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**Lean NAFLD from the General French Population have more Severe Liver Disease and Poorer Outcomes (NASH-CO Study)**

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**ABSTRACT**

**BACKGROUND AND AIMS** - While obesity is a major risk factor, non-alcoholic fatty liver disease (NAFLD) has also been reported in lean subjects. In this clinical setting, severity of liver injury and clinical outcomes are debated and few studies have been conducted at a general population level. This study aimed to assess prevalence, characteristics and mortality outcomes of lean NAFLD in the French adult population. **METHOD** - The study population consisted of 127, 291 participants from the nationwide CONSTANCES cohort. After exclusion of subjects with excessive alcohol consumption, viral hepatitis or other liver diseases, 110, 120 were analyzed. Non-invasive diagnosis of NAFLD and advanced fibrosis was performed using the combination of Fatty Liver Index and Forns Index. Outcomes analyzed were liver-related events, hepatocellular carcinoma (HCC), cardiovascular disease (CVD), extrahepatic cancer (EHC), chronic kidney disease (CKD), liver transplantation and overall mortality. The median follow-up was 30 months. **RESULTS** - The prevalence of NAFLD was 18.1% in overall population and 5.3% in lean subjects, while 16.3% of NAFLD subjects were lean. Compared to non-lean, lean NAFLD were significantly younger and more frequently women, had fewer metabolic risk factors, were more frequently tobacco user and moderate alcohol consumer (all P value <0.001). Prevalence rates of elevated ALT and advanced fibrosis were significantly higher in lean compared to non-lean NAFLD (34.4% vs 20.9%, P < 0.001 and 3.6% vs 1.7%, P < 0.001, respectively). When adjustment for usual risk factors, NAFLD in lean subjects was associated with increased risk of liver-related events (aHR = 5.48, 95%CI 3.43–8.75), HCC (aHR = 3.35, 1.72–6.55), CVD (aHR = 1.72, 1.25–2.37), EHC (aHR = 2.90, 2.27–3.71), CKD (aHR = 2.11, 1.43–3.11) and overall mortality (aHR = 2.26, 1.76–2.91). Among NAFLD subjects, lean status was associated with increased risk of hepatic events (aHR = 9.10, 95%CI 4.48–18.48), HCC (aHR = 3.86, 1.35–11.03), EHC (aHR = 2.46, 1.78–3.38) and overall mortality (aHR = 3.76, 2.41–5.85), irrespective of usual risk factors. **CONCLUSION** - From a large French community-based cohort, this study confirms the significant prevalence of lean NAFLD and suggests that NAFLD is more severe in terms of advanced fibrosis, liver disease progression and overall mortality in lean compared to non-lean subjects, despite fewer metabolic risk factors. Differences in lifestyle, genetics and microbiota may explain those results.

**KEYWORDS:** -

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