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Non-Alcoholic Fatty Liver Disease in a sample of individuals with Bipolar Disorders: Results From the FACE-BD Cohort

Short title: NAFLD and bipolar disorders

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Abstract (n= 250 words)**Objective**

Non-Alcoholic Fatty Liver Disease (NAFLD) is becoming the most common liver disease in Western populations. While obesity and metabolic abnormalities are highly frequent in bipolar disorders (BD), no studies have been performed to estimate the prevalence of NALFD in individuals with BD. The aim of our study is to estimate the prevalence of NAFLD and to identify the potential associated risk factors in a large sample of BD individuals.

Methods

Between 2009 and 2019, 1969 BD individuals from the FACE-BD cohort were included. Individuals with liver diseases, Hepatitis B or C, and current alcohol use disorders were excluded from the analyses. A blood sample was drawn from participants. Screening of NAFLD was determined using Fatty Liver Index (FLI). Individuals with $FLI > 60$ were considered as having NAFLD.

Results

The prevalence of NAFDL in this sample was estimated at 28.4%. NAFLD was observed in 40% of men and 21% of women. NAFLD was independently associated with older age, male gender, sleep disturbances and current use of atypical antipsychotics or anxiolytics. As expected, the prevalence of NALFD was also higher in individuals with overweight and in those with metabolic syndrome.

Conclusions

This study reinforces the view that individuals with BD are highly vulnerable to metabolic and cardiovascular diseases. The prevalence of NAFLD in individuals with BD was two times higher than the prevalence reported in the general population. The regular screening of the MetS in individuals with BD should be therefore complemented by the additional screening of NAFLD among these vulnerable individuals.

Key words: psychiatric disorders, liver diseases, fatty liver disease, metabolic abnormalities

Significant Outcomes

- The prevalence of NAFLD in individuals with BD was two times higher than the prevalence reported in the general population.
- Screening of NAFLD should be recommended among males, older individuals, those currently treated with atypical antipsychotics and those having poor sleep quality or taking anxiolytics/hypnotics.
- Psychiatrists should promote healthy lifestyle to prevent the occurrence of fatty liver disease, including controlling body weight gain, restricting intake of sugar and fat, improving sleep and increasing physical activities.

Limitations

- We used a non-invasive index to estimate the prevalence of NAFLD and we did not confirm histologically the diagnosis of liver fibrosis.
- Due to the cross-sectional nature of the study, we were unable to draw any firm conclusions concerning the causal nature of the associations observed.
- Our sample may be not fully representative of all individuals with BD, particularly those being chronically hospitalized or outpatients with low levels of symptoms or more favorable course were not referred in the Expert Center.

Introduction

Bipolar disorder (BD) is a chronic and severe mental disorder which generally appears in young adults and affects approximately 2-4% of the population ¹. BD is characterized by periods of major depression that alternate with periods of (hypo)-mania (excessively elevated or irritable mood, hyperactivity among other symptoms), interspaced by periods or remission. A growing literature has repeatedly demonstrated that individuals with BD are at higher risk of premature death.² Beyond the well-known increased mortality due to suicide, mortality rates due to medical causes (mostly cardiovascular diseases) are between 1.5 and 3 times higher in adults with BD as compared to the general population³ and life expectancy has been estimated roughly 15 years shorter for individuals with BD as compared to the non-mentally ill general population.⁴

Among medical comorbidities, metabolic syndrome (MetS) is highly prevalent in individuals with BD^{5,6,7} for example being two times higher (estimated prevalence of 20%) than in the general population in France. MetS is defined by the association of 3 or more of the following 5 criteria: high waist circumference, hypertriglyceridemia, low HDL cholesterol level, high blood pressure and high fasting glucose concentration. It is suggested to appear earlier in men with BD as compared to women with BD ^{6,8}. Its prevalence tends to increase during the follow-up of patients with BD⁹. MetS is strongly associated with Non-Alcoholic Fatty Liver Disease (NAFLD)¹⁰.

