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# Prevalence of Type 2 Diabetes and Prediabetes in Children with Nonalcoholic Fatty Liver Disease

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## Abstract

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**Conflict of Interest:** The authors have no conflicts of interest to disclose.

Both Kimberly P. Newton and Jeffrey B. Schwimmer had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Importance—**Nonalcoholic fatty liver disease (NAFLD) is the major chronic liver disease in children in the United States and is associated with insulin resistance. In adults, NAFLD is also associated with type 2 diabetes. The prevalence of type 2 diabetes in children with NAFLD is unknown.

**Objective—**The study aims were to determine the prevalence of type 2 diabetes and prediabetes in children with NAFLD, and assess type 2 diabetes and prediabetes as risk factors for nonalcoholic steatohepatitis (NASH).

**Design—**This was a multi-center, cross-sectional study.

**Settings—**Twelve pediatric clinical centers across the United States participating in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) NASH Clinical Research Network (NASH CRN).

**Participants—**Children < 18 years of age with biopsy-confirmed NAFLD enrolled in the NASH CRN.

**Main Outcomes and Measures—**The presence of type 2 diabetes and prediabetes as determined by American Diabetes Association screening criteria using clinical history and fasting laboratory values.

**Results—**There were 675 children with NAFLD included with a mean age of 12.6 years and mean BMI of 32.5 kg/m2. The estimated prevalence of prediabetes was 23.4% (95% CI 20.2 – 26.6%) and of type 2 diabetes was 6.5% (95% CI 4.6–8.4%). Girls with NAFLD had 1.6 (95% CI 1.04 – 2.40) times greater odds of having prediabetes, and 5.0 (95% CI 2.49 – 9.98) times greater odds of having type 2 diabetes than boys with NAFLD. The prevalence of NASH was higher in those with type 2 diabetes (43.2%) compared to prediabetes (34.2%) or normal glucose (22%) ($p<0.001$). The odds of having NASH was significantly higher in those with prediabetes (OR 1.9; 95% CI 1.21–2.9) or type 2 diabetes (OR 3.1; 95% CI 1.5–6.2) compared to those with normal glucose.

**Conclusions and Relevance—**Nearly 30% of children with NAFLD have type 2 diabetes or prediabetes. These children have greater odds of having NASH, and thus, are at greater long-term risk for adverse hepatic outcomes.

## INTRODUCTION

There are an estimated 7 million children in the United States with nonalcoholic fatty liver disease (NAFLD) and it is now the most common cause of chronic liver disease in the pediatric population. [1] NAFLD encompasses a broad spectrum of disease severity ranging from isolated steatosis in its mildest form to steatohepatitis with advanced fibrosis and cirrhosis [2, 3]. Moreover, NAFLD can lead to liver failure requiring liver transplantation and hepatocellular carcinoma even in children [4, 5], and has now become the second leading cause of liver transplantation in the United States in adults [6, 7]. NAFLD has serious health consequences outside of the liver as well, and is associated with metabolic impairment and increasing risk for cardiovascular disease, insulin resistance and subsequent type 2 diabetes mellitus. [8, 9]

In adults with NAFLD, abnormal glucose metabolism is common. Furthermore, the presence of type 2 diabetes in adults with NAFLD is a clinically relevant risk factor for the more progressive form of NAFLD, nonalcoholic steatohepatitis (NASH), as well as a predictor of liver-related mortality [10, 11]. The impact of type 2 diabetes in children with NAFLD has been less well defined. Although insulin resistance occurs in a majority of children with biopsy-proven NAFLD, the prevalence of type 2 diabetes and prediabetes is an unaddressed gap in knowledge. To date, sample sizes have been too small to support a stable estimate of the prevalence of type 2 diabetes or prediabetes in the pediatric NAFLD population, and targeted analysis of meaningful clinical-histopathologic correlates with type 2 diabetes has not been reported. [12–17]

In order to further understanding of the relationship between NAFLD and type 2 diabetes in the pediatric population, we performed a multi-center cohort study with the following study aims: 1) to determine the prevalence of type 2 diabetes and prediabetes in children with well-characterized NAFLD, 2) to determine differences in demographic and key clinical parameters between children with NAFLD who have type 2 diabetes, prediabetes, or normal glucose metabolism, and 3) to assess the relationship between histologic features and severity of NAFLD and the presence of type 2 diabetes and prediabetes in children with NAFLD.

## METHODS

### Study Population

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) NASH Clinical Research Network (NASH CRN) includes 12 participating pediatric clinical centers across the United States (see acknowledgments). Participants in this study were selected from children enrolled in the following NASH CRN studies: longitudinal cohort studies of Database and Database 2 (NCT01061684), and randomized controlled trials of TONIC (NCT00063635), and CyNCh (NCT01529268). NAFLD Database began enrollment in September 2004, TONIC in August 2005, Database 2 in October 2009, and CyNCH in June 2012. These studies were approved by the institutional review board at each participating center. Written consent for all participants was obtained from a parent or guardian, and written assent was obtained from all children 8 years or older prior to participation. For this analysis, we included children who were < 18 years of age with biopsy-confirmed NAFLD.

