

Non-Alcoholic Fatty Liver Disease and Risk of Acute Myocardial Infarction and Stroke: Analysis of 18 Million Patients in Four European Primary Care Databases

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Background: Many consider non-alcoholic fatty liver disease (NAFLD) to be a high cardiovascular risk state. Whether a NAFLD diagnosis confers an excess cardiovascular risk over and above that of the classical risk factors is an important clinical question. Cohort studies with varying degrees of adjustment have suggested that it is, but this hypothesis has not been tested in real world data. Here, we identified NAFLD or NASH patients from 18 million patients' records held in four European primary care databases and estimated their risk of cardiovascular events compared to individually matched patients.

Methods: Primary care data were extracted from the UK, Netherlands, Italy and Spain. Adult patients with a diagnosis of NAFLD (including a minority with NASH) and without past liver disease or alcohol abuse were enrolled and followed up for incident acute fatal or non-fatal myocardial infarction (MI) and ischaemic or unspecified stroke events. Within a database, each NAFLD patient was matched to up to 100 "non-NAFLD" patients according to practice site, gender, age $\pm$ 5 years, and visit recorded within $\pm$ 6 months. Hazard ratios (HR) were estimated using Cox models adjusted for age and smoking status, and stratified by matching. Estimates were pooled across studies by random effects meta-analyses.

Results: 121,159 patients with an incident NAFLD diagnosis were identified out of 17.7 million patients. Average follow-up from index date ranged from 2.1 - 5.5 years in the four databases. At baseline, NAFLD patients had more traditional cardiovascular risk factors: higher body mass index, systolic blood pressure, proportion of current smokers and patients with type 2 diabetes compared to controls. The pooled HR for incident MI, adjusting for age and smoking status, was 1.17 [95% CI 1.05; 1.30; I-squared: 66%, p-value heterogeneity=0.032]. This pooled HR was attenuated with progressive adjustments for type 2 diabetes, systolic blood pressure, total cholesterol, statin use and hypertension [1.01; 0.91-1.12; I-squared=48.4%, p=0.121]. Pooled HR for stroke adjusting for age and smoking status was 1.18 [1.11; 1.24], which was attenuated to 1.04 [0.99; 1.09] after adjustment for risk factors. Further sensitivity analyses excluding NASH patients showed comparable results.

Conclusion: The diagnosis of NAFLD in current routine care does not necessarily equate to a higher independent cardiovascular risk. However cardiovascular risk assessment in these patients should be conducted in the same way as the general population.

Table 1 – Association of NAFLD with incident cardiovascular outcomes

Exposure (data pooled)	N. exposed patients	Acute myocardial infarction		Stroke	
		N. events in exposed patients	Hazard ratio (95% CI)	N. events in exposed patients	Hazard ratio (95% CI)
Adjusted for age and smoking	120795	1035	1.17 (1.05; 1.30)	2187	1.18 (1.11; 1.24)
Adjusted for age, smoking, diabetes, SBP, TC, statin use and hypertension	78217	747	1.01 (0.91; 1.12)	131	1.04 (0.99; 1.09)

N: Number of; CI: Confidence interval; SBP – systolic blood pressure; TC total cholesterol