Due to dramatic modifications in lifestyle and an increasing prevalence of obesity in the last two decades in Western populations, NAFLD is becoming the most common liver disease and is expected to become a leading cause of liver transplantation over the next decades.¹¹ NAFLD is defined by liver steatosis, the accumulation of triglycerides in the hepatocytes, in the absence of chronic alcohol use. This condition encompasses a spectrum of diseases from Non-Alcoholic Fatty Liver (NAFL) to Non-Alcoholic Steato-Hepatitis (NASH), fibrosis and

cirrhosis. In the United States and in Europe, the prevalence of NAFLD is estimated to be between 20% and 30% in the general population, with a prevalence of NASH estimated to 5%¹². In France, a recent study including 118 664 individuals from the general population, the NASH-CO Study, reported a prevalence of NAFLD of 16.7%. This prevalence has been estimated with a non-invasive index (the Fatty Liver Index, FLI).^{13,14} Furthermore, NAFLD has been associated with metabolic and cardio-vascular disorders, such as type 2 diabetes mellitus, hypertension, dyslipidemia, and obesity, and is now regarded as the liver manifestation of the MetS.¹³

While metabolic abnormalities and obesity are highly frequent in BD, no study has been performed in individuals with BD to estimate the prevalence of NALFD and to identify the potential associated risk factors.

Aims of the Study

Within the FondaMental Advanced Centers of Expertise for Bipolar Disorders (FACE-BD) cohort in France which is a large multicenter cohort of French individuals with BD, we therefore assessed (1) the prevalence of hepatic steatosis and advanced fibrosis and (2) the associations with sociodemographic, clinical, and treatment-related factors.

Methods

Study population

The FondaMental Advanced Centers of Expertise for Bipolar Disorders (FACE-BD) cohort is collected from a national network of 11 centers of expertise in France, which have been developed under the aegis of the Fondation FondaMental (www.fondation-fondamental.org)¹⁴ and which is supported by the French Ministry of Health.

Outpatients (16 years old or above) are referred to the centers by their general practitioners or psychiatrists for an in-depth clinical, physical and neuropsychological assessment. Those with

a diagnosis of BD according to the DSM-IV-TR criteria (all subtypes [I, II, and not otherwise specified: NOS]) were subsequently enrolled in the FACE-BD cohort.

Exclusion criteria for this study were individuals with known liver diseases, viral hepatitis B and C and current alcohol use disorders.

The assessment protocol was approved by the institutional review board (Comité de Protection des Personnes Ile de France IX; January 18, 2010), in accordance with the French laws for non-interventional studies and requires only an information letter. All authors had access to the study data and reviewed and approved the final manuscript.

Data collected

At baseline, a specialized team (nurse, psychiatrist, (neuro)psychologist) interviewed the individuals using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)¹⁵ and systematically recorded information related to the patient's education, marital status, onset and course of BD, as well as psychiatric and somatic comorbidities. Age at onset of BD is defined at the age at which a given participant first met the DSM-IV criteria for a mood episode whatever its polarity (i.e. major depressive episode, mania, hypomania or mixed episode), according to the retrospective assessment with the SCID. Current depressive and manic symptoms were respectively assessed with the Montgomery Asberg Depression Rating Scale (MADRS)¹⁶ and the Young Mania Rating Scale (YMRS).¹⁷ Daily tobacco smoking and alcohol and cannabis use disorders were defined according to the SCID. Smoking status was categorized into two groups: current smokers and non/past smokers. Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI).¹⁸ Childhood history of maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ)¹⁹. Information regarding current psychotropic treatments (first-generation neuroleptics, antidepressants, atypical antipsychotics, mood stabilizers including lithium and anticonvulsants, anxiolytics) were recorded. All patients were on stable medication for more than 4 weeks.