### NAFLD Diagnosis

A diagnosis of NAFLD was based on liver histology with ≥ 5% of hepatocytes containing macrovesicular fat, exclusion of other causes of chronic liver disease by clinical history, exclusion of potentially hepatotoxic medications (e.g. chronic corticosteroids, valproic acid, methotrexate, etc.), laboratory studies, and histology. [2] Liver biopsy specimens were stained with hematoxylin-eosin and Masson's trichrome stain and centrally reviewed by the Pathology Committee of the NASH CRN according to the NASH CRN scoring system, which has been validated in the pediatric population[20]. The Pathology Committee was blinded to all demographic and clinical data. Biopsies were scored for the degree of steatosis present in hepatocytes as follows: grade 0, < 5% steatosis; grade 1, 5 to 33%; grade 2, 34 to

66%; and grade 3, > 66%. Liver biopsies were diagnosed as nonalcoholic steatohepatitis (NASH), borderline NASH, or NAFLD not NASH based on the aggregate presence and degree of the individual features of nonalcoholic fatty liver disease. A typical set of minimum criteria to diagnose NASH would include > 5% macrovesicular steatosis, lobular inflammation and hepatocyte injury as manifest by ballooning degeneration. Cases determined to be NAFLD not NASH show > 5% steatosis with no or minimal inflammation. This assignment of NASH, borderline NASH, or NAFLD was made as a consensus agreement of the NASH CRN pathology group at the time of central review of cases as per protocol.

## Outcomes

Children with an existing clinical diagnosis of type 1 diabetes were excluded from the study. As has been done in other large epidemiologic studies [18], we assigned our case definitions for prediabetes and type 2 diabetes on a one- time laboratory measurement based on parameters defined by the ADA. Children were considered to have prediabetes if they met at least one of the two criteria: 1) fasting serum glucose between 100 mg/dL and 125 mg/dL; or 2) HbA1c ≥ 5.7 % and < 6.5 %. Children were considered to have type 2 diabetes if they met at least one of the three criteria: 1) fasting serum glucose ≥ 126 mg/dL; 2) HbA1C ≥ 6.5%; or 3) existing clinical diagnosis of type 2 diabetes. [19]. Children were considered to have normal glucose metabolism if neither the criteria for prediabetes nor type 2 diabetes were met.

## Covariates

A structured interview was used to obtain demographic data on study participants. Weight and height were measured to the nearest 0.1kg and 0.1 cm respectively. Weight, height, and waist measurements were performed in duplicate while wearing light clothing without shoes. BMI was calculated as weight (kg) divided by height (m) squared. BMI percentile was determined according to age and gender based on data from the Centers for Disease Control and Prevention. To compare BMI among different ages and in both boys and girls, the BMI Z-score was calculated.

Participants fasted overnight for 12 hours before phlebotomy via venipuncture. Each clinical center performed reported laboratory assays on site to include the following tests: glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyltransferase (GGT).

## Statistical Analysis

Standard descriptive statistics were used to compare children with NAFLD across three subgroups based upon glucose status (normal glucose metabolism, pre-diabetes, and type 2 diabetes). The proportion of prediabetes and type 2 diabetes along with its 95% confidence interval was reported. Risk factors for having prediabetes and type 2 diabetes in children with NAFLD were identified using a multinomial logistic regression model with the odds of prediabetes and the odds of type 2 diabetes as the outcomes, and the following candidate set of risk factors: age, sex, race/ethnicity, BMI, waist circumference, study, and clinical center.

Parallel analyses were done separating children with NAFLD into those with and without NASH. Using glucose status (normal glucose, prediabetes and type 2 diabetes) as the exposure variable, the odds of having NASH among children with NAFLD was determined using multiple logistic regression with the presence of NASH as the binary outcome, and inclusion of the following covariates: age, sex, race/ethnicity, BMI, waist circumference, study, and clinical center. All analyses were two-sided, with p-value <= 0.05 considered to be statistically significant. Analyses were performed using R version 3.2.2.

