European Review for Medical and Pharmacological Sciences 2016; 20: 5081-5097

Psychological factors associated with NAFLD/NASH: a systematic review

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Abstract. – OBJECTIVE: Nonalcoholic fatty liver disease (NAFLD) represents one of the most common chronic liver diseases worldwide. So far, the pathogenesis of NAFLD and its more severe variant nonalcoholic steatohepatitis (NASH) is yet unclear, with many mechanisms being proposed as possible causes. This article aims to review the psychological factors associated with NAFLD/NASH.

MATERIALS AND METHODS: Three main categories of factors have been investigated: emotional, cognitive and behavioral. Five electronic databases were searched, limited to studies published in the English language, during the period 2005-2015: PubMed, Thomson ISI – Web of Science, Scopus, ProQuest, and ScienceDirect.

RESULTS: Results indicated the most relevant emotional factors to be depression and anxiety. The areas of investigation for cognitive functioning concern those contents and processes related to the ability to initiate and maintain lifestyle changes. The most important behavioral factors identified are physical activity, nutrition/food intake and substance consumption: coffee, alcohol, cigarettes.

CONCLUSIONS: Some of the factors identified act as protective factors, other as vulnerability factors. NAFLD/NASH may be considered a cognitive-behavioral disease, the most effective management being lifestyle changes, with emphasis on diet and exercise.

Key Words
Nonalcoholic fatty liver disease (NAFLD), Nonalcoholic steatohepatitis (NASH), Cognitive factors, Behavioral factors, Emotional factors.

Introduction

Nonalcoholic fatty liver disease (NAFLD) represents one of the most common chronic liver diseases worldwide. NAFLD is an umbrella term used to name a condition identified in 1981 in pregnant women[1]. The term was introduced in 1986 to describe a spectrum of diseases ranging from a simple benign fatty liver (hepatic steatosis) to nonalcoholic steatohepatitis (NASH), to progressive fibrosis and cirrhosis[2].

Chronologically, the nonalcoholic steatohepatitis (NASH) was coined before NAFLD, in 1980, by Ludwig et al[3]. They described the pattern of liver injury observed in a group of patients treated at Mayo Clinic. It refers to a condition of fat accumulating in the liver, due to causes different from excessive alcohol consumption (less than 20 g per day) or any other specific causes of hepatic steatosis[3]. Most of these patients were obese women, thus associating from the very beginning NASH with one of the most debilitating conditions of the present time-obesity[3]. Of all the patients affected by NAFLD, only those with histologic evidence of steatohepatitis are shown to progress to fibrosis or cirrhosis[4]. Some studies[5] show between 10%-29% of patients with NASH will develop cirrhosis within a 10-year period, underlying the importance of prevention and early treatment. The most important histologic feature of NAFLD is the accumulation of triacylglycerols and diacylglycerols in hepatocytes[6]. Visceral fat provides most of the triglycerides leading to steatosis offering a possible explanation for the cases of generally lean individuals, centrally obese, who develop NAFLD[7].

Although the world-wide prevalence has not yet been determined, rates of 10-24% were estimated in various general populations[8]. The prevalence of NAFLD increases significantly, up to 74% in obese individuals[8]. In the United States alone, this condition represents over 75% of the chronic liver disease[1].

NAFLD is reported among all racial and ethnic groups. Hispanics have the highest prevalence of NAFLD, 45%. For the non-Hispanic whites, prevalence was estimated to be 33%, while for the

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African Americans 24%[1]. In China[9], the community prevalence of nonalcoholic fatty liver disease was estimated at a relatively lower rate of 15%. In India, the prevalence of NAFLD is around 9% to 32% in the general population, with higher prevalence in overweight or obese individuals[10]. Women tend to develop the disease later than men (in the sixth decade of life *vs.* the fourth), the condition being more frequent in male than female[1]. NAFLD is a disease affecting people regardless of age; it has been reported[1] in children as young as 2. Some studies[8] indicate 2.6% of children are affected, with higher rates in case of obese child population ranging from 22.5% to 52.8%.

The pathogenesis of NAFLD is not yet fully clarified. It might be multifactorial, with many mechanisms as possible causes; among the most important are insulin resistance, oxidative stress, apoptosis, and adipokines[7,11]. Based on available data from clinical, experimental and epidemiological studies, there is now a consensus that primary NAFLD is the hepatic manifestation of the metabolic syndrome[11,12].

Insulin resistance, mostly in the context of extra weight and obesity, generates higher levels of hepatic free fatty acid (FFA); this condition facilitates the development of NAFLD[6]. FFA oxidation leads to the generation of toxic reactive oxygen species resulting in hepatic injury and inflammation. As a consequence, the initiation and progression of fibrosis are likely to follow[6].

Associated Conditions

NAFLD has been associated with many other conditions, among them obesity and visceral fat, diabetes mellitus, hyperlipidemia, and hypothalamic-pituitary dysfunction[8]. Some studies show that obese pregnant women can pass on their metabolic phenotype to their children. In turn, early childhood obesity predicts the development of nonalcoholic fatty liver disease later on[13]. In adolescence, a range of liver problems are associated with greater rates of weight-for-height change between 1-10 years, mediated by concurrent body fatness[14]. Other researches underline that overweight and obesity lead to increased quantities of hepatic-free fatty acids, generating an environment appropriate for the development of NAFLD[6]. As such, the prevalence of NAFLD in obese persons can go as high as 74%[8].

An independent risk factor for the development of NAFLD was identified in dietary fructose[6].

