Nonalcoholic Fatty Liver Disease Increases the Risk of Anxiety and Depression

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Nonalcoholic fatty liver disease (NAFLD), depression, and anxiety disorders are frequent diseases, and data on mutual influence are inconsistent. The aim of this study was to explore the incidence of depression and anxiety in a large primary care cohort in Germany and to study the impact of NAFLD over a 10-year time frame. Patients with NAFLD diagnosed between 2010 and 2015 were matched to a cohort without NAFLD controlling for age, sex, physician, index year, and Charlson comorbidity index. The primary outcome of the study was the incidence of depression, anxiety, and first prescription of antidepressant drugs. We compared 19,871 patients with NAFLD to 19,871 matched controls. Within 10 years of the index date, 21.2% of patients with NAFLD and 18.2% of controls were diagnosed with depression ($P < 0.001$). On regression analysis, the hazard ratio (HR) for incidence of depression was 1.21 ($P < 0.001$). This association was similar for the endpoint of the first prescription of antidepressant drugs (HR, 1.21; $P < 0.001$). Anxiety disorders were diagnosed in 7.9% of patients with NAFLD and 6.5% of controls during the observation time ($P = 0.003$). The HR for incidence of anxiety was 1.23 ($P < 0.001$). This association remained significant in women ($P < 0.001$), while there was only a trend in men (HR, 1.15; 95% confidence interval, 0.99-1.34; $P < 0.067$). The risk of developing anxiety disorders was higher in younger patients. *Conclusion:* NAFLD constitutes an independent risk factor for emerging depression and anxiety even after controlling for confounding comorbidities. (*Hepatology Communications* 2020;4:1293-1301).

Globally, nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, with an estimated prevalence of 24%.[1,2] NAFLD constitutes a progressive disease spectrum encompassing noninflammatory steatosis (nonalcoholic fatty liver), hepatitis (nonalcoholic steatohepatitis [NASH]), and end-stage liver disease with associated complications.[3] At an individual level, patients are burdened with the risk of developing end-stage liver disease and associated complications. At the societal level, the disease generates high economic and health care expenditures.[4] In 2013, end-stage liver disease related to NAFLD was the second most common cause for liver transplantation in the United States.[5]

Depression constitutes the third leading cause of disability worldwide, and the burden for patients and the impact on health care systems is high.[6] More recently, emerging evidence challenges the high likelihood of coexistence of metabolic diseases and depression by chance and suggests shared underlying pathophysiological mechanisms related to the overarching theme of metabolic inflammation.[7] Metabolic inflammation, which in part originates in the liver, acts as a unifying link with systemic

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICD-10, International Classification of Diseases, Tenth Revision; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey.

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subclinical inflammation that emerges from and promotes chronic disease states.[8] From a clinical perspective, NAFLD and depression share common risk factors, including diabetes mellitus type 2 and obesity.[9,10] A recent study using the National Health and Nutrition Examination Survey (NHANES) observed an association between depression and NAFLD in the United States.[11] However, other recent studies produced conflicting evidence on the potential relation between NAFLD and depression.[12,13] Anxiety is another frequent psychiatric disorder in the Western world. Only a few studies investigated the potential association between NAFLD, disease severity, and anxiety disorders.[14,15] Population-based data investigating this topic are currently lacking, and no analysis emanating from primary care cohorts in Germany is available.

We chose the Disease Analyzer database that captures diagnoses, prescriptions, and risk factors for 7.49 million cases of patients treated in primary care in Germany and has been shown to be representative of a primary care population.[16,17] Our analysis was performed focusing on the emergent risk of depression and anxiety disorders in patients with NAFLD compared to matched controls in this primary care population-based design.

Patients and Methods

DATABASE

This study was based on data from the Disease Analyzer database (IQVIA, Frankfurt, Germany), which compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists.[17] The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to the International Classification of Diseases, Tenth Revision [ICD-10]), prescriptions (according to the Anatomical Therapeutic Chemical Classification system), and the quality of reported data are being monitored by IQVIA. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices.[17]

STUDY POPULATION

This retrospective cohort study included adult patients (≥18 years) with an initial diagnosis of NAFLD/NASH without liver cirrhosis (ICD-10: K75.8, K76.0) in 1,262 general practices in Germany between January 2000 and December 2015 (index date; Fig. 1). A further inclusion criterion was observation time at least 12 months before the index date. Patients with depression (ICD-10: F32, F33) or anxiety disorder (ICD-10: F41) diagnoses before the index date were excluded.

