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Incidence of Depression and Anxiety in a Cohort of Adolescents with Nonalcoholic Fatty Liver Disease

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Abstract

Objectives: To determine the incidence of clinically diagnosed depression and anxiety in adolescents with NAFLD.

Methods: This was a prospective, longitudinal cohort study between January 1, 2012 and July 1, 2018 conducted in a Children's Hospital Pediatric Gastroenterology Clinic. Participants included adolescents age 12-17 years at baseline with biopsy-confirmed NAFLD. The primary outcomes were having depression and/or anxiety based upon a clinical diagnosis established by a physician or psychologist. The rates of depression and anxiety were measured at baseline and longitudinally throughout follow-up.

Results: 160 adolescents with NAFLD were followed for a mean of 3.8 years. At baseline, 8.1% had a diagnosis of depression. During follow-up, an additional 9.5% (95% CI, 4.7%-14.3%) developed depression. The incidence density of depression was 27 new cases per 1000 person-years at risk. In adolescents with NAFLD, 6.3% had anxiety at baseline and 6.7% (95% CI,

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2.6%-10.7%) developed anxiety during follow-up. The incidence density of anxiety was 18 new cases per 1000 person-years at risk. The change in alanine aminotransferase was significantly worse for adolescents with NAFLD who developed depression compared to those who did not develop depression ($p<0.01$).

Conclusions: Adolescents with NAFLD had a high incidence of clinically diagnosed depression and anxiety. The rates were higher than expected relative to the available data in the general population. Addressing this mental health burden will require efforts at both the patient level and the systems level.

Keywords

mental health; pediatrics; suicide; DSM-V; epidemiology

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease among the U.S. pediatric population. The prevalence of NAFLD increases with age from 11.3% in individuals aged 10-14 years, to 17.3% in those aged 15-19 years.¹ The prevalence of NAFLD in children with obesity is higher, as obesity is a significant risk factor for this disease.² Given the high prevalence of NAFLD, it is important to consider its interaction with all dimensions of health, including mental health. Among mental health diagnoses, depression and anxiety are particularly common, especially in adolescents. According to the 2016 National Survey of Children's Health, the prevalence of diagnosed depression and anxiety in adolescents aged 12-17 years is 6.1% and 10.5%, respectively.³ While these mental health disorders are common, screening for depression and anxiety in adolescents is limited, including among pediatric gastroenterologists caring for children with NAFLD.^{4,5}

The association between NAFLD and medical co-morbidities is well-established; however, its interconnection with clinically-diagnosed depression and anxiety disorders has been understudied. Thus far, mental health-related research in children with NAFLD has mostly been limited to the examination of quality of life and psychosocial outcomes. One study employed the Children's Depression Inventory (CDI) assessment to analyze depressive symptoms in 48 children with NAFLD and showed higher total CDI scores and negative mood.⁶ In a national study, children with NAFLD had impaired quality of life with the largest decrements being in emotional functioning.⁷ Children with NAFLD also had significantly elevated scores on anxiety and depression self-rating scales when compared to healthy controls.⁸

While the aforementioned studies suggest that pediatric patients with NAFLD may be at increased risk for depression and anxiety, these data were derived from survey-based analysis rather than formal clinical diagnoses. Although surveys are useful screening tools, they do not provide a definitive diagnosis of a mental health disorder and also may risk self-reporting bias, including social desirability and recall bias.⁹ Furthermore, there is currently a lack of longitudinal data available regarding the incidence of mental health disorders in adolescents with NAFLD, as prior studies were cross-sectional. Our study aim was to

determine the incidence of clinically diagnosed depression and anxiety in adolescents with NAFLD.

METHODS

Study Population

This was a prospective, longitudinal cohort study performed in a Children's Hospital Pediatric Gastroenterology Clinic. Participants were enrolled between January 1, 2012 and December 31, 2014 and followed through July 1, 2018. We enrolled adolescents, age 12-17, newly diagnosed with NAFLD who were willing to provide follow-up access to their medical records, including mental health care, through age 21. A diagnosis of NAFLD was based on liver histology with $\geq 5\%$ of hepatocytes containing macrovesicular fat, and exclusion of other causes of liver disease based on clinical history, laboratory studies, and histology. Liver histology was evaluated using a standardized scoring system.¹⁰ Written informed consent/assent was obtained from the parents and participants. Institutional review board approval was obtained from UC San Diego and Rady Children's Hospital San Diego.