Steatosis can also come as a consequence of multiple rare genetic conditions, which influence the liver processing of nutrients and lipids. Mutations that contribute to either an increase in lipid synthesis/uptake or a decrease in hydrolysis/export (e.g., glycogen storage diseases, ATGL defects, or very-low-density lipoproteins mutations) were associated with NAFLD[15]. Some other conditions associated with NAFLD include parental nutrition, acute starvation, abdominal surgery, use of several drugs (e.g. amiodarone, tamoxifen, glucocorticoids, synthetic estrogens, diltiazem, aspirin, methotrexate, highly active antiretroviral therapy), hepatitis C, HIV and metabolic disorders[16,17].

A complication of hepatic steatosis, the nonalcoholic steatohepatitis (NASH) is proven to be associated with cardiovascular diseases and malignancy. In a study of biopsy-proven NASH[18], the main causes of death in patients were cardiovascular disease and malignancy. Also, studies[19] show both hepatic steatosis and the more aggressive NASH are associated with type 2 diabetes mellitus.

Methods

Psychological Risk and Protective factors for NASH/NAFLD

A systematic review was conducted in an attempt to answer the question "Which are the most important psychological factors (emotional, behavioral and cognitive) associated with NASH/NAFLD?".

Five electronic databases were searched, limited to studies published in the English language, during the period 2005-2015: PubMed, Thomson ISI - Web of Science, Scopus, ProQuest, and ScienceDirect.

The search terms used were *nonalcoholic steatohepatitis* along with each of the following: (1) "*psychological risk factors*", (2) "*psychological factors*", (3) "*psychological predictors*", (4) "*behavioral factors*", (5) "*emotional factors*", (6), "*affective factors*", (7) "*cognitive factors*", (8) "*resilience factors*", (9) "*anxiety*", (10) "*depression*".

Studies published in a peer-reviewed journal from January 2005 to December 2015, which evaluated risk and resilience psychological factors associated with NAFLD/NASH were included in this review. These conditions were selected because of the shared common elements regarding their biological and psychological mechanisms.

Inclusion Criteria

At least one psychological factor associated with NASH/NAFLD was included in each study cognitive, emotional/affective or behavioral. Studies were specifically designed to investigate the association of risk and protective factors with NAFLD/NASH manifestations. Studies were clinical trials, single-case experiments, cohort trials, or surveys.

Exclusion Criteria

Non-English language studies were excluded. Also, studies conducted on animals, and children or adolescents (age <18) were excluded. Studies focusing on treatment or different forms of intervention to change factors contributing to the onset or exacerbation of NAFLD/NASH symptoms were not included. Also, studies focusing primarily on factors other than the psychological ones targeted (e.g., obesity, hypertension, age, low birth weight, coronary artery disease, metabolic risk factors, pain, impaired glucose tolerance, type 2 diabetes, cirrhosis) were excluded.

Results

A total of 4583 abstracts were initially identified by using the ten established search combinations in the five databases. Of these abstracts, 107 met the search criteria and were later analyzed about exclusion criteria. In Figure 1, we detail the process by which 29 final articles were selected for analysis.

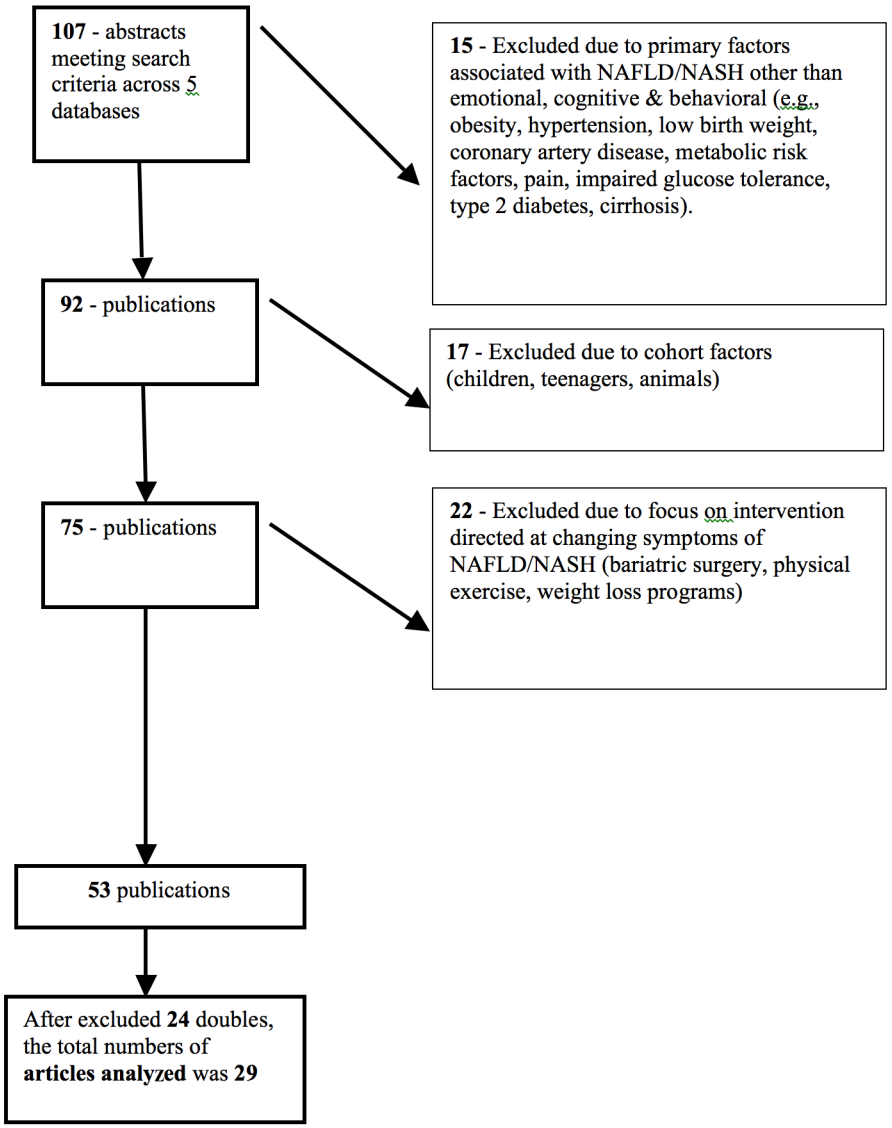

Figure 1. Articles included and excluded in the final analysis.