## RESULTS

### Study Population

We included 675 children enrolled in the NASH CRN. There were 2 children with a prior diagnosis of type 1 diabetes who were excluded from the analysis. The demographic and clinical parameters are shown in Table 1. The mean age of the participants was 12.6 (SD 2.7) years. The mean BMI of participants was 32.5 (SD 6.3) $kg/m^2$ and the mean BMI z-score was 2.3 (SD 0.4). The distribution of disease severity was as follows: NAFLD but not NASH in 26.7% (180 of 675), borderline NASH in 47.1% (318 of 675) and definite NASH in 26.2 % (177 of 675). The majority of participants 71.1% (480 of 675) were boys. There was no significant difference between boys and girls with respect to age (p=0.67) or race/ethnicity (p=0.18). Boys had a significantly higher mean BMI z-score than girls (mean 2.3 (SD 0.4) vs. mean 2.2 (SD 0.4); p<.001).

### Type 2 Diabetes and Prediabetes in Children with NAFLD

For children with NAFLD, the estimated prevalence of prediabetes was 23.4% (95% CI 20.3–26.7). The estimated prevalence of type 2 diabetes was 6.5% (95% CI 4.7–8.4%). A clinical diagnosis of type 2 diabetes had been established prior to enrollment in the NASH CRN in 33 of the 44 children (75%). As shown in Table 1, the mean age for children with prediabetes and type 2 diabetes was slightly, but significantly higher than children with normal glucose metabolism. Girls with NAFLD were significantly more likely to have type 2 diabetes than boys with NAFLD (13.7% vs. 3.5%, p < 0.001). BMI varied significantly in children with NAFLD by glucose status (normal glucose 32.0 $kg/m^2$, prediabetes 33.3 $kg/m^2$, type 2 diabetes 35.5 $kg/m^2$; p<0.001) however the BMI z-score was not significantly different between groups. Waist circumference also varied significantly across groups (normal glucose 103 cm, prediabetes 107 cm, type 2 diabetes 113 cm; p<0.001). After controlling for these covariates, girls with NAFLD had 1.6 (95% CI 1.0 – 2.4) times greater odds of having prediabetes, and 5.0 (95% CI 2.5 – 10.0) times greater odds of having type 2 diabetes than boys with NAFLD. (Online Supplement Table 1) Serum GGT activity was significantly higher across groups by glucose status (normal glucose 45 (SD 32) U/L, prediabetes 47 (SD 37) U/L, type 2 diabetes 61 (SD 44) U/L; p= 0.02). There was also a significant difference in serum triglyceride concentration by glucose status (normal glucose 145 (SD 83) mg/dL, prediabetes 150 (SD 82) mg/dL, type 2 diabetes 196 (SD 132) mg/dL; p= 0.002). There was no significant difference in ALT, AST, total cholesterol, LDL-cholesterol, or HDL-cholesterol by glucose status.

### NAFLD Histologic Features and Severity

Among children with NAFLD, NASH was present in 21.9% of those with normal glucose metabolism, 34.2% of those with prediabetes, and 43.2% of those with type 2 diabetes ($p<0.001$). (Table 2) After controlling for age, sex, race/ethnicity, BMI and waist circumference among children with NAFLD, the odds of NASH was significantly higher in those with prediabetes (OR 1.9; 95% CI 1.21 – 2.86) or type 2 diabetes (OR 3.1; 95% CI 1.51–6.22) compared to those with normal glucose metabolism. (Table 3) There was no difference in steatosis grade or inflammation among groups, however the ballooning degeneration was significantly different among children with normal glucose, prediabetes and type 2 diabetes ($p<0.001$); children with normal glucose had less ballooning degeneration than those with prediabetes or type 2 diabetes. (Table 2) Among children with NAFLD, those with NASH had significantly higher mean fasting glucose (93 (SD 25) vs. 87 (SD 13) mg/dL; $p = 0.001$) and insulin concentrations (46 (SD 69) vs. 30 (SD 28) uU/ml, $p = 0.003$) than children without NASH.

## DISCUSSION

We studied the prevalence of type 2 diabetes and prediabetes in a large multi-center cohort of children with NAFLD from pediatric centers across the United States. Nearly 30% of children with NAFLD had abnormal glucose metabolism with 6.5% satisfying our criteria for type 2 diabetes. Notably, independent of age and BMI, girls with NAFLD were more likely to have type 2 diabetes than boys with NAFLD. Finally, among children with NAFLD, children with type 2 diabetes had more than three times the odds of having nonalcoholic steatohepatitis (NASH), which is the more progressive form of NAFLD.

Among our cohort, the prevalence of children with type 2 diabetes was much higher than would be expected, based on contributions from obesity alone. The best available epidemiologic study of diabetes, the SEARCH study, estimated U.S. population prevalence for type 2 diabetes for 10–19 year olds at 0.42 per 1000 (95% confidence interval of 0.29–0.45) [21]. Because type 2 diabetes occurs predominantly among the 20% of youth with obesity, an estimated diabetes rate among obese youth of 0.42 per 200 remains well below 1%, much less than 6.5% prevalence observed in our cohort of children with NAFLD. Although the NASH CRN enrollment does not aim to represent the population, the findings suggest that youth with NAFLD have substantially higher risk of type 2 diabetes than obese youth in general [22, 23]. It is possible we over-diagnosed type 2 diabetes based on using single measurements of fasting glucose and HbA1C to classify glucose status in this study. That said, most of those youth who met criteria of type 2 diabetes were given this diagnosis by clinicians: the minority were assigned a diagnosis of type 2 based on single lab measurements.