Outcomes

The study outcomes were a diagnosis of depression and/or a diagnosis of anxiety. To reduce the overestimation and underestimation bias of surveys, we based the diagnosis of depression and anxiety on clinical diagnoses made by treating psychologists and/or psychiatrists. In accordance with Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria and diagnostic hierarchy rules, mental health conditions were classified as: depressive disorder (major depressive disorder, single episode; major depressive disorder, recurrent; depressive disorder, unspecified) and anxiety disorder (generalized anxiety disorder; social phobias; specific phobias; anxiety disorder, unspecified).¹¹

Covariates

At clinical encounters, weight and height were measured to the nearest 0.1 kg and 0.1 cm. 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. BMI z-scores were calculated to compare BMI among different ages and in both boys and girls. We recorded laboratory values for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT).

Statistical Analysis

Statistical analyses were performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria). The target study sample was a minimum of 153 patients based upon an alpha of 0.05, power 0.9, and a projection that the incidence density for anxiety in the study cohort (≈ 8.1) would be at least 3 times greater than the general population (2.7). To characterize the study population, baseline demographic and clinical characteristics were analyzed using standard descriptive statistics (mean \pm standard deviation, frequencies, proportions, and percentages). These demographic and clinical variables included: gender, age, race/ethnicity (Hispanic, non-Hispanic white, and non-Hispanic non-white), BMI, BMI

z-score, and BMI percentile category (overweight and obese). Outcomes of interest include diagnosed depressive disorder and/or anxiety disorder.

Using chi-square test for categorical data and t-test for continuous data, we compared these unadjusted characteristics by diagnosis of depression and/or anxiety at baseline. Next, ANOVA and chi-square tests were performed to compare depression and/or anxiety status by age and sex. All analyses were 2-sided with a P value less than 0.05 considered statistically significant.

At clinical follow-up visits, the same demographic, clinical, and hematological data were recorded to account for any new clinical and psychiatric events. The incidence of depression and anxiety following diagnosis of NAFLD was calculated separately. Participants with the respective mental health conditions at baseline were excluded from incidence analyses. Person-years at risk were calculated as the sum of each participant's time at risk of developing the respective disorders. Incidence density was calculated as the number of incident cases of depressive or anxiety disorders per total person-years of the population at risk. Cumulative incidence was calculated as the number of incident cases of depression or anxiety per participants at risk at baseline ($t = 0$). Change in ALT from baseline to the diagnosis of depression or anxiety, or to the final follow-up time point if there was not an incident mental health diagnosis was classified as improved (decrease of $>20\%$ from baseline), stable (within 20% of baseline) or worse (increase of $>20\%$ from baseline). ANOVA tests were performed to compare the difference in group distribution of change in ALT (improved, stable, worse) between adolescents with incident depression or anxiety and adolescents who did not develop either condition.

RESULTS

Study population

Out of 183 eligible adolescents with NAFLD, 160 adolescents with NAFLD chose to participate and were enrolled. Details for the study cohort are shown in Table 1. The mean age of participants was 15 ± 1.8 years and the majority were male (117/160). The mean BMI of participants was 33.9 ± 7.0 kg/m² and the mean BMI z-score was 2.20 ± 0.5 . Among adolescents with NAFLD, 18% had definite nonalcoholic steatohepatitis (NASH) and 35% had borderline NASH.

Baseline Depression and Anxiety

In adolescents with NAFLD, 8.1% (13/160) were diagnosed with depression and 6.3% (10/160) were diagnosed with anxiety prior to being diagnosed with NAFLD. Overlap in mental health diagnoses meant that a total of 11.3% (18/160) had depression or anxiety at baseline. Participants with depression or anxiety at baseline were significantly older than those without depression or anxiety (16 ± 1.7 vs 14 ± 1.8 years, $p < 0.0001$). Adolescents with depression or anxiety had a significantly higher BMI (35.6 ± 6.0 vs 33.9 ± 7.0 ; $p < 0.0001$) and BMI z-score (2.30 ± 0.4 vs 2.20 ± 0.5 , $p < 0.0001$) than adolescents without depression or anxiety at baseline. Adolescents with and without depression or anxiety at baseline did not differ significantly with regard to sex or race/ethnicity. The distribution of liver histology

severity did not significantly differ between those with and without depression or anxiety (Table 1).

