging from hepatic steatosis to steatohepatitis and cirrhosis.[1] While hepatic steatosis is generally thought to be benign from a liver standpoint, nonalcoholic steatohepatitis (NASH) is a progressive disease that can lead to cirrhosis and liver failure.[1] Based on several observational studies, reviews, and meta-analyses, it is currently believed that patients with NAFLD have higher overall mortality and patients with NASH have higher liver-related mortality, in comparison to the general population.[1,2] However, the two papers listed above appear to convey opposing views of the prognosis of NAFLD.[3,4] In the first paper, Lazo et al. report that NHANES III participants with moderate to severe hepatic steatosis did not have increased risk of overall, cardiovascular, or liver-related mortality.[3] In the second paper, Charlton et al. conclude that NASH is the third most common indication for liver transplantation in the United States and it is on a trajectory to become the most common indication for liver transplantation in the United States in the next 10–20 years.[4]

The mortality rate in individuals with NAFLD was initially examined by Adams et al. in a population-based cohort study.[5] This study consisted of 420 Olmsted county residents with well-phenotyped NAFLD who were followed for a mean duration of 7.6 ± 4.0 years. Compared to an expected survival of the general population, individuals with NAFLD had significantly higher overall mortality (standardized mortality ratio, 1.34, 95% CI 1.003–1.76, P=0.03). This study was followed by several other population-based as well as community-based studies which generally suggested that NAFLD is associated with excess overall mortality.[1,2] In a well conducted meta-analysis, Musso et al. have examined the relationship between NAFLD and various clinical outcomes.[2] The pooled data from 7 studies (3 population-based and 4 community-based studies) observed that overall mortality was significantly higher in NAFLD compared to general population (OR 1.57, 95% CI 1.18–2.10, P=0.002).[2]

The National Health and Nutrition Examination Survey III (NHANES III) enrolled 14,797 adults aged 20–74 between 1988 and 1994; participants were passively followed for mortality until December 2006 using the National Death Index. At baseline, all participants were extensively characterized including a gallbladder ultrasound which was subsequently utilized to assess for the presence of steatosis that was characterized as none to mild or moderate to severe hepatic steatosis. In addition to the publication by Lazo et al.[3], there have been four other papers which have explored the relationship between NAFLD and mortality among NHANES III participants (Table 1).[6–9] Three studies used biochemical criteria for defining suspected NAFLD whereas two studies defined suspected NAFLD based on imaging criteria. When interpreting the mortality data from NHANES III participants linked to the National Death Index, one should keep in mind that causes of death were attributed based on ICD-9 and ICD-10 codes which may be prone to misclassification.

The study by Dunn et al.,[6] published in 2008, was based on individuals aged 35–84 years at baseline and consisted of 980 individuals with suspected NAFLD and 6,594 controls. The presence of suspected NAFLD was defined biochemically (ALT > 30 U/L in men and >19 U/L in women) and by excluding competing etiologies such as excessive alcohol consumption, iron overload, medications, and viral hepatitis. Over a mean follow-up of 8.7 years (range 0.05 – 11.7 years), all-cause mortality was not higher among participants with

suspected NAFLD compared to controls without suspected NAFLD (HR 1.37, 95% 0.98–1.91). Interestingly in the 45–54 age group, after controlling for 15 relevant covariates, participants with suspected NAFLD (n=239) had significantly higher all-cause mortality (HR 4.10, 95% CI 1.27–13.23) and cardiovascular mortality (HR 8.43, 95% CI 2.43–22.72). However, participants with suspected NAFLD in the 55–85 age group (n=352) did not have an increased all-cause or cardiovascular mortality compared to controls (n=3,598). The authors did not report the results of the analyses that combined both of these age groups, i.e. 45–84 years.

The study by Ong et al.[7] published in 2008 was based on all adult NHANES III participants (≥17 years) and it consisted of 817 participants with suspected NAFLD and 10,468 controls. The presence of suspected NAFLD was defined biochemically (ALT > 40 U/L or AST>37 in men or ALT or AST >31 U/L in women) after excluding common competing etiologies. The median duration of follow-up was 8.7 years. After controlling for relevant covariates, individuals with suspected NAFLD had significantly higher overall mortality (HR 1.038, 95% CI 1.036–1.041) and liver-related mortality (HR 9.32, 95% CI 9.21–9.43).

The study by Ruhl and Everhart[8] published in 2009 examined the relationship between ALT and GGT levels and mortality among 14,950 participants in NHANES III who were negative for hepatitis B or hepatitis C. Elevated ALT was defined as >30 U/L in men and >19 U/L in women and elevated GGT was defined as >51 U/L in men and >33 U/L in women. The median duration of follow-up was 8.8 years (range, 0.02–12.1 years). In the multivariate analysis, elevated ALT was significantly associated with liver-related mortality (HR 8.2, 95% CI 2.1–13.9) but not all-cause or cardiovascular mortality. This relationship between elevated ALT and excessive liver-cause mortality was strengthened after controlling for individuals with excessive alcohol consumption in the analyses.