Although systemic insulin resistance is believed be important in the pathogenesis of both pediatric NAFLD and type 2 diabetes, there are no longitudinal studies that evaluate the cause-effect relationship between these two associated conditions. Several studies in children have shown that higher intrahepatic fat content is associated with greater degrees of insulin resistance and impaired glucose regulation prior to the onset of overt diabetes [24, 25]. Moreover, children diagnosed with NAFLD have been shown to have significantly higher

rates of impaired fasting glucose compared to overweight and obese matched controls [8]. In our cross-sectional analysis, over 6% of children with NAFLD had diabetes. However, among pediatric populations with type 2 diabetes, 50–60% have suspected NAFLD, based upon elevated ALT [26, 27]. As such, our study contributes to the collective body of evidence supporting the contention that NAFLD may be a precursor to type 2 diabetes development.

A major finding in this study was that children with NAFLD who had type 2 diabetes had 3.1 times the odds for NASH. Although prognostic implications of NASH in childhood are not fully known, in adulthood, the NASH phenotype conveys substantially greater risk for cirrhosis [10]. Furthermore, the risk of a more pronounced hepatic injury is compounded by the presence of type 2 diabetes. Younossi et al demonstrated that in 132 adult subjects with histologically-confirmed NAFLD, 25% of those with type 2 diabetes had cirrhosis, compared to only 10% of those without diabetes [11]. Type 2 diabetes has also been shown to be independent risk factor for hepatocellular carcinoma development in adults with NAFLD [28]. Finally, adults with type 2 diabetes have nearly three times the risk of dying from chronic liver disease [29]. The current study advances the literature by showing that, as early as childhood, prediabetes and type 2 diabetes emerge as clear risk factors for NASH, with potential downstream implications for future morbidity and mortality.

There was a striking influence of gender on type 2 diabetes risk in children with NAFLD in this study. Epidemiologic data to date have consistently demonstrated that NAFLD in children affects predominantly boys [30–32]. However, we showed that among the sub-population of children with abnormal glucose metabolism, there was a notable female predominance, with over 60% of those with type 2 diabetes being girls as compared to only 25% with NAFLD alone. This female predominance is consistent with what has been previously described in large epidemiologic studies of children with type 2 diabetes. [33, 34]. The reason for this gender difference is not explained by other demographic or clinical factors, and thus remains unclear. From this information, it seems that although girls are less likely to have NAFLD overall, they are more likely to have associated comorbidities which increase their risk for many negative health consequences [9]. As such, understanding these gender differences is a major unmet research need.

This is the first study to examine the prevalence of abnormal glucose metabolism in a large multi-center cohort of children with biopsy-proven NAFLD. This study was performed by the NASH CRN, which has diverse geographic representation of children with accurate and rigorously characterized NAFLD. There were limitations in this study in that there was only a single time point measure of glucose metabolism. In the clinical world, diagnosis of prediabetes and diabetes is more complex and based on multiple measurements, assessment of symptoms, and islet cell antibody status. In addition, study subjects did not undergo oral glucose tolerance testing. Therefore the true prevalence of abnormal glucose metabolism may be overestimated or underestimated. Moreover, there have been acknowledged challenges using HbA1C in childhood to characterize abnormal glucose metabolism, as the ideal cut point to capture those at greatest risk for prediabetes, diabetes and diabetic sequelae is controversial [35, 36]. In addition, HbA1c has had a heterogeneous diagnostic performance among different racial/ethnic populations [37] and can be inaccurate when nonglycemic test factors such as hemoglobinopathies, iron deficient anemia or impaired renal function are

present [38, 39]. Despite this, HbA1C parameters chosen in this study were consistent with most recent American Diabetes Association recommendations for screening [19] and are regarded as effective in screening for prediabetes and diabetes in overweight and obese populations [40].

In children with NAFLD, both type 2 diabetes and prediabetes are common. As many as one in three children with NAFLD will have abnormal glucose metabolism. The presence of type 2 diabetes in children with NAFLD identifies the highest risk population for NASH. Although children with NAFLD overall are typically boys, girls with NAFLD are more likely to have diabetes. Special attention should be given to children with the combination of type 2 diabetes and NASH, as they are at particularly high risk for premature morbidity and mortality. In conclusion, children with NAFLD merit a detailed clinical evaluation of abnormal glucose metabolism, along with long term monitoring for progression of liver disease, diabetes and the consequences of both.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Contributors' Statements:**

**Kimberly P. Newton:** Conceptualized and designed the study, performed the study, carried out the initial analyses, drafted the initial manuscript, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

**Jiayi Hou:** Carried out the initial analyses and performed the statistical analysis.

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**Michele Donithan:** Coordinated and supervised data collection and distribution and approved final manuscript as submitted.