Patients with NAFLD were matched to patients without NAFLD by age, sex, physician, index year, obesity diagnosis, and Charlson comorbidity index (CCI). The CCI is a weighted index that accounts for the number and severity of comorbidities in administrative database studies and includes a wide range of comorbidities (macrovascular diseases, pulmonary diseases, gastrointestinal diseases, liver and renal diseases, diabetes, tumors, and acquired immune deficiency syndrome).[18] Obesity diagnosis is not contained in the CCI but is known to be associated with depression.[19] Moreover, obesity is considered an important risk factor for NAFLD.[20] Therefore, we matched for

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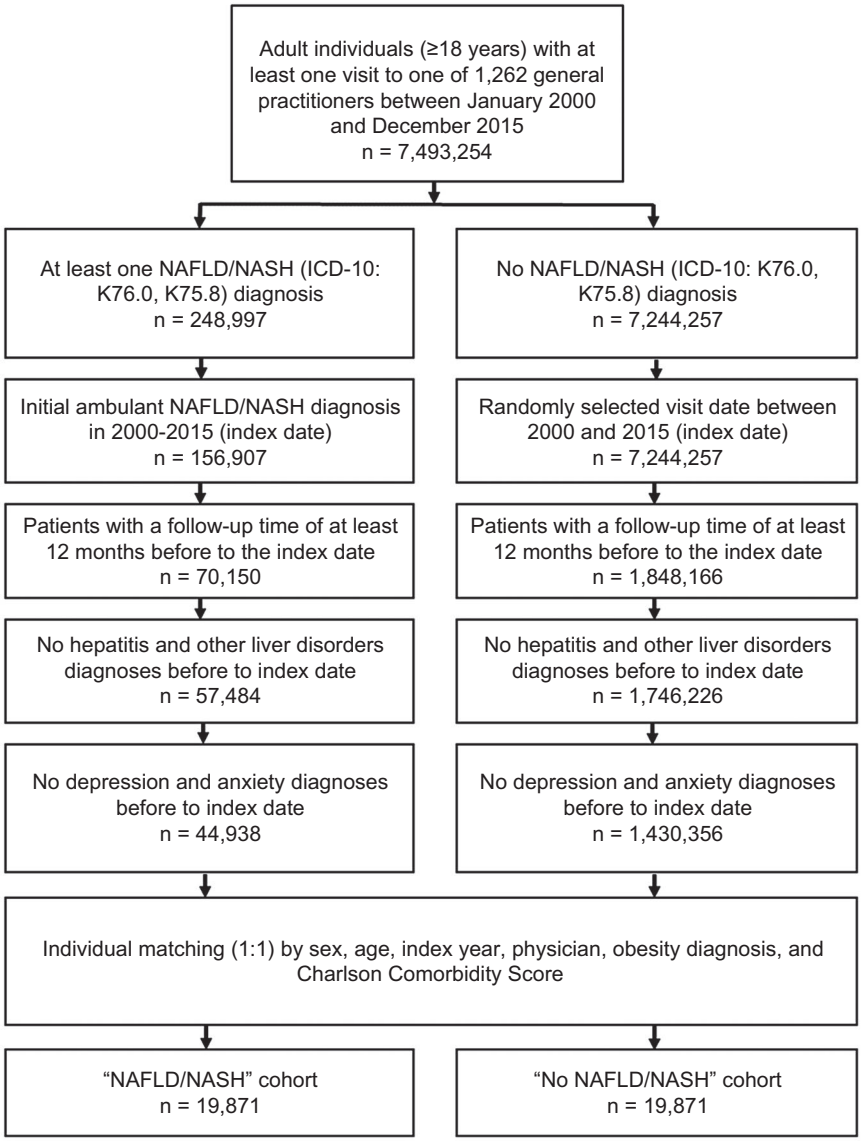

FIG. 1. Selection of study patients.

obesity, albeit with an overall low coding rate in the entire cohort that represents a likely undercoding. For the controls, the index date was that of a randomly selected visit between January 2000 and December 2015 (Fig. 1).

