Low and High Birth Weights Are Risk Factors for Nonalcoholic Fatty Liver Disease in Children

Kimberly P. Newton, MD[1,2], Haruna S. Feldman, PhD[3], Christina D. Chambers, PhD, MPH[3], Laura Wilson, ScM[4,5], Cynthia Behling, MD, PhD[6], Jeanne M. Clark, MD, MPH[4,5], Jean P. Molleston, MD[7], Naga Chalasani, MD[8], Arun J. Sanyal, MD[9], Mark H. Fishbein, MD[10], Joel E. Lavine, MD, PhD[11], and Jeffrey B. Schwimmer, MD[1,2], for the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)*

Objectives To examine the distribution of birth weight in children with nonalcoholic fatty liver disease (NAFLD) compared with the general US population, and to investigate the relationship between birth weight and severity of NAFLD.

Study design A multicenter, cross-sectional study of children with biopsy-proven NAFLD enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network Database. Birth weight was categorized as low birth weight (LBW), normal birth weight (NBW), or high birth weight (HBW) and compared with the birth weight distribution in the general US population. The severity of liver histology was assessed by birth weight category.

Results Children with NAFLD (n = 538) had overrepresentation of both LBW and HBW compared with the general US population (LBW, 9.3%; NBW, 75.8%; HBW, 14.9% vs LBW, 6.1%; NBW, 83.5%; HBW 10.5%; $P < .0001$). Children with HBW had significantly greater odds of having more severe steatosis (OR, 1.82, 95% CI. 1.15-2.88) and nonalcoholic steatohepatitis (OR, 2.03; 95% CI, 1.21-3.40) compared with children with NBW. In addition, children with NAFLD and LBW had significantly greater odds of having advanced fibrosis (OR, 2.23; 95% CI, 1.08-4.62).

Conclusion Birth weight involves maternal and in utero factors that may have long-lasting consequences. Children with both LBW and HBW may be at increased risk for developing NAFLD. Among children with NAFLD, those with LBW or HBW appear to be at increased risk for more severe disease. *(J Pediatr 2017;187:141-6).*

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the pediatric population.[1,2] NAFLD encompasses a broad spectrum of disease severity, ranging from isolated steatosis in its mildest form to nonalcoholic steatohepatitis (NASH) accompanied by inflammation, and hepatocellular injury with or without fibrosis in its more severe form.[3] NAFLD is typically discovered in early adolescence; the average age at diagnosis is 12 years.[3] Children with NAFLD have varying degrees of disease severity at the time of diagnosis, with NASH affecting 20%-30% and advanced fibrosis seen in 10%-15%.[4,5] Exposure variables that are meaningfully associated with the onset of the pathological process or the range of outcome severity in children with NAFLD have been underexplored, however.

The perinatal period is a critical time in development that may have a long-lasting influence on the development of NAFLD. From animal studies, we have learned that the states of both undernutrition[6] and overnutrition in utero[7] have the capacity to program the developing fetus in terms of lipid and glucose metabolism, thereby altering the risk for development of a range of cardiometabolic

BMI	Body mass index
HBW	High birth weight
LBW	Low birth weight
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NASH CRN	Nonalcoholic Steatohepatitis Clinical Research Network
NBW	Normal birth weight
VLBW	Very low birth weight

From the [1]Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California San Diego School of Medicine, La Jolla; [2]Division of Gastroenterology, Department of Pediatrics, Rady Children's Hospital, San Diego; [3]Division of Dysmorphology and Teratology, Department of Pediatrics, University of California San Diego, La Jolla, CA; [4]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University; [5]Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD; [6]Department of Pathology, Sharp Medical Center, San Diego, CA; [7]Department of Pediatrics, Riley Children's Hospital; [8]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN; [9]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA; [10]Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; and [11]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Columbia University, New York, NY

*A list of members of the NASH CRN is available at www.jpeds.com (Appendix).