Emotional/Affective Factors

Depression and anxiety were the two emotional factors mostly investigated in relationship to NAFLD/NASH.

Depression is currently one of the leading causes of death and disability in the general adult population, and expected to become the second leading cause of disability in all age groups by 2020[20]. In a foreword by Deborah Wan, president of World Federation of Mental Health issued for the 20th Anniversary of World Mental Health Day in October 2012 it is specified that unipolar depressive disorders were the third leading cause of the global burden of disease in 2004 and will move into the first place by 2030[21]. It is also the most common mental disorder in patients with chronic conditions[22]. It is yet unclear if chronic conditions lead to depression, or major depression constitutes a risk factor for chronic illnesses. The relationship could be both ways. However, in an attempt to clarify this issue, Pattern et al[23] proved that a set of different conditions characterized particularly by pain, inflammation and/or autonomic reactivity (e.g., arthritis, peptic ulcer, migraines) has a higher incidence in people with major depression.

There were several studies discussing the role of depression and anxiety in relationship to NAFLD/NASH, in which clear associations between emotional symptoms and liver disease symptoms could be identified.

Stewart et al[24] explored possible associations between anxiety, depression, personality factors, readiness for behavior change and weight outcomes in 58 overweight or obese participants with NAFLD. Anxiety and depression, as well as cognitive complaints, were considered psychological symptoms and were assessed using the Brief Symptom Inventory. Although mean scores for anxiety, depression and cognitive dysfunction were in the average range, these symptoms were significantly more frequent than in the general population. Also, depression, low conscientiousness, and high neuroticism were associated with higher weight at 6-month follow-up.

The study of Youssef et al[25] explored the association of depression and anxiety with the severity of histological features of NAFLD in 567 patients. Results indicate that depression is significantly associated with more severe hepatocyte ballooning in a dose-dependent manner. Patients with subclinical depression had 2.1 times higher likelihood of having more severe hepatocyte ballooning grade than patients without depressive symptoms. Also, patients with clinical depression had 3.6 times higher likelihood of having more severe hepatocyte ballooning grade when compared to the non-depressed individuals. In conclusion, there seems to be a dose-dependent association between severity of depressive symptoms and severity of hepatocyte ballooning. These associations were not supported for anxiety symptoms.

Some studies[26] suggest emotional problems like anxiety and depression could influence the progression of chronic liver diseases, among which NAFLD/NASH. Elwing et al[26] compared patients diagnosed with nonalcoholic steatohepatitis (NASH), a more severe form of NAFLD, to matched controls without a liver disease in regards to emotional disorders. Major depressive disorder and generalized anxiety disorder diagnoses were established based on the DSM-IV criteria; they preceded the diagnosis of liver disease. The authors concluded that major depressive disorder, as well as generalized anxiety disorder, appeared more frequently in patients with NASH and were associated with more advanced liver histological abnormalities.

Also, patients with chronic hepatitis C and NAFLD seem to have a higher prevalence of depression than patients with hepatitis B and the general population[27]. In this study, depression was self-reported and confirmed by the history of prescription medication. The main factors independently associated with depression in NAFLD were hypertension, smoking, history of lung disease, being female and non-African-American[27].

Depression seems to be associated not just with NAFLD, but also with other liver diseases. The prevalence of depression in hepatitis C patients is known to be high, ranging from 20% to 60%[27]. In a recent investigation of the relationship between liver diseases, major depression and suicide attempts, Le Strat et al[29] found that participants with a liver disease were 2.2 times more likely to have major depression, after adjustment for a number of socio-demographical, medical and behavioral factors (e.g., age, sex, race, marital status, educational level, past history of cardiovascular disorder or heart attack, hypertension, arthritis, average volume of alcohol consumed daily and smoking status). Liver diseases were associated with both major depression and suicide attempts among adults in the community[29].

Other studies could not find a clear association between NAFLD/NASH in particular

and major depression, although there is a proven pattern of relations between liver diseases and depression. Upon examination of four chronic liver diseases (i.e., chronic hepatitis C, chronic hepatitis B, alcohol-related liver disease, and nonalcoholic fatty liver disease), the authors of a 2013 study[30] concluded that chronic hepatitis C alone had a strong association with depression.

Another investigation by Surdea-Blaga and Dumitrascu[31] provided results indicating there are no differences when comparing the scores of depression, anxiety, or distress in women with NASH and women with viral hepatitis. In this research depression, anxiety and distress scores were not statistically different in patients with NAFLD and normal LST as compared with patients with NASH and elevated LST.

In conclusion, at the moment there are a relatively small number of studies investigating the relationship between NAFLD and depression. Results are conflicting and some confounders like obesity and diabetes mellitus may be worth investigating. Also, designing further studies with relevant control groups and more valid forms of measurement for emotional problems might be of help in clarifying the issue.

Concerning the relationship between anxiety and NAFLD, the data collected in several investigations indicate it is similar to that found in the case of depression. In the 2013 study by Youssef et al[25], subclinical and clinical anxiety was noted in 45% and 25% of patients with NAFLD, respectively. Another paper[26] reported that generalized anxiety disorder is overrepresented in NASH subjects and is associated with more advanced liver histological abnormalities. The 2011 investigation by Surdea-Blaga and Dumitrascu[31] found no differences in anxiety among patients with NAFLD and normal LST and patients with NAFLD and elevated LST as well as patients with viral hepatitis.