Incident Depression

The study cohort had a mean follow-up of 3.8 ± 2.3 years. Following diagnosis with NAFLD, 14 adolescents were diagnosed with depression during follow-up. The distribution of age at diagnosis for depression and anxiety are shown in Figure 1. Adolescents with NAFLD ages 15 to 17 were at greater risk for development of depression when compared to those ages 12 to 14 (adjusted odds ratio [aOR] = 1.60, 95% confidence interval [CI] = 1.11, 2.52). The incidence of depression was not significantly different by sex ($p=0.458$). The mean duration from diagnosis of NAFLD to diagnosis of depression was 1.8 ± 1.4 years. In adolescents diagnosed with NAFLD, there were 512 total person-years at risk (mean 3.5 years of follow-up) for diagnosis of depression. The incidence density of depression in adolescents with NAFLD was 27 new cases per 1000 person-years at risk. The cumulative incidence of depression in adolescents with NAFLD was 9.5% (95% CI, 4.7%-14.3%), or 10 new cases per 100 persons at risk. The cumulative prevalence of depression in adolescents with NAFLD was 16.9% (95% CI, 11.0%-22.7%). Among adolescents with NAFLD, the change in ALT was significantly worse for those who developed depression compared to those who did not develop depression (improved 21%, stable 36%, worse 43% vs. improved 42%, stable 35%, worse 23%; $p<0.01$).

Incident Anxiety

Following diagnosis with NAFLD, 10 adolescents were diagnosed with anxiety during follow-up, including 5 with co-occurring depression. In contrast to depression, older age (15 to 17) was not associated with greater odds for development of anxiety (aOR = 1.09, 95% CI = 0.76, 1.61). The mean duration from diagnosis of NAFLD to diagnosis of anxiety was 3.0 ± 1.8 years. In adolescents diagnosed with NAFLD, there were 541 total person-years at risk (mean 3.6 years of follow-up) for diagnosis of anxiety. The incidence density of anxiety in adolescents with NAFLD was 18 new cases per 1000 person-years at risk. The cumulative incidence of anxiety in adolescents with NAFLD was 6.7% (95% CI, 2.6%-10.7%), or 7 new cases per 100 persons at risk. The cumulative prevalence of anxiety in adolescents with NAFLD was 12.5% (95% CI, 7.3%-17.7%). Change in ALT was not significantly worse for adolescents with NAFLD who developed anxiety compared to those who did not develop anxiety ($p=0.98$).

Suicidality

There were five patients that experienced suicidal ideation or attempt after a mean of 3.8 ± 2.2 years following the diagnosis of NAFLD. Of these five patients, three were hospitalized. The mean age at the time of suicidal ideation or attempt was 17.2 ± 2.4 years. All five individuals were female reflecting a rate of suicidal ideation or attempt of 11.6% (5/43) in female adolescents with NAFLD.

DISCUSSION

We followed a cohort of adolescents with NAFLD longitudinally for an average of 4 years in order to determine the incidence of clinically diagnosed depression and anxiety. These were common at baseline, with more than 1 in 10 adolescents having one or more mental health conditions. Following diagnosis with NAFLD, an additional 9.5% of adolescents developed depression. The incidence density of depression in adolescents with NAFLD was 27 new cases per 1000 person-years at risk. Notably, older age at baseline was associated with greater odds of developing depression. Among adolescents with NAFLD, 6.7% developed anxiety during follow up. The incidence density of anxiety was 18 new cases per 1000 person-years at risk. In addition to measuring these rates of mental health conditions, we observed that adolescents whose liver chemistry worsened over time were more likely to develop depression.

The incidence of depression was higher in our cohort of adolescents with NAFLD than would be expected based upon data from the general population. At the time of diagnosis with NAFLD, adolescents had a higher rate of depression than reported rates in the general population. A study of the general American population estimated that the national prevalence of depression was 4.6%.¹² In our cohort of adolescents with NAFLD, the baseline prevalence of depression was 8.1%. Furthermore, longitudinal studies capturing incidence of clinically diagnosed depression are extremely limited. One study of a large cohort of adolescents ages 14-18 reported the incidence of clinically diagnosed depression as 7.8% by age 24.¹³ Over an average of only 3.8 years of follow up, the incidence of depression in our cohort of adolescents with NAFLD was 9.5%. Prior studies have also shown that obesity in adolescence is a risk factor for depression in adulthood; however, these studies do not provide the data to compare rates directly to our cohort.¹⁴ In our study, obesity was common, but BMI z-score was not a risk factor for incident depression. In addition, some studies have shown that the risk for future depression in adolescents with obesity is primarily in females, but most of our patients with NAFLD were male.¹⁵ Further attention to the differences between males and females with NAFLD is warranted.