The study by Stepanova and Younossi[9] was published in 2012 and it examined the relationship between suspected NAFLD and cardiovascular mortality among 20,050 adult participants in NHANES III with hepatobiliary ultrasound results. Suspected NAFLD was defined as the presence of moderate to severe hepatic steatosis by ultrasonography in the absence of competing etiologies such as hepatitis B or C, iron overload, or excessive alcohol consumption. Their mean length of follow-up was 181 months. Although individuals with suspected NAFLD had significantly higher overall and cardiovascular mortality on the univariate analysis, there was no independent association between suspected NAFLD and either overall mortality or cardiovascular mortality. When authors performed subgroup analyses between suspected NAFLD patients with and without elevated liver enzymes, their findings did not change significantly.

Finally, the study by Lazo et al.[3] published in 2011 consisted of 11,371 adult participants in NHANES III with liver imaging and mortality data available from the National Death Index. Over a median follow-up of 14.5 years, compared to individuals without hepatic steatosis, after controlling for 10 covariates, individuals with suspected NAFLD with or without elevated liver enzymes did not have increased incidence of all-cause, cardiovascular, cancer, or liver-related mortality (Table 2). In a subgroup analysis, compared to controls, individuals with NAFLD (either with normal or elevated liver enzymes) in the age group 41–55 did not have increased all-cause mortality. Although not reported in the published paper, the authors described via personal communication that their study had a “positive control” which revealed a significant independent relationship between self-reported diabetes or hypertension and all-cause (HR 2.05, 95% CI 1.54–2.74 for diabetes and HR 1.73, 95% 1.39–2.17), cardiovascular (HR 2.71, 95% CI 1.65–4.43 for diabetes and HR 2.37, 95% CI 1.42–3.95 for hypertension), and cancer-related mortality (HR 2.15, 95% CI 1.18–3.92 for diabetes and HR 1.97, 95% CI 1.02 – 3.81 for hypertension).

Based on these five studies, one could summarize that the three studies which were based on biochemical criteria showed an association between suspected NAFLD and mortality whereas the two studies which defined suspected NAFLD radiologically failed to observe a similar association. Among NHANES III participants, the prevalence of suspected NAFLD is ~ 7% when defined biochemically, however it is much higher (16–18%) when suspected NAFLD was identified using imaging criteria. Although unexplained elevations in liver enzymes is prognostically important among all NHANES III participants, it is intriguing that elevated ALT did not portend additional significance among those with moderate to severe hepatic steatosis. It may be worthwhile for the NHANES III cognoscente to consider a side by side comparison of individuals with biochemically and radiologically suspected NAFLD to better understand the mortality discrepancy between these two groups.

Is NAFLD really a serious condition? How do we reconcile the seemingly contradictory observations made by Lazo et al. and Charlton et al. about the significance of NAFLD? We argue that NAFLD is a serious condition only in a subgroup of individuals and the challenge is to precisely identify those at risk for increased morbidity and mortality. The observations made by Charlton et al. are consistent with what we as hepatologists are experiencing in our clinical practice. We are seeing an increasing number of individuals with newly diagnosed cirrhosis and decompensated cirrhosis due to NAFLD/NASH in our general hepatology and liver transplant clinics. Additionally, over the last decade we have seen an increasing number of cryptogenic and NASH cirrhotics on our inpatient liver wards. This burden due to NAFLD was not shown in the study by Lazo et al. because the duration of follow-up was likely insufficient, likely reflected in the fact that only 44 deaths were due to liver disease. We should be reminded that NASH accounts for only a small proportion of all individuals with NAFLD, and it is largely those with NASH who are at higher risk for liver-related adverse outcomes. Therefore, NAFLD at-large may not the right cohort to investigate liver-related morbidity and mortality, but we should focus on at-risk NAFLD patients. In cohort studies where liver histology is available, obviously these at-risk NAFLD patients are those with steatohepatitis and/or advanced fibrosis, but in epidemiological studies where liver histology is not available, alternate methods should be sought for characterizing at-risk NAFLD patients. Lazo et al.[3] selected individuals with suspected NAFLD and elevated liver enzymes as the at-risk group (erroneously defined them as NASH) but the prognostic significance of elevated liver enzymes in individuals with NAFLD is very limited. So, what is a better marker for the presence of NASH among individuals with NAFLD in epidemiological studies? One possibility is the presence of the metabolic syndrome. Several cohort studies have identified the metabolic syndrome as a strong predictor for the presence of NASH among individuals with NAFLD.[1] Future epidemiological studies may consider NAFLD + metabolic syndrome as an at-risk group, but the NHANES III cohort with mortality data available only until December 2006 is not optimal for investigating liver-related mortality because of very few liver-related deaths.