Other more specific emotions, like fear of falling, also play a part in the evolution of NAFLD[32]. Fear of falling highly influences the involvement in physical activity, which is central to NAFLD management[32]. Self-efficacy, expressed as confidence to perform, seems to be involved as a possible mechanism underlying the fear of falling.

Although the relationship between liver diseases and anger received less attention, a study conducted by the Duke University Medical Center researchers deserves consideration[33]. The team found that healthy people prone to anger, hostility and mild to moderate depressive symptoms produce higher levels of C-reactive protein (CRP), known to promote cardiovascular disease and stroke. CRP is a substance involved in plaque development and plaque's clogging up of arteries, and is produced by the liver in response to inflammation. Moreover, another team of Israeli researchers[34] found that elevation of liver enzymes correlate with higher CRP concentrations that could be indicative of a worsening of liver disease. Starting from these conclusions, further researches should attempt to investigate the possible role of anger, hostility, and depression as possible contributors to liver inflammation.

In summary, the relationship between NAFLD/NASH and emotional problems like depression and anxiety, in particular, is receiving more and more attention, as some correlation between these conditions begins to emerge. However, results are mixed and further studies might benefit from designs specifically elaborated to clarify causality.

Cognitive Factors

Some cognitive factors relevant to patients' ability to engage in necessary lifestyle changes were also investigated in relationship to NAFLD/NASH.

Frith et al[32] assessed two of the cognitive factors relevant to the uptake of physical exercise in patients with NAFLD: confidence to exercise and perceived benefits of exercise. They concluded that confidence to exercise (i.e., the belief one can engage in and complete physical exercises) was significantly lower in NAFLD patients when compared to the primary biliary cirrhosis (PBC) patients and comparable to that of alcoholic liver disease (ALD) patients. However, patients in all three groups had similar levels of exercise expectations, thus understanding the benefits of working out. Consequently, although the NAFLD patients understand the importance to exercise, they seem to lack the confidence to engage in physical activity.

In individuals with NAFLD, ratings of perceived exertion (RPE) were related to the level of physical activity in adulthood[35]. Ratings of perceived exertion refer to perception of effort and are defined by sensations of effort, constraints, discomfort and fatigue one feels when engaging in physical activity. The way people assess their feelings of physical stress, effort and fatigue while doing exercises influences further involvement in such activities and regulation of effort.

Therefore, in patients with NAFLD, the way they perceive exertion depends on the glucose level, as well as self-reported physical activity. As such, because RPE can stimulate or deter a person to engage in exercises, it could be used to prescribe appropriate physical activities for patients with NAFLD.

Stewart et al[24] brought further evidence suggesting that overweight/obese NAFLD patients have a readiness to change consistent mostly with the pre-contemplation and contemplation stages of the Stages of Change Model[36]. Only about 10% of their 58 patients sample were either preparing to or were actively making lifestyle changes, an important requirement for the management of NAFLD. These conclusions were further supported by the results of a 2013 study by Centis et al[37]. In a sample of 138 NAFLD patients, the authors found that in case of physical activity about 50% of subjects could be classified in either pre-contemplation or contemplation stages. In case of diet, no subjects were classified in the pre-contemplation phase, 36% were in the contemplation phase, while 64% were distributed in determination to change, actions for changing and changed maintenance phases. Such findings suggest that, for reasons that could involve various thoughts and cognitions (i.e., information scarcity, personal beliefs, low self-efficacy beliefs, etc.) NAFLD patients have little motivation for changing their diet or engaging in physical activity.

Some studies found cognitive dysfunction (e.g., memory impairment, attention deficit, etc.) to be significantly more frequent in the overweight/obese NAFLD population than in the general population[24]. However, in a study by Felipo et al[38] only a small number of patients with NASH, a more advanced form of NAFLD, could be classified as having mild cognitive impairment associated with hyperammonemia and inflammation. None of the patients with NAFLD showed any cognitive impairment. Further data are needed to clarify whether NAFLD patients are at risk for cognitive dysfunction.

In summary, for NAFLD patients, the most relevant areas of investigation for cognitive functioning concern those contents and processes related to the ability to initiate and maintain lifestyle changes. The cognitive mechanisms underlying dietary behaviors and engagement in physical activity are some of the most important targets for further investigation.

Behavioral Factors

Physical Activity

The level of physical activity seems to be affected in patients with NAFLD. Elliott et al[39] assessed the extent of impairment in daily activity patients diagnosed with NAFLD and ALD have when compared with healthy controls. Results indicate all liver disease patients experience significant difficulties in their daily activities, across eight domains of physical functioning: dressing, arising, eating, walking, hygiene, reach, grip, and activity. In case of NAFLD patients, age, fatigue, autonomic dysfunction, and cognitive difficulty are associated with worsening functional difficulty. The impairment appears to persist in time, and was observed over a 3 year period in this study.

Koehler et al[40] found that total physical activity was associated with NAFLD in an elderly population. Also, Oni et al[41] indicated that people with higher levels of physical activity had lower odds of having NAFLD. The association was maintained independentely of obesity and the metabolic syndrome.

Although the overall level of physical activity seems to be important in NAFLD, Kistler et al[42] brought evidence supporting that it is the intensity of physical exercise that is associated with the severity of NAFLD. The authors suggest that intensity of exercise may be more important than duration or total volume. Results presented in this particular study indicate that neither moderate intensity exercise, nor total exercise per week was associated with NASH or stage of fibroses. It appears that vigorous physical exercise is beneficial to NAFLD to a much higher extent than physical activity in general.

Conversely, reduced physical activity seems to impact NAFLD in a negative manner. Hua et al[43] found that elderly day nappers had a significantly higher prevalence of NAFLD. Longer habitual day napping was associated in a dose-dependent manner with NAFLD.

In summary, intense physical exercise may act as a protective factor against the debut and aggravation of NAFLD symptoms.

