Trends in Nonalcoholic Fatty Liver Disease–related Hospitalizations in US Children, Adolescents, and Young Adults


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Objective: To investigate temporal trends of nonalcoholic fatty liver disease (NAFLD) and obesity among hospitalized US children, adolescents, and young adults over the past 2 decades and to examine potential sex disparities in NAFLD hospitalizations.

Methods: Hospitalization discharges with NAFLD or obesity were identified among children and young adults (6–25 years, weighted n = 91,687,413) from the 1986 to 2006 National Hospital Discharge Survey data. Age- and sex-specific rates and trends in hospitalizations with NAFLD and obesity were estimated. Rates were standardized to age distribution of the 2000 US Census population. Sex disparities were examined for the most recent period 2004 to 2006 (weighted n = 12,969,532).

Results: Between 1986 to 1988 and 2004 to 2006, hospitalization rates with a diagnosis of NAFLD increased from 0.9 to 4.3/100,000 population (P < 0.001). During the same time, hospitalizations with a diagnosis of obesity increased from 35.5 to 114.7/100,000 population (P < 0.001). During 2004 to 2006, hospitalization rates with a diagnosis of NAFLD were higher among females than among males (5.9 vs 2.7/100,000 population, P < 0.001), as were hospitalizations with a diagnosis of obesity (140.8 vs 61.5/100,000 population, P < 0.001). Obesity and diabetes were reported in 43.3% and 31.9%, respectively, of discharges with NAFLD.

Conclusion: The prevalence of NAFLD among young hospitalized patients increased in the past 2 decades, paralleling obesity-related hospitalizations. This could be a consequence of the obesity epidemic or of increased screening for liver disease. JPN 48:597–603, 2009. Key Words: Adults—Children—Hospitalizations—Nonalcoholic fatty liver disease—Obesity. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Nonalcoholic fatty liver disease (NAFLD) is characterized by an accumulation of fat in the liver (1,2) and is mainly attributed to obesity and insulin resistance (2,3). The pathological spectrum of NAFLD not only includes simple fatty liver (hepatic steatosis) but also hepatic fibrosis (steatohepatitis, NASH), and may progress to cirrhosis and hepatocellular carcinoma (4). More recent reports found an association between NAFLD and endothelial dysfunction and cardiovascular disease in adults (5,6) and carotid atherosclerosis in children (7).

The prevalence estimates of NAFLD range from 0.7% in children ages 2 to 4 years to 17.3% in adolescents ages 15 to 19 years based on liver biopsies from autopsies (8). Results from the US National Health and Nutrition Examination Survey (NHANES 1999–2004) suggest a prevalence of NAFLD of 8% in adolescents ages 12 to 19 years based on elevated serum activity of the liver enzyme alanine aminotransferase (ALT) (9). Among obese children and adolescents, reports of NAFLD are significantly higher, with estimates ranging from about 10% (6) to 25% (10–12) based on elevated ALT compared with 42% to 77% based on ultrasound (10,11,13).

Although obesity has become an increasingly important public health problem, little is known about hospitalization rates with a diagnosis of NAFLD among children, adolescents, and young adults. Therefore, the objectives of this study were to investigate temporal trends in hospitalizations with a diagnosis of NAFLD in US children, adolescents, and young adults during the last 2 decades and to examine whether NAFLD hospitalizations differ by sex in recent years. Furthermore, we examined trends in hospitalizations with a
diagnosis of obesity and other nonalcoholic chronic liver diseases.

METHODS

Study Design and Data Source

We performed a temporal trend analysis using the National Hospital Discharge Survey (NHDS) data files for the years 1986 through 2006 inclusive. The study cohort consisted of children, adolescents, and young adults ages 6 to 25 years (weighted \(n = 91,687,413\)). The NHDS 2004 to 2006 data were used to assess sex-specific differences in hospitalizations with mention of NAFLD (weighted \(n = 12,969,532\)).

The NHDS data files contain discharges from noninstitutional hospitals, excluding federal, military, and Veterans Affairs Medical Centers, located in 50 states and the District of Columbia. Only short-stay hospitals (hospitals with an average length of stay for all patients of less than 30 days) or those whose specialty is general (medical or surgical) or children's general hospitals are included in the survey (14). The survey has been conducted annually by the National Center for Health Statistics since 1965. Starting with 1979 data, the NHDS has followed guidelines of the Uniform Hospital discharge dataset, which is a minimum dataset of items uniformly defined (15). NHDS data are weighted to reflect the US civilian, noninstitutionalized population. Estimates of the US civilian population are based on census figures provided by the US Bureau of the Census for each year (http://wonder.cdc.gov/population.html).