**Jeanne M. Clark:** Coordinated and supervised data collection and distribution and approved final manuscript as submitted.

**Jeffrey B. Schwimmer:** Conceptualized and designed the study, performed the study, carried out the initial analyses, drafted the initial manuscript, critically reviewed and revised the manuscript, approved the final manuscript as submitted, and provided supervision.

## References


1. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics. 2006; 118(4):1388–1393. [PubMed: 17015527]
2. Lindback SM, Gabbert C, Johnson BL, Smorodinsky E, Sirlin CB, Garcia N, et al. Pediatric nonalcoholic fatty liver disease: a comprehensive review. Advances in pediatrics. 2010; 57(1):85–140. [PubMed: 21056736]
3. Molleston JP, Schwimmer JB, Yates KP, Murray KF, Cummings OW, Lavine JE, et al. Histological abnormalities in children with nonalcoholic fatty liver disease and normal or mildly elevated alanine aminotransferase levels. The Journal of pediatrics. 2014; 164(4):707–713. e703. [PubMed: 24360992]
4. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut. 2009; 58(11):1538–1544. [PubMed: 19625277]
5. Nobili V, Alisi A, Grimaldi C, Liccardo D, Francalanci P, Monti L, et al. Non-alcoholic fatty liver disease and hepatocellular carcinoma in a 7-year-old obese boy: coincidence or comorbidity? Pediatric obesity. 2014; 9(5):e99–e102. [PubMed: 24302697]
6. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011; 141(4):1249–1253. [PubMed: 21726509]
7. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015; 148(3):547–555. [PubMed: 25461851]
8. Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. Circulation. 2008; 118(3):277–283. [PubMed: 18591439]
9. Schwimmer JB, Zepeda A, Newton KP, Xanthakos SA, Behling C, Hallinan EK, et al. Longitudinal assessment of high blood pressure in children with nonalcoholic fatty liver disease. PloS one. 2014; 9(11):e112569. [PubMed: 25419656]
10. Loomba R, Abraham M, Unalp A, Wilson L, Lavine J, Doo E, et al. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. Hepatology. 2012; 56(3):943–951. [PubMed: 22505194]
11. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2004; 2(3):262–265. [PubMed: 15017611]
12. Aygun C, Kocaman O, Sahin T, Uraz S, Eminler AT, Celebi A, et al. Evaluation of metabolic syndrome frequency and carotid artery intima-media thickness as risk factors for atherosclerosis in patients with nonalcoholic fatty liver disease. Digestive diseases and sciences. 2008; 53(5):1352–1357. [PubMed: 17939039]
13. Carter-Kent C, Yerian LM, Brunt EM, Angulo P, Kohli R, Ling SC, et al. Nonalcoholic steatohepatitis in children: a multicenter clinicopathological study. Hepatology. 2009; 50(4):1113–1120. [PubMed: 19637190]
14. Manco M, Marcellini M, Devito R, Comparcola D, Sartorelli MR, Nobili V. Metabolic syndrome and liver histology in paediatric non-alcoholic steatohepatitis. International journal of obesity. 2008; 32(2):381–387. [PubMed: 18087267]
15. Patton HM, Lavine JE, Van Natta ML, Schwimmer JB, Kleiner D, Molleston J, et al. Clinical correlates of histopathology in pediatric nonalcoholic steatohepatitis. Gastroenterology. 2008; 135(6):1961–1971. e1962. [PubMed: 19013463]
16. Patton HM, Yates K, Unalp-Arida A, Behling CA, Huang TT, Rosenthal P, et al. Association between metabolic syndrome and liver histology among children with nonalcoholic Fatty liver

disease. The American journal of gastroenterology. 2010; 105(9):2093–2102. [PubMed: 20372110]