Among the many implications of depression is the risk for suicidality. The Centers for Disease Control and Prevention reported that suicide rates in teens and young adults have increased 56% over the past decade.¹⁶ Five female patients in our cohort experienced suicidal ideation or attempt. One population-based study of young adults between the ages of 18 and 35 found that obesity was associated with a higher prevalence of suicide risk for women, but not men.¹⁷ However, the reasons for the association between obesity and suicide risk in adults is not well understood.¹⁸ The prevalence, incidence and consequences make depression an important clinical problem in adolescents with NAFLD.

The incidence of anxiety was also higher in our cohort of adolescents with NAFLD than would be expected based upon data from the general population. In contrast to depression, the prevalence of anxiety at the time of diagnosis with NAFLD was not higher than the reported prevalence in the general population. The aforementioned study of the general American population estimated that the national prevalence of anxiety was 7.9%.¹² In our cohort of adolescents with NAFLD, the prevalence of anxiety was 6.3%. In another pediatric

study sampled from the general population, the incidence of clinically diagnosed anxiety was 2.7 cases per 1000 person-years at risk.¹⁹ The incidence of anxiety in adolescents with NAFLD was 18 cases per 1000 person-years at risk. Though these nationally representative cohorts vary in age and duration of follow up from this study, they represent some of the only available data on the incidence of mental health conditions in adolescents. The higher incidence of clinically diagnosed depression and anxiety in adolescents with NAFLD compared to these existing data warrants further longitudinal investigation.

The reality of successfully detecting mental health disorders and providing access to treatment for these disorders is a major challenge in the care of adolescents with NAFLD. Most patients with NAFLD are likely to have delays in diagnosis of depression, as only 12% of pediatric gastroenterologists screen for depression in this population.⁴ Moreover, pediatric gastroenterologists have reported that limited access to psychologists is a significant barrier in the management of children with NAFLD.⁴ This is also true more broadly; for example, in California, approximately 60% of children with a mental health condition do not receive care for it.²⁰ Inadequate treatment of depression or anxiety is likely to adversely impact the treatment of NAFLD itself. Currently, the mainstay of treatment for NAFLD is diet and exercise. Depression and anxiety may adversely impact patient adherence to these recommendations due to lack of motivation, hopelessness, loss of pleasure and/or worry.²¹ The way in which the counseling for a lifestyle intervention is done should take these mental health symptoms into consideration because they can influence how a given recommendation will be received. Moreover, some medications that are used for the treatment of depression or anxiety can be hepatotoxic.^{22,23} Thus, the high rates of depression and anxiety in adolescents with NAFLD present a need for improvements in both individual patient care and a system-wide approach to pediatric mental health.

Clinical confirmation of the diagnoses of depression and anxiety among adolescents with NAFLD was a strength of the study. Epidemiological studies traditionally have employed questionnaires rather than formal clinical diagnoses. These surveys are subject to biases that can both underestimate and overestimate rates of mental health disorders.²⁴ Our reliance on formal clinical diagnosis assures the accuracy of these diagnoses but may still have underestimated the rates of depression and anxiety due to issues of access to mental health care. Another strength of this study was the longitudinal nature of the data. Prior to this study, analysis of mental health disorders in adolescents with NAFLD has been limited to cross-sectional studies only. A limitation of the study design was the lack of a control group, in particular for obesity. In addition, the study cohort was largely skewed towards males as is the case for most studies of pediatric NAFLD. Given the known differences in depression and anxiety by sex, studies with larger numbers of females with NAFLD will be important to understand these differences by sex. In addition, the cohort was predominantly of Hispanic ethnicity. Prior research suggests that rates of depression may be higher in a non-Hispanic population. Among children with NAFLD, non-Hispanic children reported lower quality of life than Hispanic children.⁷ Moreover, the National Institute of Mental Health reported that Hispanic adolescents have a lower rate of depression than non-Hispanic white adolescents.²⁵ However, socio-cultural factors may influence the risk for depression among Hispanic adolescents and should be considered in future investigations.