In the NHDS dataset, people with multiple discharges during the year may be sampled more than once; therefore, all resulting estimates presented in this study are per discharge, not per person.

Diagnosis Ascertainment

Hospital discharges of children, adolescents, and young adults ages 6 to 25 years were extracted from the NHDS datasets. The NHDS dataset includes a maximum of 7 diagnoses. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes listed in the first through the seventh position were used to ascertain the following variables of interest: NAFLD (571.8); nonalcoholic chronic liver disease including NAFLD (571.8), chronic hepatitis (571.4), and nonalcoholic and biliary cirrhosis (571.5, 571.6), and other unspecified chronic liver disease without mention of alcohol (571.9); and obesity (278.0). We also extracted diagnoses of hypertension (272.0–272.4), diabetes mellitus (250), disorders of lipid metabolism (272.0, 272.1, 272.4), and cardiovascular disease (390–459). Alcohol-related disorders were defined as a listed diagnosis of any of the following ICD-9-CM codes: 291, 303.305, 980, V791, 944.6, 944.0–946.3, 946.7–946.9, 571.0–571.3. For girls and young women, hospital discharges related to complications of pregnancy, childbirth, and normal delivery were defined as primary diagnosis of any of the following ICD-9-CM codes: 630–669, V27.

Statistical Analysis

The characteristics of all hospital discharges for the 3-year periods of 1986 to 1988 and 2004 to 2006 are presented to reflect changes over the observation period. Hospital discharges with diagnoses of NAFLD, nonalcoholic chronic liver diseases, and obesity were calculated per 100,000 population for each 3-year period to assess temporal trends. We combined years to improve stability of the annual estimates. Age-specific hospitalization rates (per 100,000) were calculated using the 2000 US standard population.

Sex disparities in hospitalizations with a diagnosis of NAFLD were analyzed for the most recent 3-year period (2004–2006). Estimates are provided for children and adolescents (6–18 years) and young adults (19–25 years). The distribution of NAFLD and nonalcoholic chronic liver disease between categories defined by sex or age group or both were compared using the \(\chi^2\) test based on adjusted weights. The average length of hospital stay is given as mean and standard deviation (SD); hospital discharges with a length of less than 1 day were counted as 0.5 days. Student t test was used to compare length of stay between males and females. SPSS for Windows version 16.0 (SPSS Inc, Chicago, IL) was used for all analyses.

We excluded those with a discharge diagnosis of NAFLD or other defined liver conditions that had an additional concurrent diagnosis suggesting alcohol abuse (excluded cases for NAFLD: 1986–2006 weighted \(n = 813\) and 2004–2006 weighted \(n = 0\), excluded cases for other nonalcoholic chronic liver disease: 1986–2006 weighted \(n = 2490\) and 2004–2006 weighted \(n = 0\)). For secondary analysis on sex disparities, we excluded hospital discharges among females with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery (excluded discharges: 2004–2006 weighted \(n = 5,749,465\); 62.1% of all female discharges).

RESULTS

Discharge characteristics are similar between 1986 to 1988 and 2004 to 2006 with respect to sex, age group, and the number of pregnancy and delivery-related discharges (Table 1). The number of discharges with unknown race information, however, was higher in 2004 to 2006. Over the 2 decades of the study period, hospitalizations with a discharge diagnosis of NAFLD increased from 0.9

<table>
<thead>
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<tbody>
<tr>
<td>Weighted n</td>
<td>16,889,666</td>
<td>12,969,532</td>
</tr>
<tr>
<td>Male, %</td>
<td>30.4</td>
<td>28.6</td>
</tr>
<tr>
<td>Age group, %</td>
<td></td>
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<tr>
<td>Children (6–11 y)</td>
<td>11.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Adolescents (12–18 y)</td>
<td>27.8</td>
<td>27.9</td>
</tr>
<tr>
<td>Young adults (19–25 y)</td>
<td>61.1</td>
<td>60.7</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66.4</td>
<td>55.0</td>
</tr>
<tr>
<td>Black</td>
<td>16.7</td>
<td>15.4</td>
</tr>
<tr>
<td>Other</td>
<td>5.2</td>
<td>5.1</td>
</tr>
<tr>
<td>Missing or unknown</td>
<td>11.7</td>
<td>24.5</td>
</tr>
<tr>
<td>Primary diagnosis of combined complications of pregnancy and childbirth, and deliveries (ICD-9-CM code 630–669, V27; %)</td>
<td>39.9</td>
<td>44.8</td>
</tr>
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</table>

