Associations of beverage consumption with nonalcoholic fatty liver disease among children
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A. Study Purpose and Rationale

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease resulting from excess fat accumulation in the liver in the absence of alternative etiologies. NAFLD comprises of a spectrum of diseases that involve fatty infiltration of the liver, typically >5% of the liver by imaging, direct quantification, or histologic estimation. The various phenotypes of this disease include pediatric NAFL, steatosis without specific inflammatory changes with or without fibrosis, NASH, characterized by hepatic steatosis with inflammation, with or without ballooning injury to hepatocytes and fibrosis, NAFLD with fibrosis, which refers to NASH with periportal, portal, or sinusoidal or bridging fibrosis, and NAFLD with cirrhosis. NAFLD has been associated with increased risk of type 2 diabetes, end-stage liver disease, hepatocellular carcinoma, and cardiovascular disease. In conjunction with the highest rates of childhood obesity prevalence in the world, NAFLD has become the most common pediatric liver disease in the US. Additionally, NAFLD is now one of the leading indications for liver transplantation in adults.

Consumption of free sugars is an emerging risk factor for NAFLD that may exert effects independent of adiposity. According to NHANES, almost two-thirds of children consumed at least one sugar-sweetened beverage on a given day with an average of approximately 7% of total daily caloric intake from sugar-sweetened beverages. A recent interventional study in humans shows that limiting consumption of sugar may provide therapeutic benefit to children with proven NAFLD. However, whether consumption of free sugars leads to development of steatosis, NASH, or fibrosis is unknown. Understanding modifiable behaviors that could prevent NAFLD is needed to inform prevention and treatment targets. The goal of this study is to further understand how consumption of beverages with free sugars relates to steatosis, NASH, and fibrosis.

B. Study Design and Statistical Analysis

We will leverage an ongoing cohort of 200 prospectively recruited pediatric patients undergoing liver biopsies for evaluation of chronic liver disease. The main outcomes will be liver biopsy histopathology steatosis grade, fibrosis stage, and whether NASH is present. Using validated beverage frequency questionnaires, we will calculate habitual beverage consumption according to discrete categories of sugar-sweetened beverages, 100% fruit juice, or water. We will examine distributions of variables using descriptive statistics and relationships between exposures and outcomes using appropriate bivariate tests. We will perform linear regressions to assess relationships between exposures and outcomes, adjusting for potential confounders including child age, sex, race/ethnicity, and body mass index.

C. Study Procedure

This will be a retrospective review of a the cohort of pediatric patients undergoing liver biopsies as part of their outpatient hepatology treatment/workup. There are no procedures or interventions for this study.

D. Study Drugs - N/A
E. Medical Device - N/A

F. Study Questionnaires

All patients will be provided with the Pediatric Liver Scan Questionnaire, composed of the Pediatric Liver Scan Survey, Pediatric Quality of Life, and Alcohol Use Disorder.

G. Study Subjects

Children under age 22 years presenting for outpatient care of suspected or established NAFLD or chronic liver disease at Columbia University Medical Center (CUMC) and who are undergoing liver biopsy for clinical evaluation unrelated to this research proposal.

H. Recruitment of Subjects

Only parents or legal guardians of children with suspected liver disease will be approached to be in the study. Subjects will be primarily recruited from our Pediatric Gastroenterology Clinic at Columbia University. The study investigator and study physicians are the clinicians for this clinic, so the subjects approached to provide permission for their child's participation in the study will be their patients. Guardians of eligible children will be referred to study staff for enrollment after clinical decision to perform liver biopsy has been made. Study staff will obtain health care provider approval prior to screening. During screening, we will 1) explain that we are conducting a research study to improve the diagnosis of liver disease; 2) reassure that care in the GI program will in no way be affected by their decision about participation; and 3) confirm eligibility.

I. Confidentiality of the Study Data

Every reasonable effort will be made to keep records confidential. We will store data on a secure CUMC approved server. Each participant will receive a unique, random code. The file with the identity of subjects linked to their code will be in a password-encrypted software spreadsheet. No subject information with identifiable data will be transmitted outside the Columbia internet. All laboratory specimens, evaluation forms, reports, and other records that are part of the study data collection and entry materials will be identified by coded number only to maintain subject confidentiality. All records will be kept in locked file cabinets with access limited to study team. All computer entry and networking programs will identify subjects by participant identification number. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB. Consent procedures and forms, and the communication, transmission and storage of participant data will comply with individual site IRB and NIH requirements for compliance with HIPAA.

J. Potential Conflict of Interest

There are no potential conflicts of interest.

K. Location of the Study

Columbia University Medical Center

L. Potential Risks

Children enrolled in this study will be subject to minimal risk because the main study outcomes are based on liver biopsy histology that will be obtained for clinical care that is unrelated to this study. A theoretical risk of taking part in this study is the possibility of a loss of confidentiality or privacy. The study team plans to protect confidentiality as described in section 9 above. Other data for this study will be obtained by history, non-invasive anthropometric measurement, and non-invasive radiologic testing that does not involve radiation exposure. Study staff will ask parents non-threatening demographic data. Parents have the option of refusing to answer any question that makes them uncomfortable. Blood draw can be mildly painful and can cause

bruising and very rarely dizziness or fainting, blood clots, bleeding, or an infection at the site. If numbing cream is used for blood draws, it may cause pain, skin irritation, or rash. Some of the specimens collected may be used for DNA sequencing, however there is no risk related to DNA sequencing as the specimens will be de-identified and randomly coded so that the results cannot be linked back to the actual identify of the research subject. Performing CAP/LS takes under 30 minutes and does not involve radiologic exposure. MRI for the purpose of this study will also take approximately 15-30 minutes to obtain images, and does not involve radiation exposure. No more than minor discomfort is involved with collection of study data.

M. Potential Benefits

There is no immediate clinical benefit to participants in this study. The potential benefit to the human subjects will be a sense of contributing to advances in medical knowledge. This study may accelerate non-invasive detection of pediatric NAFLD and improve the non-invasive measurement of hepatic steatosis and fibrosis in children. Our results could lead to application of Controlled Attenuation Parameter (CAP)/Liver Stiffness (LS) measures in children, which may allow for non-invasive measurement of steatosis and fibrosis which currently is obtained through liver biopsy. Study results could open up new avenues to inform innovative approaches to reduce NAFLD, the most common cause of chronic liver disease in children.

N. Alternative Therapies

N/A - Not to participate in the project.

O. Compensation to Subjects

References:

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