Food Intake/Diet

Improper food intake, low on nutrients and high in saturated fat and carbohydrates seems to be a significant risk factor for NAFLD/NASH. Some investigations have attempted to assess the impact of different foods and nutrients on liver functioning.

Yu et al[44] explored the role of dietary choline – found in eggs, soy foods, red meat, fish and vegetables – in relation to NAFLD. Lack of choline is known to stimulate liver fat accumulation. Conversely, higher dietary choline intake seems to be associated with lower risk of NAFLD in normal-weight Chinese women.

Zelber-Sagi et al[45] concluded that the intake of soft drinks and meat was significantly associated with an increased risk for NAFLD. Also, the NAFLD patients appear to have a tendency to consume lower quantities of fish rich in omega-3. Body mass index (BMI), waist circumference and percent dietary fat intake proved to be independent nutritional risk factors for NAFLD[46]. Most NAFLD patients presented a significantly high intake of meats, fats, sugars, legumes (beans), and vegetables and a low consumption of cereals, fruits, and dairy products compared with the recommendations[47]. Low nutrient food intake seems to be relatively common in NAFLD patients.

Kim et al[48], indicated that NAFLD patients consumed more low-nutrient food, and more high-sodium food than HBV (hepatitis B virus) patients. Also, NAFLD patients ingested fewer calories from fruits than chronic viral hepatitis patients.

In women, vitamin K and vegetable intakes were shown to have a beneficial effect on lowering the NAFLD risk. In men, low intakes of vitamin C, Vitamin K, folate, omega-3 fatty acids, nuts and seeds were associated with a high risk for developing NAFLD[49].

Musso et al[50] showed that subjects with NAFLD had lower vitamins A and E intakes than control subjects. Nitrotyrosine and adiponectin concentrations and vitamin A intake independently predicted alanine aminotransferase concentrations in NAFLD patients and liver histology in a subgroup of biopsy-proven NASH subjects.

According to Kang et al[51], in NAFLD patients, the metabolic syndrome is associated with more carbohydrate and less fat intake and greater histological severity.

In summary, in the development of NAFLD and the severity of symptoms, poor nutrition seems to play a central role and needs further investigation.

Substance Consumption: Coffee, Alcohol, Smoking

Some pretty usual lifestyle habits seem to develop as protective factors against the onset of NAFLD. As such, greater consumption of coffee has been associated with a significantly reduced prevalence of cirrhosis in patients with chronic liver disease. Walton et al[52] indicated that patients with cirrhosis drank significantly less coffee than those without cirrhosis. Moreover, some studies identified an increased activity of the autophagy-lysosomal pathways in mice fed caffeine, inferring a biochemical explanation for the protective role of caffeine[1].

In regards to coffee consumption, it is yet unclear if the beneficial effect is due to coffee in itself or just the caffeine component.

Alcohol represents another frequently used substance that has been investigated in relation to NAFLD. Kwon et al[53] concluded that patients who used alcohol moderately had a decrease in the histological severity of NAFLD. Other studies have shown that moderate wine drinking (i.e., one glass of wine per day) was correlated with a decreased prevalence of suspected NAFLD[54]. When comparing nondrinkers and moderate drinkers with NAFLD, data show lower rates of steatohepatitis in the moderate drinkers[55].

In summary, moderate alcohol consumption (especially wine) may have favorable effects on patients with NAFLD or at risk for NAFLD.

Contrary to the effect of coffee consumption and moderate alcohol drinking, smoking seems to have a detrimental effect on the evolution of NAFLD. Not only does active smoking contribute to the exacerbation of symptoms, but also passive smoking appears to negatively influence liver functioning. Liu et al[56] showed that passive smoking during childhood and adulthood was associated with a 25% increase in the risk for NAFLD. The combination of active smoking and body mass index (BMI) was also associated with a high risk for NAFLD. In a 2012 study, Koehler et al[40] proved that pack years of smoking, as well as other variables, were associated with NAFLD. Smoking also influences the severity of NAFLD. A study by Zein et al[57] indicated smoking history to be associated with advanced liver fibrosis in NAFLD patients.

In summary, cigarette smoking may aggravate fatty liver.

Table I. Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
Emotional/affective factors					
S3.	Stewart KE, et al (2015)	58 overweight/obese participants with NAFLD	Associations between depression, anxiety, low conscientiousness, neuroticism), readiness for behavior change and weight outcomes in NAFLD patients were explored.	Cognitive: readiness for behaviour change, cognitive dysfunction. Emotional: depression, anxiety.	Depression, low conscientiousness, and high neuroticism were associated with higher weight at 6-month follow-up. Of all the patients, only 10.4% were actively working on or preparing to change, although all received nutritional education and guidance. Readiness for change was not found to predict subsequent change in weight. Cognitive dysfunction symptoms (e.g., memory problems, attention problems) were significantly more frequent in the NAFLD sample than in the general population. Compared to the general population, depression and cognitive dysfunction in particular were significantly more frequent in the NAFLD sample.
S10.	Lee K, et al (2013)	10,231 subjects diagnosed with Chronic hepatitic C, Chronic hepatitis B, alcohol related liver disease, and nonalcoholic fatty liver disease. 50% of the subjects were male.	Cohort study. Univariate and multivariate analyses were performed to determine the variables associated with different types of chronic liver diseases and depression.	Emotional: depression	Depression was not associated with NAFLD. Depression was strongly associated with Chronic hepatitis C. NAFLD patients were less likely to smoke and have never used illicit drugs.
S14.	Youssef NA, et al (2013)	567 patients with biopsy-proven NAFLD. Subclinical depression was noted in 53%, clinical depression was noted in 14%, subclinical anxiety was noted in 45% and clinical anxiety was noted in 25% of subjects.	Multiple logistic regression was used to analyze the association of depression and anxiety with severity of histological features of NAFLD.	Emotional: anxiety and depression	Depression proved to be significantly associated with more severe hepatocyte ballooning in a dose-dependent manner.
S21.	Weinstein AA, et al (2011)	878 patients with chronic liver disease. 207 of all patients (23.6%) were diagosed with depression (NAFLD 27.2%, hepatitis C 29.8%, hepatitis B 3.7%).	Comparisons were conducted using the Mann-Whitney test and Kruskal-Wallis test. Regression models were used to identify independent predictors of depression.	Emotional: depression	Patients with NAFLD and hepatitis C have a higher prevalence of depression than hepatitis B patients and the general population. For NAFLD, independent predictors of depression were the presence of hypertension, smoking, history of lung disease, being female and non –African- American.