Additionally, we compared the frequency of the following relevant comorbidities between both groups: diabetes mellitus (ICD-10: E10-E14), cardiovascular diseases (ICD-10: I20-I25, I48), asthma/chronic obstructive pulmonary disease (COPD) (ICD-10: J44-J46), chronic kidney disease (ICD-10: N18-N19), and cancer (ICD-10: C00-C99).

STUDY OUTCOMES AND COVARIATES

The main outcome of the study was the incidence of depression or anxiety disorder diagnoses as a function of NAFLD. As the secondary analysis, the first prescription of antidepressants as a function of NAFLD was explored.

STATISTICAL ANALYSES

Differences in the sample characteristics between those with and without NAFLD were tested using

chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. Hazard regression models were conducted to study the association between NAFLD and depression/anxiety disorder/prescription of antidepressants incidence. To reduce potential bias, these models were adjusted for presence of diabetes mellitus, cardiovascular diseases, asthma/COPD, and cancer. All models were performed separately for five age groups for women and men. $P < 0.05$ was considered statistically significant. Analyses were carried out using SAS version 9.4.

Results

BASIC CHARACTERISTICS OF THE STUDY SAMPLE

The present study included 19,871 patients with NAFLD and 19,871 patients without NAFLD. The basic characteristics of study patients are displayed in Table 1. The mean age was 58.5 (SD, 14.2) years; 42.5% were women. The mean CCI was 1.0 (SD, 1.2) in both cohorts without a significant difference. This cohort exhibited a comparable age but also a male predominance compared to results that used liver histology to define NAFLD in German cohorts.[21] Frequencies of diabetes mellitus, cardiovascular diseases, asthma/COPD, and cancer differed significantly between the groups (Table 1).

ASSOCIATION OF NAFLD AND INCIDENCE OF DEPRESSION

Within 10 years of the index date, 21.2% of patients with NAFLD and 18.2% of individuals without NAFLD were diagnosed with depression (log-rank $P < 0.001$) (Fig. 2). In regression analyses, NAFLD was significantly associated with the incidence of depression (hazard ratio [HR], 1.21; $P < 0.001$). This association was similar in women (HR, 1.22; $P < 0.001$) and men (HR, 1.20; $P < 0.001$) but differed among age groups (Table 2). Importantly, as we controlled for age, sex, physician, index year, obesity diagnosis, and CCI and adjusted for diabetes, cardiovascular diseases, asthma/COPD, and cancer, the incidence was independent of these potential confounders.

TABLE 1. BASIC CHARACTERISTICS OF THE STUDY SAMPLE AFTER 1:1 MATCHING BY AGE, SEX, PHYSICIAN, INDEX YEAR, OBESITY DIAGNOSIS, AND CCI

Variable	Proportion Affected Among Patients With NAFLD/NASH (%) n = 19,871	Proportion Affected Among Patients Without NAFLD/NASH (%) n = 19,871	*P* value
Age (mean, SD)	58.5 (14.2)	58.5 (14.2)	1.000
Age 18-40	11.1	11.1	1.000
Age 41-50	17.6	17.6	
Age 51-60	24.5	24.5	
Age 61-70	24.1	24.1	
Age >70	22.8	22.8	
Women	42.5	42.5	1.000
Men	57.5	57.5	
CCI excluding liver disease (mean, SD)	1.0 (1.2)	1.0 (1.2)	1.000
CCI 0	41.3	41.3	1.000
CCI 1	32.7	32.7	
CCI 2	16.3	16.3	
CCI 3	6.1	6.1	
CCI >3	3.6	3.6	
Diabetes mellitus	11.6	10.1	<0.001
Cardiovascular diseases	43.8	40.4	<0.001
Asthma/COPD	10.3	13.7	<0.001
Chronic kidney disease	0.6	0.6	0.423
Cancer	1.6	2.2	<0.001