A physical exam was performed by a physician or a nurse. Height and weight were measured and Body Mass Index (BMI) was calculated. Systolic / diastolic blood pressure were measured after a rest period of at least 5 minutes. A routine blood testing was performed to collect liver biochemistry (ALT (alanine aminotransferase) and AST (aspartate amino transferase), total bilirubin, albumin, alkaline phosphatase, and gamma glutamyl transpeptidase), triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol, as well as glucose if a fasting period of at least 10 hours was confirmed. Metabolic syndrome (MetS) was defined according to the revised criteria of the ATEP III ²⁰, which requires that 3 or more of the following 5 criteria be met: high waist circumference (> 94 cm for men and > 80 cm for women), hypertriglyceridemia (≥ 1.7 mmol/L or on lipid-lowering medication), low HDL cholesterol level (< 1.03 mmol/L in men and < 1.29 mmol/L in women), high blood pressure ($\geq 130/85$ mm Hg or on antihypertensive medication), and high fasting glucose concentration (≥ 5.6 mmol/L or on glucose-lowering medication).

Definition of NAFLD and severe fibrosis

Screening of Non-Alcoholic Fatty Liver Disease (NAFLD) and severe liver fibrosis were determined using the Fatty Liver Index (FLI) and the Forns Index (FI) respectively. FLI was calculated as $e^y/(1+e^y) \times 100$, where $y=0.953 \times \ln(\text{triglycerides, mg/dL}) + 0.139 \times (\text{BMI, kg/m}^2) + 0.718 \times \ln(\text{GGT, U/L}) + 0.053 \times (\text{waist circumference, cm}) - 15.745$.²¹ The FLI can range from 0 to 100. A score lower than 30 rules out a fatty liver disease (negative likelihood ratio=0.2), and a score equal or greater than to 60 suggests a fatty liver disease (positive likelihood ratio = 4.3). FLI scores ≥ 30 and <60 were considered indeterminate. FI was calculated by applying the following regression equation: $7.811 - 3.131 \times \ln(\text{platelet count, } 10^9/\text{L}) + 0.781 \times \ln(\text{GGT, IU/L}) + 3.467 \times \ln(\text{age, year}) - 0.014 \times (\text{cholesterol, mg/dL})$. Individuals with a FI >6.9 were considered as at high risk of severe fibrosis.

Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous variables as mean \pm SD (Standard Deviation). We investigated the associations between FLI and FI, and demographic factors, clinical factors, and psychotropic medications using χ^2 tests for categorical variables and t tests or Mann-Whitney Wilcoxon tests for continuous variables. A multivariate multinomial logistic regression analysis was used to estimate the odds ratio (OR) for factors associated with NAFLD, after adjusting for confounding factors. Variables included in this model were selected based on a threshold P value ≤ 0.10 in univariate analyses. Finally, a sensitivity analysis excluding individuals with lifetime alcohol use disorders was performed. Statistical analyses were performed with SAS (release 9.3; SAS Statistical Institute, Cary, NC) and R Statistical Software version 3.4.4. All statistical tests were two-tailed, with α level set at .05.

Results

Between 2009 and 2019, 2552 individuals were enrolled in the FACE-BD cohort and had recorded clinical and biological information about NAFLD. After exclusion of individuals with liver diseases (n=140), Hepatitis B and C (n=35), current alcohol use disorders (n=127), or missing data, analyses were performed in a sample of 1969 individuals with BD (see Flowchart Supplementary Figure 1).

Among them, 60.5% were women. The mean age was 40.5 years (± 12.7). Regarding BD type, 47.4% had type 1, 42.7% had type 2 and 9.9% had type NOS. The mean age at BD onset was 23.8 years (± 9.4), and time since diagnosis ranged from 0 (first episode) to 65 years (median=14.7 years). Regarding current mood state, 44.5% of the participants were euthymic (MADRS < 8 AND YMRS < 8), 46% had a current depressive episode, 4.5% had current (hypo)mania and 5% had a current mixed episode.

Prevalence of NAFLD

The prevalence of NAFLD in this sample was estimated at 28.4%. NAFLD was present in 39.8% of men and 20.5 % of women (Figure 1). The frequency of NAFLD increased linearly with age in both genders, and was significantly higher in men as compared to women whatever the class of age (Figure 2). In patients with NAFLD, prevalence of severe fibrosis (FI) was estimated at 1.1% individuals and up to 3.3% in individuals with both NAFLD and type II diabetes mellitus.