Similarly, NAFLD at-large as defined by Lazo et al.[3] may not be at-risk for overall mortality or cardiovascular mortality, but in their cohort the overall mortality was 21% over a median follow-up of 14.5 years and nearly 40% of all deaths were due to cardiovascular disease. Therefore, for patients with NAFLD, their mortality comparison to those without NAFLD is largely irrelevant; more salient and striking is the fact that one in five of those with NAFLD will not survive beyond 15 years. More research is needed to better understand which patients with NAFLD are at-risk for overall and cardiovascular mortality, so they can be therapeutically targeted.

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Table 1

NHANES III-based studies which investigated relationship between suspected NAFLD and mortality in the United States population

Author (Year)	Study Population	Definition of NAFLD	Study Groups	Duration Follow- up	Main Observations	Comments
Dunn et al (2008)	Adults aged 35–84 years	Unexplained ALT > 30 U/L in men and >19 U/L in women	980 with suspected NAFLD and 6,594 controls	Mean 8.7 years	All-cause mortality was not higher in NAFLD compared to controls (adjusted HR 1.37, 95% 0.98–1.91)	Individuals with suspected NAFLD in the 45–54 age group had significantly higher all-cause (adjusted HR 4.10, 95% CI 1.27–13.23) and cardiovascular mortality (HR 8.43, 95% CI 2.43–22.72)
Ong et al (2008)	Adults ≥ 17 years	Unexplained ALT > 40 U/L or AST>37 in men or ALT or AST >31 U/L in women	817 with suspected NAFLD and 10,468 controls	Median 8.7 years	Suspected NAFLD was associated with significantly higher overall mortality (adjusted HR 1.038, 95% CI 1.036–1.041) and liver-related mortality (adjusted HR 9.32, 95% CI 9.21–9.43)	
Ruhl and Everhart (2009)	14,950 adult participants who are negative for HBV or HCV	Abnormal ALT was defined as >30 U/L in men and >19 U/L in women	2156 with elevated ALT and 12,794 controls	Median 8.8 years	Elevated ALT was significantly associated with liver-related mortality (HR 8.2, 95% CI 2.1–13.9) but not all-cause or cardiovascular mortality	Original analyses did not exclude individuals with excessive alcohol consumption. However, in the sensitivity analysis that excluded individuals with excessive alcohol consumption, the relationship between elevated ALT and liver-related mortality strengthened.
Lazo et al (2011)	11,371 adult participants with liver imaging results available	Moderate to severe hepatic steatosis without common competing etiologies	• 8,856 individuals without hepatic steatosis • 2,089 individuals with hepatic steatosis and normal liver enzymes • 426 individuals with hepatic steatosis and elevated liver enzymes	Median 14.5 years	NAFLD with or without elevated liver enzymes was not associated with increased all-cause, cardiovascular, or liver-related mortality.	Individuals with NAFLD had 21% overall mortality during the follow-up and 40% deaths were due to cardiovascular events. Very few liver-related deaths in this cohort (44 deaths, 0.5%)

Author (Year)	Study Population	Definition of NAFLD	Study Groups	Duration Follow- up	Main Observations	Comments
Stepanova and Younossi (2012)	20,050 adult participants with hepatobiliary ultrasound	Moderate to severe hepatic steatosis without common competing etiologies	• 9,121 individuals without hepatic steatosis • 2,066 individuals with hepatic steatosis and normal liver enzymes • 426 individuals with hepatic steatosis and elevated liver enzymes	Mean 181 months	No independent association between suspected NAFLD and either overall mortality or cardiovascular mortality	Suspected NAFLD was independently associated with increased risk of cardiovascular disease.

Table 2

Relationship between radiologically suspected NAFLD and mortality among NHANES III participants in the study by Lazo et al.[3]

	Suspected NAFLD with normal liver enzymes (n=2080)		Suspected NAFLD with elevated liver enzymes (n=426)	
	Number of events	Adjusted HR¶ (95% CI)	Number of events	Adjusted HR¶ (95% CI)
All-cause mortality	469	0.92 (0.78–1.02)	57	0.80 (0.52–1.22)
Cardiovascular mortality	192	0.86 (0.67–1.12)	16	0.59 (0.29–1.20)
Cancer-related mortality	116	0.92 (0.67–1.27)	14	0.53 (0.26–1.10)
Liver-related mortality	7	0.64 (0.12–3.59)	3	1.17 (0.15–8.93)

¶Adjusted Hazard ratio is after controlling for age, sex, education, smoking, alcohol consumption, physical activity, body mass index, hypertension, hypercholesterolemia, and diabetes.