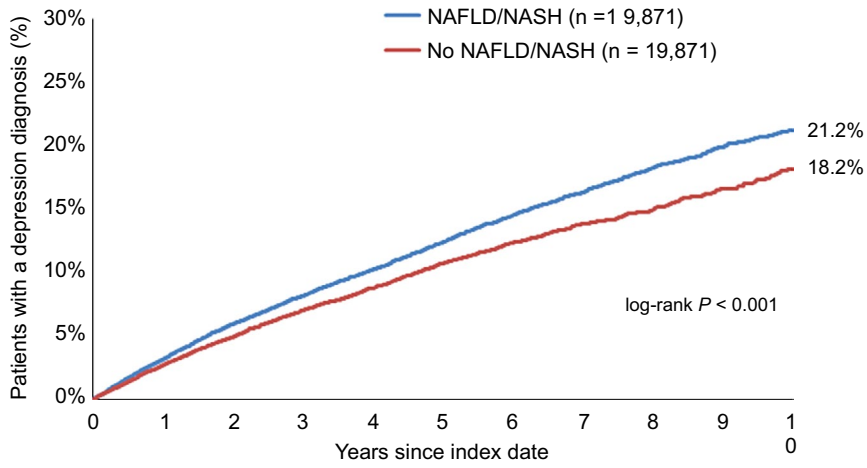

FIG. 2. Kaplan-Meier curves for time to depression diagnosis in patients with and without NAFLD.

TABLE 2. ASSOCIATION BETWEEN NAFLD/NASH AND THE INCIDENCE OF DEPRESSION AND ANXIETY DISORDER IN PATIENTS FOLLOWED IN GENERAL PRACTICES IN GERMANY

	Depression		Anxiety Disorder		Prescription of Antidepressants	
Variable	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value
Total	1.21 (1.14-1.26)	<0.001	1.23 (1.11-1.36)	<0.001	1.21 (1.13-1.29)	<0.001
Age 18-40	1.52 (1.26-1.82)	<0.001	1.65 (1.22-2.23)	<0.001	1.48 (1.18-1.85)	<0.001
Age 41-50	1.26 (1.11-1.44)	0.001	1.55 (1.23-1.95)	<0.001	1.33 (1.14-1.55)	<0.001
Age 51-60	1.11 (0.99-1.24)	0.076	0.95 (0.78-1.15)	0.595	1.16 (1.09-1.32)	0.038
Age 61-70	1.24 (1.09-1.41)	0.001	1.28 (1.03-1.60)	0.026	1.23 (1.06-1.43	0.005
Age >70	1.16 (1.03-1.31)	0.018	1.12 (0.90-1.40)	0.299	1.06 (0.93-1.21)	0.415
Women	1.22 (1.13-1.33)	<0.001	1.29 (1.13-1.48)	<0.001	1.15 (1.05-1.27)	0.002
Men	1.20 (1.10-1.30)	<0.001	1.15 (0.99-1.34)	0.067	1.24 (1.12-1.36)	<0.001

*Using Cox regression models and adjusted for diabetes mellitus, cardiovascular diseases, asthma/COPD, and cancer.

ASSOCIATION OF NAFLD AND INCIDENCE OF ANXIETY DISORDER

The incidence of anxiety disorder was 7.9% and 6.5% in patients with and without NAFLD, respectively (P = 0.003) (Fig. 3). In regression analyses, NAFLD was significantly associated with the incidence of anxiety disorder (HR, 1.23; P < 0.001). This association was significant in women (HR, 1.29; P < 0.001) but not in men (HR, 1.15; P = 0.067), and it differed among age groups, with the strongest association in young patients (age, 18-40; HR, 1.65; P < 0.001; and age, 41-50; HR, 1.55; P < 0.001) (Table 2).

ASSOCIATION OF NAFLD AND INCIDENCE OF THE FIRST PRESCRIPTION OF ANTIDEPRESSANTS

The cumulative incidence of a first prescription of antidepressant drugs was 18.4% for patients with NAFLD and 15.8% for patients without NAFLD (P < 0.001) (Fig. 4). The coded indications for a first prescription of antidepressant were as follows: 70% depression, 6% anxiety, 6% somatoform disorder or reaction to severe stress/adjustment disorder, 18% sleep disorders. In regression analyses, NAFLD was significantly associated with the incidence of a first prescription of antidepressants (HR, 1.21; P < 0.001).