Association between NAFLD and clinical and treatment-related factors

Factors associated with NAFLD were described in Table 1. As compared to individuals without NAFLD, those with NAFLD had a later age of BD onset, a longer duration of illness, a higher number of lifetime mood episodes, and more severe depressive symptoms at inclusion. The frequency of NAFLD was significantly higher in individuals with BD type 1, with lifetime alcohol use disorders, with MetS, with obesity, as well as in individuals with sleep disturbances. Regarding psychotropic medications, the frequency of NAFLD was significantly higher in individuals currently taking atypical antipsychotics, or hypnotics/anxiolytics.

A multivariate analysis showed that the risk of having NAFLD was more than three times higher in men as compared to women (OR=3.5; 95%CI=2.54-4.72) and 2 times higher in individuals with an age above 50 years old (OR=2.2, 95% CI=1.50-3.27). Moreover, the risk of having NAFLD was associated with the current use of atypical antipsychotics (OR=1.7, 95%CI=1.26-2.59) and of anxiolytics (OR=1.7, 95% CI=1.21-2.44), as well as with sleep disturbances (OR=1.1, 95%CI=1.00-1.87). The AUC of this model including all these variables is 0.72. If MetS is added in this model, most variables remained significantly

associated with NAFLD (age, gender, sleep disturbances, anxiolytics/hypnotics use), except the association with atypical antipsychotics that was no longer significant ($p=0.08$) (see supplementary Table 1). Sensitivity analysis excluding individuals with lifetime alcohol disorders ($n=399$) did not change our results (data not shown).

Discussion

This study is the first to show that NAFLD is very common in individuals with BD, with a prevalence of 40% in men and 21% in women. Even if we did not include any control group matched for sex and age in our analyses, the observed prevalence was around 2 times higher as compared to the prevalence in the French general population.^{22,23} Indeed, a recent large French population-based sample including 118 664 participants aged 18-70 years old, reported a prevalence of NAFLD (estimated using the same non-invasive indices), of 16.7% (24.6% and 10.1% among men and women respectively).

In the literature, only one study performed in individuals with BD can be used to discuss our results. In a large-scale retrospective study (N=5319), Fuller et al. reported a prevalence of liver diseases of 21.5% in veterans with BD. However, the authors estimated the prevalence of global liver diseases including HCV infection, alcoholic cirrhosis and severe liver fibrosis more than specifically NAFLD. Moreover, the results of this study are difficult to generalize to the broader population of individuals with BD since the vast majority of patients were males (90%) and individuals with an alcohol use disorder (51.1% of the sample) were not excluded. Some previous studies have been performed in other severe psychiatric disorders, mainly in schizophrenia. In a recent cross-sectional study including 202 young males with schizophrenia, Yan et al. observed a prevalence of NAFLD of 49.5%.²⁴ Using the Fatty Liver Index in a sample of 205 drug-naïve individuals with first episode of schizophrenia, Morlán-Coarasa et al., showed a prevalence of NAFLD of 7%.²⁵ Hence, this suggests that the frequency of NAFLD may probably be high in individuals with BD and, more in general, in those with severe mental disorders.

Our study further investigated the factors (demographical and clinical factors, medications) being associated with NAFLD in individuals with BD. NAFLD was independently associated

with older age, male gender, sleep disturbances and current use of atypical antipsychotics or anxiolytics. As expected, the prevalence of NAFLD was higher in individuals with overweight and in those with MetS. Therefore, our results are consistent with numerous studies reporting a linear increase of NAFLD prevalence with age and a strong relationship with gender, obesity and metabolic syndrome.²⁶

Regarding currently used medications, we observed an association between NAFLD and the use of atypical antipsychotics. This is consistent with numerous evidences showing that atypical antipsychotics induce substantial weight gain and other metabolic side effects^{27,28} and it is well known that obesity, type 2 diabetes mellitus and metabolic syndrome are consistently identified as the most important risk factors of NAFLD in the general population.²⁶ All these components of metabolic syndrome have been also associated with atypical antipsychotics use in individuals with psychiatric disorders.^{5,6} Furthermore, a recent critical review showed that atypical antipsychotics are associated with NAFLD²⁹ in individuals with schizophrenia. Moreover, individuals with psychiatric disorders tend to have poor lifestyle with sedentary activity³⁰, unhealthy eating³¹ and tobacco or drugs consumption , all these behaviors increasing the risk of developing cardio-metabolic abnormalities as well as NAFLD.

