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Research Paper

Ethnicity matters: A Systematic Review and Meta-Analysis of the Non-Linear Relationship Between Alcohol Consumption and Prevalence and Incidence of Hepatic Steatosis

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ABSTRACT

Background: Fatty liver (hepatic steatosis) is one of the most common diseases globally, with increasing prevalence. The role of alcohol consumption in the development of hepatic steatosis has not been systematically examined.

Methods: We searched Medline, Embase, and ProQuest Dissertations & Theses Global for original data on the relationship between alcohol consumption and hepatic steatosis measured by non-invasive imagery, excluding studies conducted in participants <18 years, or subgroups related to viral and drug-induced liver disease. We identified 18 articles reporting adjusted data (Japan = 11, other high-income countries = 7). Random-effect categorical meta-analyses (<20 g/day pure alcohol consumption vs non-drinkers) and dose-response meta-analyses for the whole range of alcohol consumption were conducted.

Results: In total, 99,370 participants and 25,662 cases of hepatic steatosis were included. In Japan, low alcohol consumption was consistently associated with substantially reduced incidence and prevalence of hepatic steatosis compared to non-drinkers (RR for <20 g pure alcohol/day = 0.75, 95% CI: 0.71–0.79, I^2 = 0%). No overall association was found in other countries (RR = 1.05, 95% CI: 0.86–1.30, I^2 = 84%). Dose-response analyses in Japan (up to 80 g/day) showed an inverse relationship in men and a J-shape in women.

Conclusions: Alcohol consumption showed a complex association with hepatic steatosis with substantial differences by ethnicity and sex. Low alcohol consumption was beneficial in Japan with good epidemiological evidence, whereas there was no association in other countries. However, heterogeneity was large in countries other than Japan. More and higher quality research in diverse ethnic populations is needed to further clarify this relationship.

1. Introduction

Liver diseases are prevalent diseases in all regions of the world (Lozano et al., 2012), and associated with marked burden of disease (Byass, 2014). Aside from viral hepatitis, the leading cause for liver disease globally, for all stages of liver disease from hepatic steatosis to liver cirrhosis, there is a basic distinction into alcoholic versus non-alcoholic forms based on the history of alcohol intake with various cut-points (mostly between 20 and 40 g pure alcohol intake per day [g/day]) (Chalasani et al., 2012; LaBrecque et al., 2014; EASL, 2012; Nascimbeni et al., 2013).

The prevalence of non-alcoholic fatty liver disease (NAFLD), now more common than alcoholic liver disease (Sattar et al., 2014), has doubled in both North America and Asia over the past two decades, and it has become one of the most widespread chronic conditions worldwide

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(about ¼ of the population), with projected further increase (Byrne and Targher, 2015; Vernon et al., 2011; Younossi et al., 2015). It is frequently associated with impaired glucose tolerance, insulin resistance, hypertension, and obesity (Yki-Jarvinen, 2014), and a risk factor for both type 2 diabetes mellitus and the metabolic syndrome (MetS) (Ballestri et al., 2015), all of which are risk factors for cardiovascular diseases and overall mortality. Hepatic steatosis might also be an independent risk factor for cardiovascular disease (Bonci et al., 2015; Lu et al., 2013; Targher et al., 2010; Loria et al., 2014). Aside from other causes of liver disease (such as use of medication or presence of hereditary disorders known to produce hepatic lipidosis, or viral hepatitis B or C), non-alcoholic hepatic steatosis is diagnosed based on hepatic fatty infiltration in the absence of excessive alcohol consumption (Neuman et al., 2014a). However, there are no systematic investigations as to what excessive alcohol consumption means for hepatic steatosis (Nascimbeni et al., 2013), or whether the relationship between alcohol consumption and hepatic steatosis is continuous or characterized by a threshold effect. Furthermore, the role of sex in this relationship is not clear (Vernon et al., 2011).

Several conflicting large-scale population-based studies published recently (e.g. (Lau et al., 2015; Moriya et al., 2015; Tsunoda et al., 2014)) indicated that moderate (or 'non-alcoholic') alcohol consumption either has a beneficial or detrimental association with prevalence or development of hepatic steatosis, questioning the distinction into non-alcoholic and alcoholic hepatic steatosis. Furthermore, the impact of irregular heavy (binge) drinking on liver disease among moderate drinkers is currently unknown (Mathurin and Deltenre, 2009; Rehm and Roerecke, 2015). In the US, an episodic heavy drinking pattern is more common than chronic heavy drinking (Naimi et al., 2003; *MMWR Morbidity and Mortality Weekly Report* 2012, 2010), and the prevalence of heavy episodic drinking is high or on the rise in many countries (Shield et al., 2013).