Continued

Table I (Cont.). Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
S22.	Surdea-Blaga T and Dumitrascu D (2011)	63 patients with NAFLD, 38 of them female. The diagnosis of liver steatosis was established based on abdominal ultrasound and the aspect of liver parenchyma.	Groups compared using ANOVA, Mann-Whitney (based on data distribution). Correlations using Pearson and Spearman coefficients.	Emotional: depression, anxiety	No differences in anxiety, depression or distress scores could be found between females with NAFLD and females with viral hepatitis. No relation could be supported between NAFLD and depression or anxiety.
S24.	Frith J, et al (2010)	230 non-alcoholic fatty liver disease – NAFLD, 110 alcoholic liver disease – ALD and 97 primary biliary cirrhosis – PBC subjects were included.	Cohort study. Three different groups (NAFLD, ALD, PBC) were compared in regards to factors pertaining to engagement in physical exercise (lack of confidence, poor understanding of the benefits of exercising, fear of falling).	Cognitive: confidence to exercise, understanding the benefits of exercise Emotional: fear of falling	Understanding the benefits of physical activity was similar in all three groups. Confidence to exercise was significantly lower in the NAFLD group. Fear of falling was similar in the NAFLD and PBC groups, and higher in the ALD group. Although they understand the benefits of performing physical activities, patients with NAFLD lack the confidence necessary and are afraid of falling. In NAFLD, fear of falling was independently associated with increasing difficulty engaging in physical activity. Both fear of falling and confidence are modifiable through psychological intervention.
S28.	Elwing JE, et al (2006)	36 nonalcoholic steato-hepatitis (NASH) patients and 36 matched controls were used.	A multivariate model incorporating a number of potential risk factors for NASH was used to assess independent effects of major depressive disorder and generalized anxiety disorder on severity of histological findings.	Emotional: anxiety and depression	Major depressive disorder and generalized anxiety disorder are more frequent in NASH subjects and are associated with more advanced liver histological abnormalities.
Cognitive factors					
S2.	Weinstein AA, et al (2016)	Convenience sample of 51 subjects diagnosed with NAFLD or Chronic hepatitis C, age 51.1 ± 8.8 years, 35% female.	Observational analytical study. Spearman rank sum correlations were performed. Groups were compared using analysis of variance.	Cognitive: perception of effort during physical activity	In individuals with NAFLD, ratings of perceived exertion (RPE) were related to a metabolic factor (fasting glucose level), and a lifestyle factor (level of physical activity in adulthood). Ratings of perceived exertion refer to perception of effort, which is a powerful regulator of effort.

Continued

Table I (Cont.). Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
S3.	Stewart KE, et al (2015)	58 overweight/obese participants with NAFLD.	Associations between depression, anxiety, personality factors (ex., low conscientiousness, neuroticism), readiness for behavior change and weight outcomes in NAFLD patients were explored.	Cognitive: readiness for behaviour change, cognitive dysfunction Emotional: depression, anxiety	Depression, low conscientiousness, and high neuroticism were associated with higher weight at 6-month follow-up. Of all the patients, only 10.4% were actively working on or preparing to change, although all received nutritional education and guidance. Readiness for change was not found to predict subsequent change in weight. Cognitive dysfunction symptoms (e.g., memory problems, attention problems) were significantly more frequent in the NAFLD sample than in the general population. Compared to the general population, depression and cognitive dysfunction in particular were significantly more frequent in the NAFLD sample.
S13.	Centis E, et al (2013)	138 NAFLD patients (73% male, age 19-73). Diagnosis confirmed by liver biopsy in 64 cases (steatohepatitis 47%)	Logistic regression analysis	Cognitive: stage of change, motivation	Physical activity – 50% were classified in either pre-contemplation or contemplation stages. Diet – 0% were classified in the pre-contemplation phase, 36% were in the contemplation phase. 64% were distributed in determination, action and maintenance phases. NAFLD patients have little readiness to lifestyle changes and motivation with regard to diet and particularly physical activity.
S15.	Felipo V, et al (2012)	29 patients with simple steatosis (NAFLD) and 11 with steatohepatitis (NASH). All NASH patients presented hepatic fibrosis.	Groups compared using ANOVA. Correlation analysis was performed.	Cognitive: cognitive deficits/impairment	Five out of 11 NASH patients, without liver cirrhosis, were classified as having mild cognitive impairment associated with hyperammonemia and inflammation. None of the patients with NAFLD showed cognitive impairment.
S24.	Frith J, et al (2010)	230 non-alcoholic fatty liver disease – NAFLD, 110 alcoholic liver disease – ALD and 97 primary biliary cirrhosis PBC subjects were included.	Cohort study. Three different groups (NAFLD, ALD, PBC) were compared in regards to factors pertaining to engagement in physical exercise (lack of confidence, poor understanding of the benefits of exercising, fear of falling).	Cognitive: confidence to exercise, understanding the benefits of exercise Emotional: fear of falling	Understanding the benefits of physical activity was similar in all three groups. Confidence to exercise was significantly lower in the NAFLD group. Fear of falling was similar in the NAFLD and PBC groups, and higher in the ALD group. Although they understand the benefits of performing physical activities, patients with NAFLD lack the confidence necessary and are afraid of falling. In NAFLD, fear of falling was independently associated with increasing difficulty engaging in physical activity. Both fear of falling and confidence are modifiable through psychological intervention.