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diseases in later life. Birth weight is a concrete measure of this fetal adaptation and programming during pregnancy, and has been examined as a risk factor for conditions associated with NAFLD in humans, including type 2 diabetes mellitus[8] and hypertension.[9] The presence of hepatic steatosis in the neonatal period has been demonstrated via imaging and histopathology in several studies, supporting the concept that the potential for NAFLD is influenced by the intrauterine environment.[10-12]

Data in both children and adults suggest that LBW is associated with elevated risk for the development of NAFLD.[13,14] There are no published data on the relationship between HBW and NAFLD. We hypothesized that birth weights outside of the normal range, either low or high, influence the risk for NAFLD. Therefore, the aims of this study were to evaluate the distribution of birth weight in children with NAFLD compared with the general US population, as well as the associations of LBW and HBW with the severity of NAFLD as determined by liver histology.

Methods

Data were obtained from children who were enrolled in the database of the National Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network (NASH CRN). Participants in this study were selected from those enrolled in NASH CRN studies at 13 participating clinical centers between 2004 and 2012.[15,16] Inclusion criteria for this analysis were age <21 years at registration, a parent-reported birth weight, and a diagnosis of NAFLD. The decision for inclusion of subjects was based on the prevailing National Institutes of Health's definition of child (<age 21 years) at the time that this study was designed and implemented. The diagnosis of NAFLD was based on liver histology showing ≥5% of hepatocytes containing macrovesicular fat and the exclusion of other causes of chronic liver disease by clinical history, laboratory studies, and histology. Children were excluded if they had an implausible birth weight (ie, numeric value representing height recorded instead of weight) or very low birth weight (VLBW; <1500 g), because the children with VLBW were excluded from the 1977 National Center for Health Statistics and 2000 Center for Disease Control and Prevention growth charts.

The Institutional Review Board at each participating center approved this study. Written informed consent was obtained from the participant if age ≥18 years or from a parent or guardian, and written informed assent was obtained from all children aged ≥8 years before participation.

Phenotyping of the Cohort

Demographic data on study participants were obtained via a structured interview. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Weight, height, and waist measurements were performed in duplicate with the children wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). BMI percentile was determined according to age and sex based on data from the Centers for Disease Control and Prevention. To compare BMI at different ages and between boys and girls, BMI *z*-scores were calculated.

Participants fasted overnight for 12 hours before phlebotomy via venipuncture. Each clinical center performed reported laboratory assays on site, including serum glucose, insulin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase.

Liver Histology

A diagnosis of NAFLD was based on liver histology with ≥ 5% of hepatocytes containing macrovesicular fat and the exclusion of other causes of chronic liver disease by clinical history, laboratory studies, and histology. Liver biopsy specimens were stained with hematoxylin and eosin and with Masson's trichrome stain and centrally reviewed by the Pathology Committee of the NASH CRN according to the NASH CRN scoring system.[17] Members of the Pathology Committee were blinded to all demographic and clinical data. Biopsy specimens were scored for the degree of steatosis present in hepatocytes as follows: grade 0, <5% steatosis; grade 1, 5%-33%; grade 2, 34%-66%; and grade 3, >66%. Liver biopsy specimens were diagnosed as NASH, borderline NASH, NAFLD, not NASH, or not NAFLD based on the aggregate presence and degree of the individual features of NAFLD. A typical set of minimum criteria for diagnosing NASH included >5% macrovesicular steatosis, lobular inflammation, and hepatocyte injury, as manifested by ballooning degeneration. Cases identified as NAFLD not NASH showed >5% steatosis with no or minimal inflammation. Cases diagnosed as borderline NASH had steatosis and inflammation but equivocal or no ballooning degeneration with or without a fibrosis pattern typical of NASH. Also included in the borderline NASH category (type 2) were cases with portal inflammation and/or fibrosis, with a zone 1 or panacinar distribution of steatosis, the pattern of fatty liver disease common in children.[1,18] This assignment of NASH, borderline NASH, or NAFLD was done by consensus agreement of the NASH CRN pathology group at the time of the central review of cases in accordance with protocol.

Exposure Variable: Birth Weight Category

Parents were asked for the participating child's birth weight. Birth weights were categorized as low birth weight (LBW; 1500-2499 g), normal birth weight (NBW; 2500-3999 g), or high birth weight (HBW; ≥4000 g).

Statistical Analyses

Descriptive statistics used to compare characteristics in children with LBW, NBW, or HBW included mean ±SD, median and range, and frequency, and percentage. ANOVA and Tukey test for pairwise comparisons were used to obtain *P* values for continuous variables. The χ^2 test and Fisher exact test were used to obtain *P* values for categorical variables. The severity of NAFLD was determined based on 3 histological measures: