

# Non-alcoholic fatty liver disease associated with high mortality rates

January 27 2010

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Researchers from the Karolinska Institute determined that patients with nonalcoholic fatty liver disease (NAFLD) have a higher overall mortality rate compared with the general population. Details of this study are available in the February issue of *Hepatology*, a journal published by Wiley-Blackwell on behalf of the American Association for the Study of Liver Diseases.

While NAFLD is the most common cause of elevated liver enzyme levels, the long-term prognosis of this condition is relatively unknown. "We wanted to determine the frequency of NAFLD and NASH in a population of subjects with elevated serum levels of aminotransaminases and compare the survival and causes of death in NAFLD subjects with those of subjects from other liver diseases, and the general population," explains research team leader Dr. Cecilia Söderberg.

The research team evaluated 256 male and female subjects between the ages of 33-57 who had undergone a liver biopsy (between 1980-1984) due to elevated liver enzymes. The biopsies were blindly scored for NAFLD and NASH. The inclusion criteria were persistently elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) for more than 6 months. Subjects with symptoms or clinical signs of liver disease, serum levels of alkaline phosphatase more than twice the upper normal limit, or with clinical or laboratory signs of kidney disease were excluded. It was understood that subjects consumed alcohol in moderation. Standardized mortality ratios were used to assess the relative risk of death.

The study findings suggest that for this study population, persistently elevated serum levels of liver enzymes was associated with an increased risk of death during the 28-year study period. Patients with NAFLD and NASH had a much higher risk of death than the general population but not as high a risk as for patients with chronic [viral hepatitis](#) or alcoholic liver disease. Cardiovascular disease and extra-hepatic malignancies were the primary and secondary causes of death among patients with NAFLD whereas liver-related causes were the third.

"This study has four major strengths," says Dr. Söderberg. "Firstly, all the subjects were enrolled consecutively during a defined period of time (1980-1984). Secondly, all underwent liver biopsy at the time of referral so that the diagnoses of NAFLD are based on histological criteria. Thirdly, re-evaluation of the initial biopsy findings was performed in all cases. And finally, even deceased subjects could be followed up through the Cause of Death Registry, so that there were no losses during follow-up."

In this month's editorial, Dr. Paul Angulo from the University of Kentucky concedes that the Söderberg study confirms the findings of earlier studies, but maintains that this research may be flawed because of the small patient population evaluated. Dr. Angulo questions the way prior studies and the study by Söderberg have classified patients as definitive NASH or non-NASH for survival comparison, stating, "The study by Söderberg et al. suggests that in using the NASH-CRN scoring system the long-term mortality of those with definitive NASH is not significantly different from those with non NASH. Unfortunately, the study by Söderberg et al. along with the two other past studies that included [liver](#) biopsy, did not analyze the prognostic relevance of inflammation and hepatocyte ballooning adjusted by presence and severity of fibrosis.

Dr. Angulo points out that based on a close analysis of the data from all

long-term mortality studies published to date, "it seems the presence and severity of fibrosis dictates both overall and liver-related mortality in NAFLD regardless of the pathologist's labeling of NASH or non NASH." He recognized that "only a large appropriately powered study of several hundreds of patients who underwent [liver biopsy](#) and have follow-up data for several years or decades will answer those questions."

**More information:**

Article: "Decreased survival of subjects with elevated liver function tests during a 28 year follow up." Cecilia Söderberg, Per Stål, Johan Askling, Hans Glaumann, Greger Lindberg, Joel Marmur, and Rolf Hultcrantz. *Hepatology*; Published Online: January 27, 2010 ([DOI: 10.1002/hep.23314](#)); Print Issue Date: February 2010.

Editorial: "Long-term mortality in NAFLD. Is liver histology of any prognostic significance?" [DOI: 10.1002/hep.23521](#) *Hepatology*; Published Online: January 27, 2010 (DOI: 10.1002/hep.23521); Print Issue Date: February 2010.

Provided by Wiley

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