Continued

Table I. Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
Behavioral factors – Physical activity					
S1.	Oni ET, et al (2015)	5,743 healthy Brazilian subjects, 43 ± 10 years old, 79% men. NAFLD was diagnosed using ultrasounds. In the total study population, NAFLD prevalence was 36% (2,075 subjects).	Multivariate logistic regression was used to evaluate association between NAFLD, physical activity and other risk factors (obesity, metabolic syndrome).	Behavioral: physical activity	NAFLD prevalence was lower at higher levels of reported physical activity. Subjects with high physical activity had lower odds of having NAFLD. The association was maintained independent of obesity and metabolic syndrome.
S7.	Hua Q, et al (2014)	Of 6,998 participants, aged 40-75 years, 6,438 eligible participants were included.	Cross-sectional studies of the community population in China. Association between the duration of habitual day napping and NAFLD in an elderly population. Logistic regression models were used.	Behavioral: habitual day napping	Day-nappers were found to have a significantly higher prevalence of NAFLD. Longer day napping was associated in a dose-dependent manner with NAFLD. It appears that inflammatory cytokines may be a link between day napping and NAFLD.
S12.	Elliott C, et al (2013)	224 non-alcoholic fatty liver disease (NAFLD), 107 alcoholic liver disease (ALD) and 100 controls were included. 45% (101) of the NAFLD patients were women (age 59 ± 13).	Groups were compared using analysis of variance, and the Kruskal-Wallis test. Multiple linear regression was also performed to determine the association between functional impairment and disease severity.	Behavioral: functional impairment	People diagnosed with NAFLD and ALD experience significant difficulties in their daily activities when compared with normal controls. Functional impairment appears to persist over time (evaluated over a 3 year period).
S17.	Koehler EM, et al (2012)	2,811 participants, mean age 76.4 ± 6.0 years. Prevalence of NAFLD was 35.1%.	Logistic regression analysis was used to assess associations between co-variables and severity of NAFLD.	Behavioral: smoking habits, physical activity	Total physical activity, pack years of smoking, age, as well as other variables were associated with NAFLD. The prevalence of NAFLD decreases with advancing age in the elderly.
S19.	Kistler KD, et al (2011)	813 adults, 302 males and 511 females with biopsy-proven NAFLD were included. Mean age 48.	Retrospective analysis on data was conducted. Groups were compared using analysis of variance, Kruskal-Wallis test, and Mann-Whitney test. Multinomial logistic regression was also used.	Behavioral: physical activity	Neither moderate intensity exercise, nor total exercise per week was associated with NASH or stage of fibroses. Data support an association of vigorous physical exercise with the severity of NAFLD. Results suggest intensity of exercise may be more important than duration or total volume.

Continued

Table I (Cont.). Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
S29.	Kang H, et al (2006)	91 patients with NAFLD, 31 patients (34%) had metabolic syndrome.	Patients with metabolic syndrome were compared with those without metabolic syndrome. The contribution of different factors (e.g., dietary composition, physical activity) to NAFLD severity was also estimated.	Behavioral: alimentary habits, food intake Behavioral: physical activity	Patients with metabolic syndrome consumed more carbohydrates and less fat compared with those without metabolic syndrome. Total daily calories, protein consumption, and physical activity were similar for the two groups. Metabolic syndrome in patients with NAFLD is associated with more carbohydrate and less fat intake and greater histologic severity.
Behavioral factors – Food intake/diet					
S5.	Yu D, et al (2014)	56,195 Chinese women and men, 40-75 years of age. NAFLD was assessed by self-report of a physician diagnosis.	The association between choline intake and NAFLD was explored. Stratified analysis suggested a potential effect modification by obesity status in women.	Behavioral: alimentary habits, food intake	Higher dietary choline intake could be associated with lower risk of NAFLD in normal-weight Chinese women.
S6.	Han JM, et al (2014)	348 Korean adult subjects participated. NAFLD was diagnosed by ultrasound.	The association between several risk factors (individual nutrients or whole food groups) and NAFLD was explored.	Behavioral: alimentary habits, food intake	In women, vitamin K and vegetable intakes were shown to have a beneficial effect on lowering the NAFLD risk In men, low intakes of vitamin C, Vitamin K, folate, omega-3 fatty acids, nuts and seeds were associated with a high risk for developing NAFLD
S9.	Marinho Ferolla S, et al (2013)	96 non-alcoholic fatty liver disease patients. Median patient age 53 years. 77% of subjects were women. 67.7% of participants were obese. All patients underwent abdominal ultrasound, biochemical tests, dietary evaluations, food intake, anthropometric evaluations.	Coss-sectional study; groups compared with t-test and Mann-Whitney U test. Chi-square test or Fisher's exact test were used to compare proportions.	Behavioral: alimentary habits, food intake	Most patients exceeded the recommendations for energy intake and saturated fat. The patients presented a significantly high intake of meats, fats, sugars, legumes (beans), and vegetables and a low consumption cereals, fruits, and dairy products compared with the recommendations. The possible role of nutrient deficiencies in the development of NAFLD needs further investigation.