Finally, we found an association between NAFLD and sleep disturbances. This is consistent with many studies performed in the general population that showed an association between NAFLD and sleep problems. A recent study in Taiwan showed that sleep problems in general (sleep of non-organic origins and sleep disturbances) were associated with NAFLD, even in patients without obstructive sleep apnea syndrome.^{32,33} The National Health and Nutrition Examination Survey (NHANES) in 2005 to 2010 in the U.S. found that sleep disorders were associated with a 1.4 times higher risk of NAFLD.³⁴ Studies focusing specifically on obstructive sleep apnea syndrome also showed relationship between this problem and

NAFLD³⁵, with a pooled odds ratio at approximately 2 to 3 in meta-analyses.^{36,37} Some studies in individuals with BD³⁸, as well as in the general population^{32,33}, have shown that sleep disturbances may lead to insulin resistance, weight gain, metabolic syndrome, and diabetes mellitus, which are all associated with NAFLD. Finally, some studies suggested that chronic intermittent hypoxia is the principal mechanism through which obstructive sleep apnea syndrome may cause NAFLD.³⁷

This study has several strengths: the large number of individuals with BD being included, the use of reliable diagnostic criteria, and the inclusion of a large number of potential confounding factors in the multivariate analysis. Nevertheless, several limitations deserve some comments. We used a non-invasive index to estimate the prevalence of NAFLD and we did not confirm histologically the diagnosis of liver fibrosis. Due to the cross-sectional nature of the study, we were unable to draw any firm conclusions concerning the causal nature of the associations observed. Longitudinal studies would be required for this purpose. The associations between NAFLD and certain classes of medications (atypical antipsychotics and anxiolytics/hypnotics) may not be causal and should be discussed regarding the possibility of confounding by indication and/or confounding by disease severity. This refers to the situation where the clinical indication for selecting a particular treatment (eg, severity of the illness) also affects the outcome³⁹. Furthermore, our sample may be probably not fully representative of all individuals with BD, particularly those being chronically hospitalized or outpatients with low levels of symptoms or more favorable course, all of these individuals being less likely to be referred to our network. Finally, regarding the association between NAFLD and sleep disturbances, we did not include any measure of the risk of obstructive sleep apnea in our assessment package.

In conclusion, the prevalence of NAFLD in individuals with BD was two times higher than the prevalence reported in the general population. As part as the clinical follow-up, we

suggest that an additional screening of NAFLD by a non-invasive technique (FLI) should complement the regular screening of MetS, and more particularly among males, older individuals, those currently treated with atypical antipsychotics and those having poor sleep quality or taking anxiolytics/hypnotics. This NAFLD evaluation may influence the risk-benefit ratio of the treatments since some medications widely used in BD (such as valproic acid) can alter hepatic function^{40,41}, thus leading clinicians to discuss non-hepatotoxic mood stabilizing alternatives (e.g. lithium). As the ISBD (International Society for Bipolar Disorders) Vascular Task Force concluded in a recent call for action⁴², while a reduction of cardio-vascular mortality has been observed in the general population, an inverse trend has been observed in individuals with BD. Hence, there is a crucial need for a better prevention of cardio-vascular risk among individuals with BD. To prevent the occurrence of fatty liver disease and to decrease cardio-vascular risks in BD, psychiatrists should promote healthy lifestyle, including controlling body weight gain, restricting intake of sugar and fat, improving sleep and increasing physical activities.

Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with Helsinki Declaration of 1975, as revised in 2008.

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