In summary, adolescents with NAFLD had a high incidence of clinically diagnosed depression and anxiety. The rates were higher than expected relative to the available data in the general population. Longitudinal data of this nature are extremely limited and future large-scale studies are needed that focus on the pathophysiological relationship between NAFLD and mental health. NAFLD is known to be associated with multiple health burdens beyond chronic liver disease including diabetes, dyslipidemia, and hypertension.^{26,27} We demonstrated that the mental health burden that adolescents with NAFLD face is also substantial. To address this problem will require efforts at both the patient level and the systems level. We believe that screening for depression and anxiety in adolescents with NAFLD is warranted. Physicians caring for adolescents and young adults with NAFLD should be aware of the need to reevaluate for symptoms of depression and anxiety over time. Provision of adequate mental health care is a known challenge and must be addressed on a global level to assure comprehensive treatment for this population.

Conflicts of Interest and Source of Funding

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WHAT IS KNOWN:

- Nonalcoholic fatty liver disease (NAFLD) is a common chronic disease in adolescents.
- Children with NAFLD often have impairment in their quality of life.
- Gastroenterologists do not typically evaluate patients with NAFLD for depression or anxiety.

WHAT IS NEW:

- Over a 4-year average following diagnosis, 1 in 6 adolescents with NAFLD experienced clinical depression.
- Over a 4-year average following diagnosis, 1 in 8 adolescents with NAFLD experienced clinical anxiety.
- Adolescents with NAFLD whose liver chemistry worsened over time were more likely to develop depression but not anxiety.