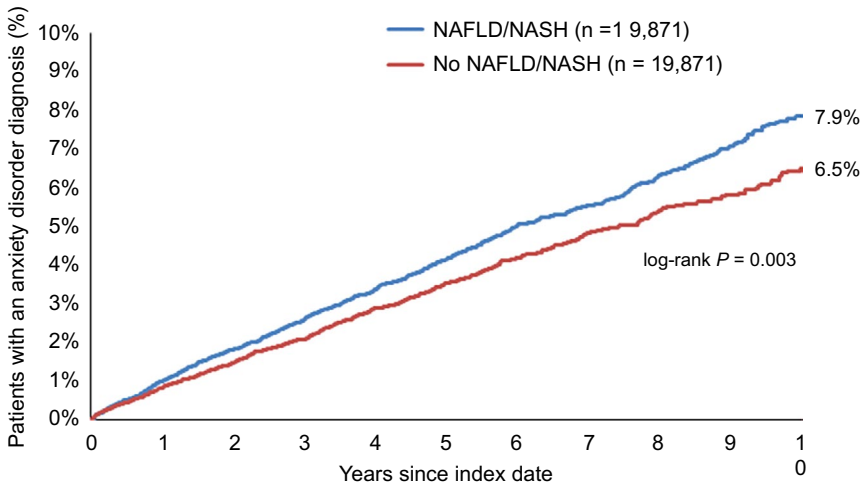

FIG. 3. Kaplan-Meier curves for time to anxiety diagnosis in patients with and without NAFLD.

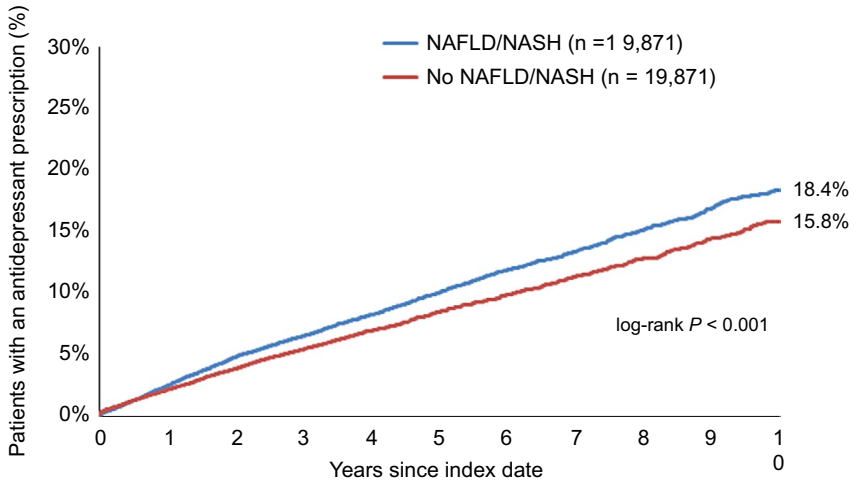

FIG. 4. Kaplan-Meier curves for time to the first prescription of an antidepressant drug in patients with and without NAFLD/NASH.

This association remained significant for women as well as men and all age groups except for patients >70 years of age (Table 2).

Discussion

In this large population-based study, we observed that NAFLD was associated with the development of depression and anxiety disorders compared to matched controls without NAFLD. Importantly, this association was completely independent of several chronic and metabolic comorbidities, excluding potential bias and imbalance related to these relevant cofactors. Interestingly, previous results[22] have shown decreased cognitive function and brain volume in NAFLD, likewise independently of visceral adipose tissue and cardiometabolic risk factors, pointing to a possible link between metabolic liver disease and mental health.

The prevalence of NAFLD in the German population has been estimated at 25%.[23] We explored a primary care provider database covering 7.49 million health care records and a coded prevalence of NAFLD that was 3.3%. This rate of coded cases is comparable to a recent analysis reporting data from the United

Kingdom, the Netherlands, Italy, and Spain[24] highlighting that NAFLD is underrecognized and undercoded in the primary care setting.[25] Currently, there is a tendency to underdiagnose NAFLD as there are no available pharmacologic treatment options. Another explanation for this gap between prevalence and diagnosis rate of NAFLD may be that the barrier to diagnose this disease in general practices, for example, is too high. However, there are several lines of data that link NAFLD to impaired health-related quality of life and cardiovascular diseases.[26,27] Thus, NAFLD could be an important indicator of comorbidities for which effective management and treatment are available. Beyond this, medical therapies for patients with NAFLD and advanced fibrosis can be expected in 2020, and identification to initiate treatment will have beneficial effects on mortality in these patients.[28] In fact, professional bodies have issued recommendations to screen for NAFLD in high-risk populations, including patients living with diabetes.[29,30]