to 4.3/100,000 population among children, adolescents, and young adults combined \((P = 0.001, \text{Fig. 1})\). During the same period, hospital discharges with a diagnosis of nonalcoholic chronic liver disease including NAFLD, chronic hepatitis, and nonalcoholic cirrhosis increased from 3.7 to 7.3/100,000 population. In the same 20-year period, hospital discharges with a diagnosis of obesity increased from 34.9 to 114.4/100,000 population (Fig. 1).

In 1986 to 1988, 25.5% of hospitalizations with a discharge diagnosis of NAFLD also had a concurrent diagnosis of obesity compared with 43.3% in 2004 to 2006 \((P < 0.001)\). A concurrent diagnosis of diabetes (including diabetes mellitus types 1 and 2) increased from 9.9% of NAFLD hospitalizations in 1986 to 1988 to 31.9% in 2004 to 2006 \((P < 0.001)\). Although hospitalizations with a NAFLD and a concurrent type 1 diabetes mellitus diagnosis remained relatively stable (9.9% vs 8.6%, respectively), NAFLD hospitalizations with a concurrent diagnosis of type 2 diabetes mellitus increased from 0% to 23.3\% \((P < 0.001)\). Hypertension as a concurrent discharge diagnosis was listed in 5.5\% of NAFLD hospitalizations in 1986 to 1988 compared with 25.8\% in 2004 to 2006 \((P < 0.001)\). A concurrent diagnosis of cardiovascular disease was reported in 13.2\% of NAFLD hospitalizations in 1986 to 1988 compared with 29.1\% in 2004 to 2006 \((P < 0.001)\). No hospital discharges with a diagnosis of lipid metabolism disorders were reported in this specific population.

We examined whether NAFLD and obesity hospitalization rates differed by sex using the 2004 to 2006 dataset. Hospitalizations with a diagnosis of obesity were more frequent in females than in males (170.8 vs

**FIG. 1.** Temporal trends in hospital discharges with mention of nonalcoholic fatty liver disease (NAFLD) and obesity in children, adolescents, and young adults (6–25 years) by 3-year period, 1986–2006. Age-specific rates are standardized to the 2000 US population.

**FIG. 2.** Age-specific rates of hospital discharges with mention of nonalcoholic fatty liver disease (NAFLD), chronic hepatitis, or nonalcoholic cirrhosis by sex, 2004 to 2006. Age-specific rates are standardized to the 2000 US population. *****Rates are different with \(P < 0.001\).
NAFLD hospitalizations were also higher among females than among males (5.9 vs 2.7/100,000 population, \(P < 0.001\)). Because of the relative infrequency of NAFLD diagnosis, we were not able to differentiate between age groups by sex. Therefore, only data on nonalcoholic chronic liver disease including NAFLD, chronic hepatitis, and nonalcoholic cirrhosis are presented. Hospital discharges with these diagnoses were also more common among females than among males (8.7 vs 6.0/100,000 population, \(P < 0.001\), Fig. 2). Sex differences in hospitalizations with a discharge diagnosis of nonalcoholic chronic liver disease persisted among children and adolescents (7.2 vs 4.4/100,000 population, \(P = 0.001\)) and young adults (11.5 vs 8.7/100,000 population, \(P = 0.001\)). Estimates for children and adolescents may be unreliable due to the low number of NAFLD diagnoses (unweighted \(n\) for males was <60).