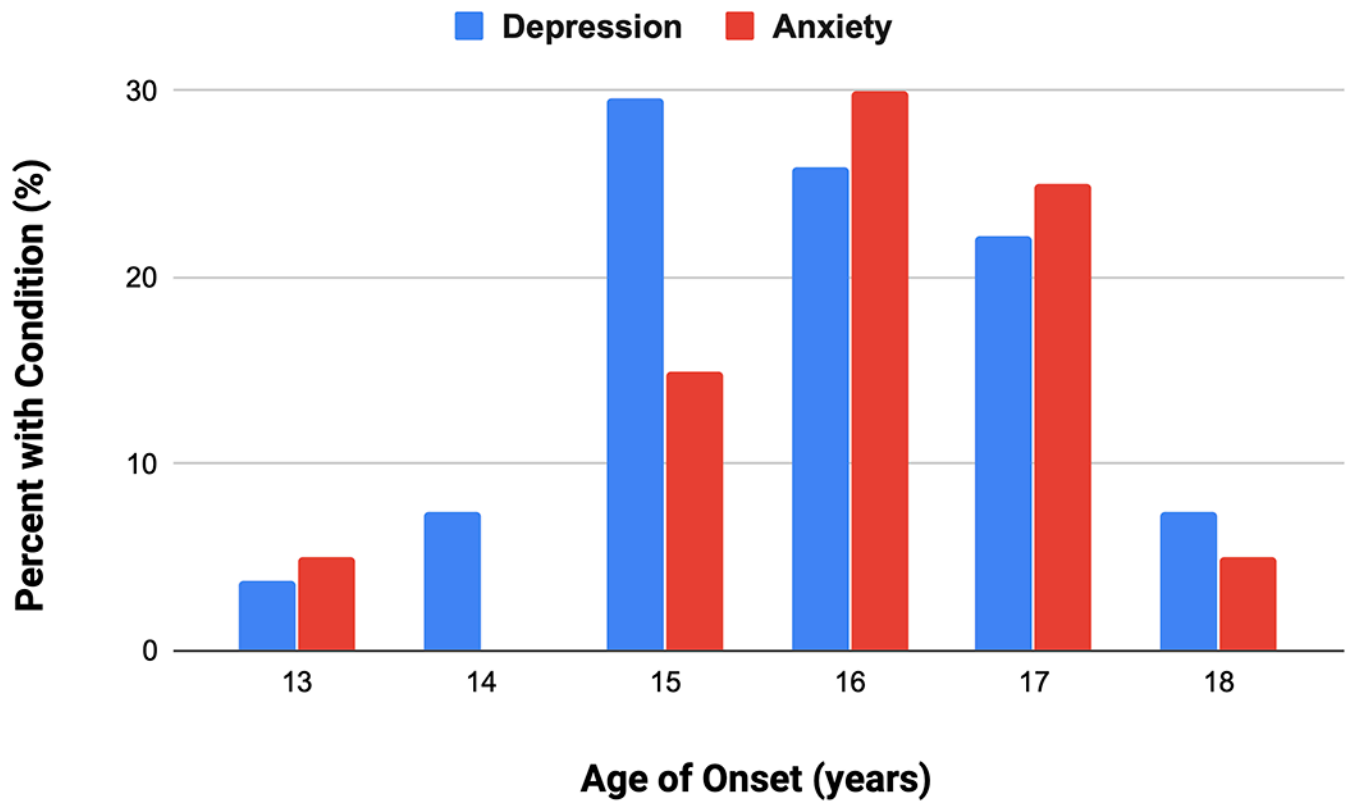
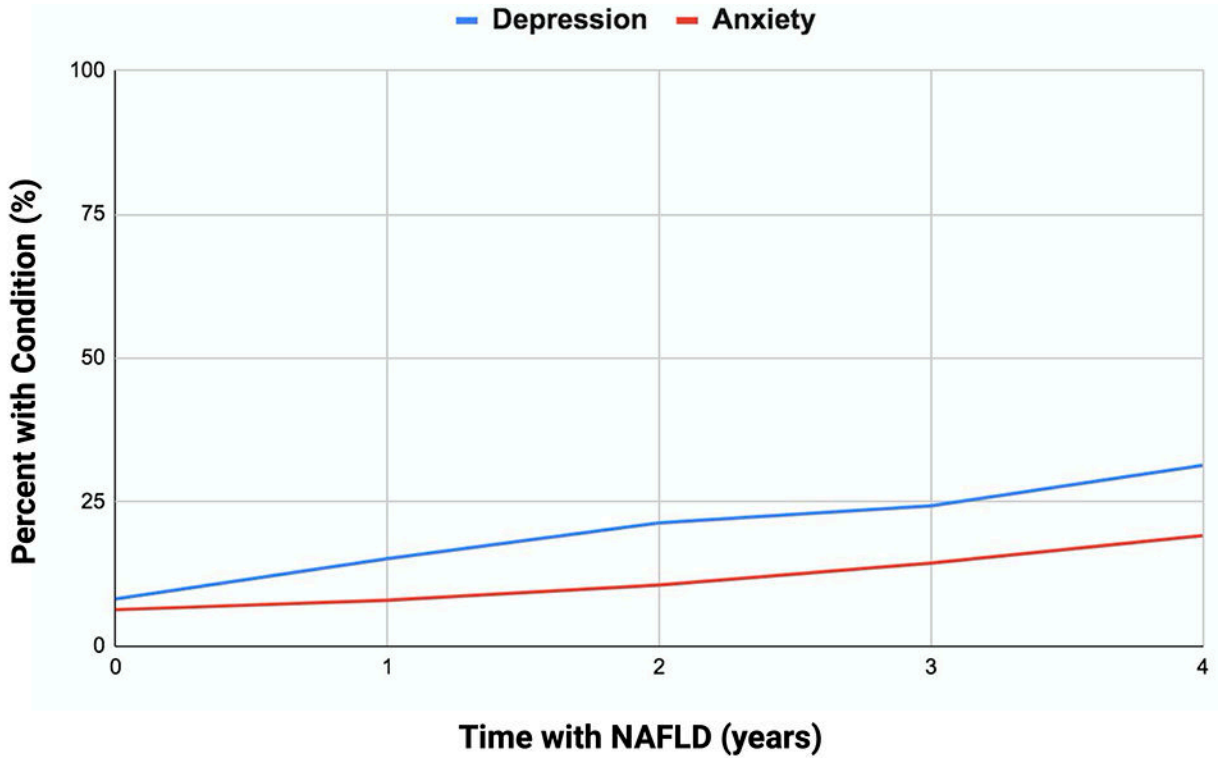


Figure 1. Distribution of Age at Onset of Depression or Anxiety in Adolescents with NAFLD
The figure shows the distribution of age in years at the time of diagnosis of depression (in blue) or anxiety (in red) for all adolescents with NAFLD that have developed one or both of these conditions. For a given condition, 100% represents the total number with that condition at baseline and/or during follow-up (N = 27 for depression; N = 20 for anxiety).