In the present study, we demonstrated that NAFLD is independently associated with the incidence of depression in women as well as men. Previous studies have reported inconsistent results. In the NHANES 2005-2010 data set, depression was not correlated with NAFLD.[13] In one set of 258 patients with liver histology, 32 patients exhibited major depressive disorders; however, no association with steatosis or the NAFLD activity score was observed.[31] In contrast, some studies demonstrated a potential association between NAFLD and depression. A study with biopsy-proven NAFLD found an association between portal fibrosis and hepatocyte ballooning and depression.[14] Another recently published study derived from the NHANES database demonstrated an association between NAFLD and the prevalence of depression.[11] On multivariate analysis, a significant association between depression and NAFLD defined by ultrasound but also with the hepatic steatosis index was observed in this cohort study.[11] The current large-scale analysis confirmed an independent impact of NAFLD on the incidence of depression in, to the best of our knowledge, the largest population-based cohort with a nationally representable sample of German adults.

The underlying mechanism linking NAFLD to anxiety and depression cannot be explored in the current cohort study design, and we did not proof causality. Nevertheless, there are several lines of evidence that support an association between NAFLD and emerging depression and anxiety. As discussed above, systemic inflammation plays an important role in the pathogenesis of both NAFLD and depression. Recent data demonstrated that central as well as peripheral inflammation links the metabolic syndrome and the occurrence of depressive disorders.[7] Additionally, the progression of both diseases is at least in part modulated by increased oxidative stress.[32] This chronic state of inflammation may also be intensified by the presence of diabetes and obesity. Those metabolic factors are also closely related to a higher risk for depressive disorders.[33] The development of mood disorders has been linked to alterations in the serotonin system,[34] and reduced serotonin function has been observed in metabolic syndrome in relation to the extent of inflammation.[35,36] Additionally, low-grade systemic/metabolic inflammation plays a major role in the development of depressive disorders as well as in NAFLD.[37]

Anxiety disorders are common in the Western population, and to the best of our knowledge, this is the first study to demonstrate an association between the incidence of anxiety and NAFLD in a population-based design. Only a few studies investigated the association between NAFLD and anxiety in the past. In a cross-sectional study including 567 patients with biopsy-proven NAFLD in the United States, anxiety and depressive symptoms correlated with histologic characteristics of NAFLD.[14] That study suggested that anxiety is a common finding in NAFLD and observed a relationship with advanced fibrosis. A smaller study indicated an association of NASH with higher rates of anxiety disorders compared to matched controls.[15] The evidence linking anxiety and NAFLD is weaker compared to the above detailed mechanisms discussed in depression, but insulin resistance has been implied.[38]

Our study has weaknesses inherent to database analysis research. The conducted analysis relies on ICD-10 codes for establishing diagnoses. This may cause misclassification bias due to miscoding or undercoding of diagnoses. However, the German Disease Analyzer database has been used, and its reliability has been validated in several medical studies.[17] A potential weakness of the current analysis is the obvious undercoding of obesity. This may cause potential bias because there is evidence that mood disorders, such as anxiety, have a bidirectional association with

obesity.[39] The coding for obesity in our study was very low (1.9%) and therefore stands in contrast with published literature from national surveys estimating the prevalence of obesity as high as 24%.[40] This gap is most likely related to the fact that coding for obesity in Germany is not relevant for reimbursements or management. This constitutes a limitation of the current study, and an uneven distribution of obesity between the two groups cannot be ruled out. However, as patients were also matched for other comorbidities and especially for diabetes, an imbalance of obesity is less likely. Furthermore, it has to be mentioned that the German Disease Analyzer database does not capture detailed laboratory values. Therefore, our current study lacks information regarding disease severity and especially fibrosis stages in patients with NAFLD. Consequently, we could not assess a potential association between NASH or advanced fibrosis and the incidence of depression or anxiety disorders. Importantly, despite the very large sample size of patients with NAFLD and controls, the effect estimates of an association between NAFLD and depression or anxiety were relatively low. The association in this retrospective study should not be overinterpreted. Prospective cohort studies that are being performed in the across the whole continuum of NAFLD are needed to establish the causal relation. Last, we note that there may be some room for selection bias in our study for those with NAFLD diagnosis. It seems possible that patients who have an established diagnosis of NAFLD may have higher levels of care-seeking behavior and are therefore more likely to be screened for depression and/or anxiety disorders.

In conclusion, our study demonstrates that NAFLD is modestly associated with an increased incidence of depression and anxiety disorders irrespective of other comorbidities in this population-based study. Therefore, work-up for mood disorders in the management of NAFLD should be performed and may improve a patient's quality of life.

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