17. Schwimmer JB, Deutsch R, Rauch JB, Behling C, Newbury R, Lavine JE. Obesity, insulin resistance, and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. The Journal of pediatrics. 2003; 143(4):500–505. [PubMed: 14571229]
18. Bullard KM, Saydah SH, Imperatore G, Cowie CC, Gregg EW, Geiss LS, et al. Secular changes in U.S. Prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999–2010. Diabetes care. 2013; 36(8):2286–2293. [PubMed: 23603918]
19. American Diabetes A. Standards of medical care in diabetes--2014. Diabetes care. 2014; 37(Suppl 1):S14–80. [PubMed: 24357209]
20. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005; 41(6):1313–1321. [PubMed: 15915461]
21. Liese AD, D'Agostino RB Jr, Hamman RF, Kilgo PD, Lawrence JM, et al. Group SfDiYS. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics. 2006; 118(4):1510–1518. [PubMed: 17015542]
22. Maffeis C, Pinelli L, Brambilla P, Banzato C, Valzolgher L, Ulmi D, et al. Fasting plasma glucose (FPG) and the risk of impaired glucose tolerance in obese children and adolescents. Obesity. 2010; 18(7):1437–1442. [PubMed: 19851301]
23. Shah S, Kublaoui BM, Oden JD, White PC. Screening for type 2 diabetes in obese youth. Pediatrics. 2009; 124(2):573–579. [PubMed: 19620188]
24. Cali AM, De Oliveira AM, Kim H, Chen S, Reyes-Mugica M, Escalera S, et al. Glucose dysregulation and hepatic steatosis in obese adolescents: is there a link? Hepatology. 2009; 49(6): 1896–1903. [PubMed: 19434725]
25. D'Adamo E, Cali AM, Weiss R, Santoro N, Pierpont B, Northrup V, et al. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. Diabetes care. 2010; 33(8):1817–1822. [PubMed: 20668154]
26. Hudson OD, Nunez M, Shaibi GQ. Ethnicity and elevated liver transaminases among newly diagnosed children with type 2 diabetes. BMC pediatrics. 2012; 12:174. [PubMed: 23134937]
27. Nadeau KJ, Klingensmith G, Zeitler P. Type 2 diabetes in children is frequently associated with elevated alanine aminotransferase. Journal of pediatric gastroenterology and nutrition. 2005; 41(1): 94–98. [PubMed: 15990637]
28. Kawamura Y, Arase Y, Ikeda K, Seko Y, Imai N, Hosaka T, et al. Large-scale long-term follow-up study of Japanese patients with non-alcoholic Fatty liver disease for the onset of hepatocellular carcinoma. The American journal of gastroenterology. 2012; 107(2):253–261. [PubMed: 22008893]
29. Zoppini G, Fedeli U, Gennaro N, Saugo M, Targher G, Bonora E. Mortality from chronic liver diseases in diabetes. The American journal of gastroenterology. 2014; 109(7):1020–1025. [PubMed: 24890439]
30. Kistler KD, Molleston J, Unalp A, Abrams SH, Behling C, Schwimmer JB, et al. Symptoms and quality of life in obese children and adolescents with non-alcoholic fatty liver disease. Alimentary pharmacology & therapeutics. 2010; 31(3):396–406. [PubMed: 19863497]
31. Schwimmer JB, McGreal N, Deutsch R, Finegold MJ, Lavine JE. Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents. Pediatrics. 2005; 115(5):e561–565. [PubMed: 15867021]
32. Schwimmer JB, Newton KP, Awai HI, Choi LJ, Garcia MA, Ellis LL, et al. Paediatric gastroenterology evaluation of overweight and obese children referred from primary care for suspected non-alcoholic fatty liver disease. Alimentary pharmacology & therapeutics. 2013; 38(10):1267–1277. [PubMed: 24117728]
33. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. Jama. 2014; 311(17): 1778–1786. [PubMed: 24794371]

34. Narasimhan S, Weinstock RS. Youth-onset type 2 diabetes mellitus: lessons learned from the TODAY study. Mayo Clinic proceedings. 2014; 89(6):806–816. [PubMed: 24702733]
35. Lee JM, Wu EL, Tarini B, Herman WH, Yoon E. Diagnosis of diabetes using hemoglobin A1c: should recommendations in adults be extrapolated to adolescents? The Journal of pediatrics. 2011; 158(6):947–952. e941–943. [PubMed: 21195416]
36. Nowicka P, Santoro N, Liu H, Lartaud D, Shaw MM, Goldberg R, et al. Utility of hemoglobin A(1c) for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes care. 2011; 34(6):1306–1311. [PubMed: 21515842]
37. Kamps JL, Hempe JM, Chalew SA. Racial disparity in A1C independent of mean blood glucose in children with type 1 diabetes. Diabetes care. 2010; 33(5):1025–1027. [PubMed: 20185743]
38. Higgins T, Stewart D, Boehr E. Challenges in HbA1c analysis and reporting: an interesting case illustrating the many pitfalls. Clinical biochemistry. 2008; 41(13):1104–1106. [PubMed: 18602911]
39. Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediatrics international : official journal of the Japan Pediatric Society. 1999; 41(4):357–362. [PubMed: 10453183]
40. Sjaarda LA, Michaliszyn SF, Lee S, Tfayli H, Bacha F, Farchoukh L, et al. HbA(1c) diagnostic categories and beta-cell function relative to insulin sensitivity in overweight/obese adolescents. Diabetes care. 2012; 35(12):2559–2563. [PubMed: 22912428]