No. at Risk					
Depression	147	114	83	68	56
Anxiety	150	120	93	74	62

Figure 2. Survival Curves of Depression and Anxiety in Adolescents with NAFLD
 The curves show the percent of adolescents with NAFLD diagnosed with depression (in blue) or anxiety (in red) at baseline and during follow-up. Percent with condition includes those adolescents who developed the conditions at each year following diagnosis with NAFLD. Percent with condition was not 0% at baseline (t=0) because some adolescents were diagnosed with depression or anxiety prior to diagnosis with NAFLD. Thereafter, percent with condition includes adolescents with NAFLD until the time they were diagnosed with depression or anxiety. Once a diagnosis of these conditions was made, adolescents were no longer included in the number at risk of developing depression or anxiety. Number at risk includes the number of adolescents with NAFLD at risk of developing depression or anxiety at each year following diagnosis of NAFLD who were not lost to follow-up.

Table 1.

Baseline Study Population Demographics

	Total (n=160)	Depression or Anxiety (n=18) ^a	No Depression or Anxiety (n=142) ^b	P Value ^c
Age, mean (SD), years	14 (1.8)	16 (1.7)	15 (1.8)	< 0.0001
Sex, No. (%)				0.133
Male	107 (75)	10 (56)	117 (73)	
Female	35 (25)	8 (44)	43 (27)	
Race/Ethnicity, No. (%)				0.149
Hispanic	126 (89)	13 (72)	121 (85)	
White, non-Hispanic	9 (6)	4 (22)	13 (9)	
Non-White, non-Hispanic	7(5)	1 (6)	8 (6)	
BMI, mean (SD), kg/m ²	33.7 (7.1)	35.6 (6.0)	33.9 (7.0)	< 0.0001
BMI z score, mean (SD)	2.19 (0.5)	2.30 (0.4)	2.20 (0.5)	< 0.0001
Liver Enzymes, mean (SD), U/L				
ALT	82.0 (94.6)	88.0 (82.3)	81.3 (96.3)	0.778
AST	48.4 (48.4)	57.8 (56.8)	47.2 (47.4)	0.382
GGT	39.4 (40.0)	53.9 (89.0)	37.6 (29.1)	0.103
Steatosis Grade, No. (%)				0.105
1	47 (29)	9 (50)	38 (27)	
2	50 (31)	5 (28)	56 (39)	
3	63 (39)	4 (22)	59 (42)	
Lobular Inflammation, No. (%)				0.596
0	86 (54)	11 (61)	75 (53)	
1	61 (38)	5 (28)	56 (39)	
2	10 (6)	2 (11)	8 (6)	
Ballooning, No. (%)				0.585
1	94 (59)	8 (44)	86 (61)	
2	53 (33)	8 (44)	45 (32)	
3	12 (8)	2 (11)	10 (7)	
Fibrosis Stage, No. (%)				0.555
0	96 (60)	11 (61)	85 (60)	
1	41 (26)	5 (28)	36 (25)	
2	6 (4)	0 (0)	6 (4)	
3	15 (9)	1 (6)	14 (10)	
4	2 (1)	1 (6)	1 (1)	
Steatohepatitis, No. (%)	84 (53)	9 (50)	75 (53)	0.764

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase

Steatosis was scored: grade 0 (none to 5%), grade 1 (5%-33%), grade 2 (34%-66%), and grade 3 (>66%). Lobular inflammation was categorized based on the assessment of all inflammatory foci: no foci, <2 foci per 200 field, 2-4 foci per 200 field, and >4 foci per 200. Portal inflammation

was categorized into 3 groups: (1) none, (2) mild, and (3) more than mild. Ballooning was categorized into 3 groups: (1) none, (2) few, and (3) many. Fibrosis was staged based on the following: stage 0 (no fibrosis), stage 1 (mild perisinusoidal or periportal), 2 (zone 3 perisinusoidal and periportal), stage 3 (bridging fibrosis), and stage 4 (cirrhosis).

^aDepression or anxiety defined as having a clinical diagnosis at baseline.

^bNo depression or anxiety defined as not having a clinical diagnosis at baseline.

^cP values are calculated based on T test for continuous variables and a χ^2 test for continuous variables.

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