The objective of this study was to determine the relationship between patterns of alcohol consumption and hepatic steatosis, taking into account confounding from other risk factors for hepatic steatosis. We systematically examined the epidemiological evidence for the relationship between patterns of alcohol consumption (including total average amount and 'binge' drinking) and prevalence and incidence of non-alcoholic hepatic steatosis, stratified by sex where possible. Non-linear dose-response analyses were conducted without a distinction between alcoholic and non-alcoholic hepatic steatosis.

2. Material and Methods

2.1. Search Strategy and Selection Criteria

Following the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) (Stroup et al., 2000), we conducted a systematic literature search (Fig. 1, Table S1) using Medline, Embase, and ProQuest Dissertations & Theses Global, updated on December 10, 2015 for keywords relating to alcohol consumption and fatty liver disease. Additionally, we searched reference lists of identified articles and published meta-analyses and reviews. Inclusion criteria were: 1) full-text article with original and adjusted population-based data (cross-sectional or cohort design) on the relationship between alcohol consumption and hepatic steatosis in comparison to non-drinkers, 2) hepatic steatosis was diagnosed using non-invasive methods (ultrasound, computed-tomography, magnetic resonance imaging, proton magnetic resonance spectroscopy), 3) results were reported in categories of alcohol consumption in relation to non-drinkers. For categorical meta-analyses, at least one category had to report results for alcohol consumption between 0 and 20 g/day (0–40 g/day in a sensitivity analysis) in comparison to non-drinkers. For a dose-response meta-analysis, results for at least three drinking groups based on average intake in g/day in comparison to non-drinkers had to be reported. We excluded studies with participants or ultrasound examinations were restricted to or based on: a) <18 years of age, b) viral hepatitis (HBV or HCV), c) drug-induced liver disease, or d) other indications of liver disease (e.g. elevated liver function tests (Bellentani et al., 1997)), e) experimental conditions. No language restrictions were applied. Two reviewers independently excluded articles based on title and abstract on the first pass, articles with unsure eligibility were obtained in full-text and discussed by two authors until consensus was reached. Authors were not contacted.

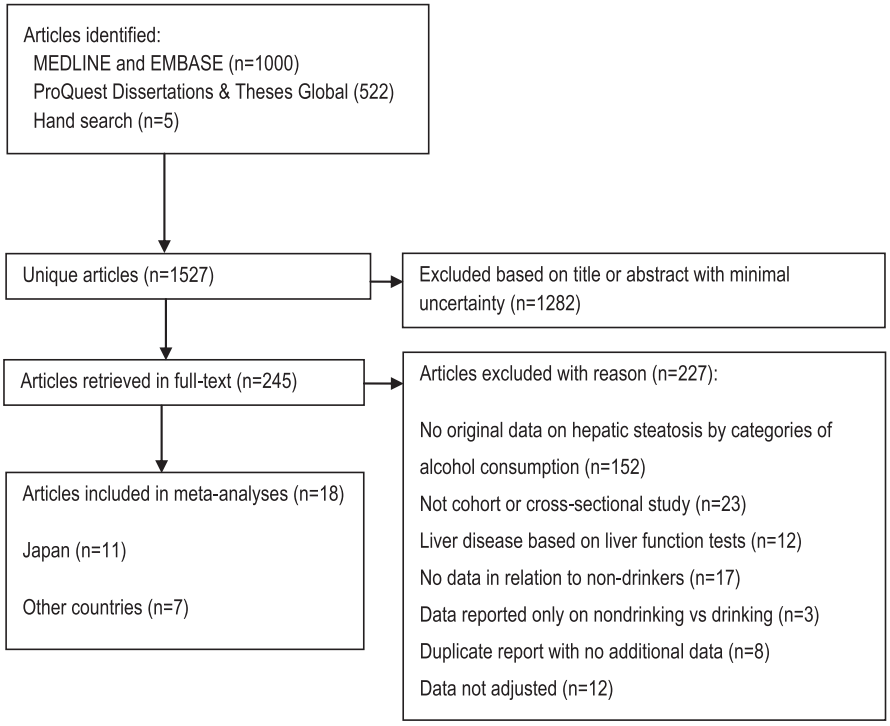

Fig. 1. Flowchart of study selection.