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**Table 1**

Demographic and Clinical Variables by Glucose Status

| **Characteristics N (%) or mean ± SD** | **Normal glucose N=473** | **Prediabetes[a] N=158** | **Type 2 Diabetes[b] N=44** | **Total N=675** | **p-value[c]** |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 12.4 ± 2.7 | 13.0 ± 2.5 | 13.8 ± 2.5 | 12.6 ± 2.7 | <.001 |
| Sex | | | | | |
| Female | 116 (24.5%) | 52 (32.9%) | 27 (61.4%) | 195 (28.9%) | <.001 |
| Male | 357 (75.5%) | 106 (67.1%) | 17 (38.6%) | 480 (71.1%) | |
| Race/Ethnicity | | | | | |
| White non-Hispanic | 127 (26.8%) | 47 (29.7%) | 17 (38.6%) | 191 (28.3%) | 0.009 |
| Hispanic | 327 (69.1%) | 95 (60.1%) | 23 (52.3%) | 445 (65.9%) | |
| Non-Hispanic | 19 (4.0%) | 16 (10.1%) | 4 (9.1%) | 39 (5.8%) | |
| **Anthropomorphic** | | | | | |
| Height (cm) | 158.6 ± 14.1 | 161.6 ± 12.9 | 163.2 ± 11.6 | 159.6 ± 13.7 | 0.012 |
| Weight (kg) | 82.3 ± 25.5 | 88.4 ± 24.7 | 96.3 ± 26.6 | 84.6 ± 25.7 | <.001 |
| BMI (kg/m$^2$) | 32.0 ± 6.4 | 33.3 ± 5.9 | 35.5 ± 6.1 | 32.5 ± 6.3 | <.001 |
| BMI Z-score | 2.3 ± 0.4 | 2.3 ± 0.4 | 2.4 ± 0.4 | 2.3 ± 0.4 | 0.250 |
| Waist circumference (cm) | 103.1 ± 15.5 | 106.5 ± 14.3 | 112.9 ± 16.6 | 104.5 ± 15.5 | <.001 |
| **Blood Pressure** | | | | | |
| Systolic BP | 121 (14) | 123 (14) | 126 (11) | 122 (14) | 0.027 |
| Diastolic BP | 68 (10) | 68 (9) | 71 (8) | 68 (10) | 0.108 |
| **Liver enzymes** | | | | | |
| ALT (U/L) | 106 (84) | 114 (91) | 114 (136) | 108 (90) | 0.572 |
| AST (U/L) | 63 (48) | 68 (54) | 72 (65) | 65 (51) | 0.33 |
| GGT (U/L) | 45 (32) | 47 (36) | 61 (44) | 46 (34) | 0.018 |
| **Serum chemistries** | | | | | |
| Serum Glucose (mg/dL) | 85 (8) | 93 (12) | 113 (53) | 88 (17) | <.001 |
| HbA1C (%) | 5.2 ± 0.3 | 5.7 ± 0.3 | 7.8 ± 3.8 | 5.5 ± 1.2 | <.001 |
| Serum insulin (uU/mL) | 32 (42) | 40 (47) | 43 (41) | 35 (44) | 0.072 |
| HDL cholesterol (mg/dL) | 39 (9) | 39 (9) | 38 (11) | 39 (9) | 0.966 |
| LDL cholesterol (mg/dL) | 100 (30) | 101 (30) | 109 (32) | 101 (30) | 0.255 |

| Characteristics N (%) or mean ± SD | Normal glucose N=473 | Prediabetes[a] N=158 | Type 2 Diabetes[b] N=44 | Total N=675 | p-value[c] |
|---|---|---|---|---|---|
| Total cholesterol (mg/dL) | 167 (39) | 169 (38) | 183 (36) | 169 (38) | 0.060 |
| Triglycerides (mg/dL) | 145 (83) | 150 (82) | 196 (132) | 149 (87) | 0.002 |

Abbreviations: BMI=body mass index, ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyl transpeptidase, HbA1c= Hemoglobin A1C, HDL=high-density lipoprotein, LDL=low-density lipoprotein.

[a] Prediabetes defined as 1) fasting serum glucose between 100 mg/dL and 125 mg/dL; or 2) HbA1c ≥ 5.7 % and < 6.5 %

[b] Type 2 diabetes defined as 1) fasting serum glucose ≥ 126 mg/dL; 2) HbA1C ≥ 6.5%; or 3) existing clinical diagnosis of type 2 diabetes.

[c] p-values are calculated based on F-test for continuous variables, and a $X^2$ test for categorical variables.