In a secondary analysis, we excluded all discharges with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery (62.1% of all female discharges) for the most recent 3-year period (2004–2006). After exclusion of pregnancy and childbirth-related diagnosis, hospitalizations with a diagnosis of obesity were still more frequent in females than in males (125.0 vs 61.5/100,000 population, respectively, \(P < 0.001\)). Discharges with a diagnosis of NAFLD (5.5 vs 2.7/100,000 population, \(P < 0.001\)) and with a diagnosis of nonalcoholic chronic liver disease including NAFLD, chronic hepatitis, and nonalcoholic cirrhosis (8.3 vs 6.0/100,000 population, \(P < 0.001\)) were also higher among females than among males after exclusion of pregnancy and childbirth-related diagnosis. Similarly, for discharges with a diagnosis of nonalcoholic chronic liver disease, the sex disparity persisted among children and adolescents (6.8 vs 4.4/100,000 population, \(P < 0.001\)) and young adults (11.0 vs 8.7/100,000 population, \(P < 0.001\)).

For hospitalizations with mention of NAFLD in the years 2004 to 2006, the mean hospital length of stay was longer for males than for females (5.1 ± 4.3 vs 3.1 ± 1.9 days, \(P < 0.001\)). After exclusion of discharges with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery, the hospital length of stay for females remained essentially unaltered (3.1 ± 2.0 days, \(P = 0.003\)) and young adults (4.5 ± 4.3 days for females (\(P = 0.003\)). The exclusion of discharges with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery resulted in a slight decrease in length of stay for females (3.5 ± 2.8 days, \(P = 0.005\)).

Because the NHDS dataset includes a maximum of 7 diagnoses, we could underestimate hospital discharges with mention of NAFLD if NAFLD were coded in the eighth or higher position. Therefore, we further investigated the mean number of diagnoses and the frequency of discharges with 7 diagnoses. The mean number of given diagnoses increased from 2.3 ± 1.4 in 1986 to 1988 to 3.7 ± 1.9 in 2004 to 2006, with 2.0% and 13.8% of discharges containing the maximum of 7 diagnoses, respectively (\(P < 0.001\)).

**DISCUSSION**

Paralleling the obesity epidemic, hospital discharges with an associated diagnosis of NAFLD increased significantly during the last 2 decades. More than 40% of these discharges also had a concurrent diagnosis of obesity. Similar to obesity-related hospitalizations, hospitalizations with mention of NAFLD, nonalcoholic hepatitis, and cirrhosis were more frequent in female than in male children, adolescents, and young adults.

During the past decade, the number of publications on NAFLD and NASH has increased dramatically, reflecting a growing interest in and awareness of these diseases (16). The revised 2007 Expert Committee recommendations on the assessment, prevention, and treatment of child and adolescent overweight and obesity now include screening the recommendations for NAFLD (17), a condition that was not included in the 1998 recommendations (18). The growing evidence that supported these recommendations may have contributed to the increasing number of hospitalizations with a diagnosis of NAFLD and other liver diseases associated with obesity.

Although adult men and women in the United States have a similar prevalence of obesity (19), previous studies have shown that hospitalized women were more likely to have a diagnosis of obesity than hospitalized men (20). In a recent report based on data from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), about 82% of patients with a principal diagnosis of obesity and 64% of patients with a secondary diagnosis of obesity were female (20). In that report, about 0.4% of patients with a principal diagnosis of obesity and 1.6% of patients with a secondary diagnosis of obesity were younger than 18 years of age (20). However, the report included discharges with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery, which may make females more likely to be hospitalized with a diagnosis of obesity.

Similar to adults, the prevalence of obesity (defined as above 95th percentile of body mass index for age) among children and adolescents in the United States is similar for boys and girls; about 16% of girls ages 6 to 11 years and 17% of girls ages 12 to 19 years were obese compared with 18% of boys in both age groups (21). The NHDS data for children, adolescents, and young adults show a similar trend as that observed in the HCUP data for all age groups combined (20), with more hospitalizations with a diagnosis of obesity in females than in males.

Comparable to hospitalizations with a diagnosis of obesity, our analyses of the NHDS data also demonstrated that female children, adolescents, and young adults are more likely to be hospitalized with an associated discharge diagnosis of NAFLD, nonalcoholic chronic hepatitis, and cirrhosis than were males. This holds true even after exclusion of discharges with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery (more than 60% of female discharges).