**Table 2**

Liver Histology Distribution by Glucose Status

| Liver histology | Normal glucose N=473 | Prediabetes[a] N=158 | Type 2 Diabetes[b] N=44 | Total N=675 | p-value[c] |
|---|---|---|---|---|---|
| **Steatosis Grade** | | | | | 0.554 |
| <33% | 125 (26.4%) | 39 (24.7%) | 10 (22.7%) | 174 (25.8%) | |
| 34–66% | 155 (32.8%) | 43 (27.2%) | 14 (31.8%) | 212 (31.4%) | |
| >66% | 193 (40.8%) | 76 (48.1%) | 20 (45.5%) | 289 (42.8%) | |
| **Lobular Inflammation** | | | | | 0.178 |
| < 2 under 20x | 271 (57.3%) | 75 (47.5%) | 23 (52.3%) | 369 (54.7%) | |
| 2–4 under 20x | 174 (36.8%) | 71 (44.9%) | 16 (36.4%) | 261 (38.7%) | |
| > 4 under 20x | 28 (5.9%) | 12 (7.6%) | 5 (11.4%) | 45 (6.7%) | |
| **Ballooning** | | | | | <.001 |
| None | 282 (59.6%) | 77 (48.7%) | 13 (29.5%) | 372 (55.1%) | |
| Few | 128 (27.1%) | 49 (31.0%) | 19 (43.2%) | 196 (29.0%) | |
| Many | 63 (13.3%) | 32 (20.3%) | 12 (27.3%) | 107 (15.9%) | |
| **Diagnosis** | | | | | <.001 |
| NAFLD, not NASH | 134 (28.3%) | 39 (24.7%) | 7 (15.9%) | 180 (26.7%) | |
| Borderline NASH: Zone 3 pattern | 81 (17.1%) | 23 (14.6%) | 13 (29.5%) | 117 (17.3%) | |
| Borderline NASH: Zone 1, periportal pattern | 154 (32.6%) | 42 (26.6%) | 5 (11.4%) | 201 (29.8%) | |
| Definite NASH | 104 (22.0%) | 54 (34.2%) | 19 (43.2%) | 177 (26.2%) | |
| **Fibrosis Stage** | N=471 | N=157 | N=43 | N=671 | 0.035 |
| 0: None | 146 (31.0%) | 48 (30.6%) | 10 (23.3%) | 204 (30.4%) | |
| 1a: Mild, zone 3 perisinusoidal | 33 (7.0%) | 7 (4.5%) | 7 (16.3%) | 47 (7.0%) | |
| 1b: Moderate, zone 3 perisinusoidal | 20 (4.2%) | 8 (5.1%) | 5 (11.6%) | 33 (4.9%) | |
| 1c: Portal/periportal only | 137 (29.1%) | 41 (26.1%) | 9 (20.9%) | 187 (27.9%) | |
| 2: Zone 3 and periportal | 59 (12.5%) | 33 (21.0%) | 8 (18.6%) | 100 (14.9%) | |
| 3: Bridging | 67 (14.2%) | 19 (12.1%) | 3 (7.0%) | 89 (13.3%) | |
| 4: Cirrhosis | 9 (1.9%) | 1 (0.6%) | 1 (2.3%) | 11 (1.6% | |

Abbreviations: NAFLD= nonalcoholic fatty liver disease, NASH= nonalcoholic steatohepatitis.

[a]Prediabetes defined as 1) fasting serum glucose between 100 mg/dL and 125 mg/dL; or 2) HbA1c ≥ 5.7 % and < 6.5 %.

[b] Type 2 diabetes defined as 1) fasting serum glucose ≥ 126 mg/dL; 2) HbA1C ≥ 6.5%; or 3) existing clinical diagnosis of type 2 diabetes.

[c] p-values are calculated based on F-test for continuous variables, and a $X^2$ test for categorical variables.

## Table 3

Risk Factors for NASH

| Characteristic | Odds Ratios for NASH OR (95% CI) |
|---|---|
| **Glucose Status** | |
| Normal glucose | 1.0 (reference) |
| Prediabetes | **1.9 (1.2,2.9)** |
| Type 2 Diabetes | **3.1 (1.5,6.2)** |
| **Age (years)** | 1.1 (1.0,1.2) |
| **Sex** | |
| Male | 1.0 (reference) |
| Female | 1.4 (0.9,2.1) |
| **Race/ethnicity** | |
| White non-Hispanic | 1.0 (reference) |
| Hispanic | 0.7 (0.5,1.1) |
| Other | 0.7 (0.3,1.6) |
| **BMI (kg/m2)** | 1.01 (1.0,1.1) |
| **Waist circumference (cm)** | 1.01 (0.98–1.03) |
| (Intercept) | - - |

Abbreviations: OR=odds ratio, CI=confidence interval, BMI=body mass index