The prevalence of NAFLD has been shown to be higher in boys than in girls in many (9,11,22–36) but not all screening studies (10,13,37–39). Some studies used ALT as a surrogate marker for NAFLD (9,11, 23,25,27,29,31,34,36,37,39) and therefore may be subject to misclassification due to the cutoff values for ALT used. It has been suggested that the normal range of some liver enzymes including ALT is higher in boys than in girls (40). Consequently, the cutoff value can lead to an overestimation of the NAFLD prevalence in boys or an underestimation in girls. However, a higher prevalence of NAFLD among boys compared with girls was also confirmed by other studies, which based the diagnosis of NAFLD on ultrasound (24,27–29,33,35), liver biopsy (22,26,30,32,39), and magnetic resonance imaging (23). The higher prevalence among boys is fairly consistent across most studies, regardless of study design. Sex hormones have been suggested to play a role in the development of NAFLD (31,41), but results from published studies are controversial and the potential mechanisms are unclear. In mice, estrogen deficiency has been shown to promote progressive accumulation of fat in liver (42), and estrogen replacement reversed liver steatosis (43). However, estrogen supplementation did not yield any protective effect on diet-induced steatohepatitis (44).

In the present study, hospitalizations with a diagnosis of NAFLD were more frequent in female than in male children, adolescents, and adults. These results may not contradict previous findings because findings based on hospitalization discharges may reflect more pronounced symptoms or more frequent screening or both in females. Our findings are comparable to the association between the rates of obesity-related hospital discharges and the obesity prevalence across sexes (20).

The high prevalence of autoimmune hepatitis among females, which is often diagnosed at ages 10 to 30 years, may partially explain a higher number of discharges with a diagnosis of chronic liver disease. However, autoimmune hepatitis is unlikely to explain the higher prevalence of hospital discharges with a diagnosis of NAFLD among females.

Strengths of the study are the large sample size of the NHDS dataset and the population-based study design enabling us to look at temporal trends of several decades. The NHDS is a nationally representative sample of inpatient discharges. The hospital response rate for this survey is around 90% in recent years, discharges are weighted and adjusted for nonresponse (14,45). We also addressed discharges with a primary diagnosis related to complications of pregnancy, childbirth, and normal delivery, which may make females more likely to be hospitalized and thus bias our results.

However, our study has several limitations. First, our estimates may be unreliable for some subgroups, particularly among male subjects, due to the relative infrequency of hospital discharges with a diagnosis of NAFLD in this particular age group. Our findings are also based on hospital discharges and not individuals. Therefore, people with multiple discharges during 1 year were counted more than once. We were also not able to assess racial and ethnic differences in hospital-discharged patients with NAFLD. The NHDS includes a maximum of 7 ICD-9-CM codes per discharge; the first diagnosis corresponds to the primary diagnosis associated with the discharge. NAFLD or obesity may have been considered a minor diagnosis compared with other diagnoses and, therefore, may have been undercoded in this dataset. We can also not exclude the possibility that NAFLD was more likely to be coded among diagnoses 1 through 7 in recent years compared with earlier years due to increasing awareness of potential NAFLD in children, adolescents, and young adults. However, most discharges used for this analysis had fewer than the maximum of 7 diagnoses. Finally, underdiagnosis among males may be leading to our differential findings by sex.

Obesity constitutes a serious and challenging health risk for children and adolescents. Childhood and adolescent obesity results in higher mortality (46), higher general morbidity (47), as well as higher risk for NAFLD (2,3), cardiovascular disease (48–50), and colorectal cancers (46,47). Insulin resistance, changes in adipose tissue hormones, such as leptin and adiponectin, earlier leptin activation of the hypothalamic–pituitary axis resulting in initiation and progress of puberty, and the presence of other features of the metabolic syndrome associated with increased adiposity may be held responsible for the increased mortality (51–53).

Although NAFLD is associated with obesity, recent studies suggest that NAFLD is an independent risk factor for cardiovascular (5–7) and chronic kidney disease (54). NAFLD may progress to more severe disease states including end-stage liver disease and hepatocellular carcinoma (4). The increasing number of hospitalizations with a diagnosis of NAFLD among children, adolescents, and young adults is alarming. Further studies are needed to gather more information on the progression of NAFLD to more severe diseases such as liver cirrhosis.

The prevalence of NAFLD among hospitalized children, adolescents, and young adults increased in the past 2 decades, paralleling the trends in obesity-related hospitalizations. This could be a consequence of the obesity epidemic or of increased screening for liver disease.
Detection and early treatment of NAFLD may prevent adverse health effects associated with NAFLD such as cardiovascular disease and end-stage liver disease.

REFERENCES