Continued

Table I (Cont.). Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
S18.	Sathiaraj E, et al (2011)	98 subjects with steatosis and 102 controls were included. Prevalence of metabolic syndrome was 44.9% among NAFLD cases and 25.5% among controls.	Multiple logistic regression analysis was performed to predict the dietary risk factors in NAFLD	Behavioral: alimentary habits, food intake	BMI, waist circumference and percent dietary fat intake proved to be independent nutritional risk factors for NAFLD.
S23.	Kim CH, et al (2010)	233 subjects, age 52.5 ± 10 years were included. 31.8% were diagnosed with NAFLD, 48.1% were diagnosed with hepatitis C virus (HCV), and 20.2% had hepatitis B virus (HBV).	NAFLD patients were compared with chronic viral hepatitis patients in regard to food intake. Multivariate analysis and univariate analysis were performed.	Behavioral: alimentary habits, food intake	NAFLD and HCV patients consumed more high-fat meat than HBV patients. NAFLD and HCV patients consumed more low-nutrient food, and more high-sodium food than HBV patients. Also, NAFLD patients consumed less calories from fruits than chronic viral hepatitis patients.
S27.	Musso G, et al (2008)	64 non-obese non-diabetic patients with NAFLD and 74 control subjects without liver disease.	NAFLD and control subjects were compared in regards to food intake.	Behavioral: alimentary habits, vitamin intake	Persons with NAFLD had lower vitamins A and E intakes than control subjects. Nitrotyrosine and adiponectin concentrations and vitamin A intake independently predicted alanine aminotransferase concentrations in NAFLD patients and liver histology in a subgroup of 29 subjects with biopsy-proven nonalcoholic steatohepatitis.
S26.	Zelber-Sagi S, et al (2007)	349 Israeli participants, 52.7% male, mean age 50.7 ± 10.4, 30.9% diagnosed with primary NAFLD.	Survey, cross-sectional study. Associations between dietary habits and primary NAFLD were explored.	Behavioral: alimentary habits, food intake	Intake of soft drinks and meat was significantly associated with an increased risk for NAFLD. Also, the NAFLD patients have a tendency toward lower intake of fish rich in omega-3.
S29.	Kang H, et al (2006)	91 patients with NAFLD, 31 patients (34%) had metabolic syndrome.	Patients with metabolic syndrome were compared with those without metabolic syndrome. The contribution of different factors (e.g., dietary composition, physical activity) to NAFLD severity was also estimated.	Behavioral: alimentary habits, food intake Behavioral: physical activity	Patients with metabolic syndrome consumed more carbohydrates and less fat compared with those without metabolic syndrome. Total daily calories, protein consumption, and physical activity were similar for the two groups. Metabolic syndrome in patients with NAFLD is associated with more carbohydrate and less fat intake and greater histologic severity.

Continued

Table I (Cont.). Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
Behavioral factors – Substance consumption: coffee, alcohol, smoking					
S4.	Kwon HK, et al (2014)	77 patients with NAFLD diagnosed by biopsy. Fifty-two patients had a history of regular alcohol consumption.	Multivariable analysis showed an association between alcohol consumption, age and disease severity.	Behavioral: lifetime alcohol consumption	Moderate lifetime alcohol consumption seems to have a protective effect on the histological severity of liver disease among NAFLD patients.
S8.	Walton HB, et al (2013)	286 patients attending the liver outpatient department at the Royal Infirmary of Edinburgh participated in the study. The control group was formed of 100 orthopedic outpatients and 120 medical students. 95 patients were diagnosed with cirrhosis.	Normal controls were compared with chronic liver disease patients (non-alcoholic fatty liver disease and alcohol related liver disease)	Behavioral: alimentary habits, coffee intake	Patients with cirrhosis drank significantly less coffee than those without cirrhosis. There weren't significant differences in the amount of coffee drunk by liver patients and the control groups. Coffee drinking is associated with a reduced prevalence of cirrhosis in patients with chronic liver disease.
S11.	Liu Y, et al (2013)	8580 subjects, 2691 men, age 40 and older. NAFLD prevalence was 29.4% in never smokers, 34.2% in former smokers, 27.8% in light smokers, 30.8% in moderate smokers, 43.5% in heavy smokers.	Community based survey in China.	Behavioral: smoking habits (active and passive smoking)	The combination of active smoking and body mass index (BMI) was associated with the highest observed odd ratio for NAFLD. In never smoking women, passive smoking during childhood and adulthood was associated with a 25% increase in the risk for NAFLD.
S16.	Dunn W, et al (2012)	251 lifetime non-drinkers were compared to 331 modest drinkers with biopsy-proven NAFLD	Multiple ordinal logistic regression was used to determine associations between alcohol consumption and severity of NAFLD/NASH	Behavioral: alcohol consumption	When compared to non-drinkers, modest drinkers had lower odds of having a diagnosis of NASH, lower odds for fibrosis and ballooning hepatocellular injury.
S17.	Koehler EM, et al (2012)	2,811 participants, mean age 76.4 ± 6.0 years. Prevalence of NAFLD was 35.1%.	Logistic regression analysis was used to assess associations between co-variables and severity of NAFLD.	Behavioral: smoking habits, physical activity	Total physical activity, pack years of smoking, age, as well as other variables were associated with NAFLD. The prevalence of NAFLD decreases with advancing age in the elderly.

Continued

Table I (Cont.). Studies selected to be reviewed.

Study	Authors, year	Sample characteristics (No, age, gender, diagnosis)	Method	Psychological factors identified	Results
S20.	Zein CO, et al (2011)	1091 subjects were included diagnosed with NAFLD. Of the total number, 63% (687) were female. Mean age 49 ± 11.9	The analysis used cross-sectional data. Bivariate analysis was performed to determine associations between smoking and the disease severity in NAFLD patients.	Behavioral: smoking habits	Smoking history was associated with advanced liver fibrosis in NAFLD patients. In summary, cigarette smoke may aggravate fatty liver.
S25.	Dunn W, et al (2008)	7,211 nondrinkers and 945 modest wine drinkers were included in the study.	Survey, cross-sectional study. Associations between alcohol consumption and NAFLD were explored.	Behavioral: alcohol consumption	The prevalence of NAFLD is significantly lower in modest wine drinkers when compared to nondrinkers.

Conclusions

Primarily associated with insulin resistance, NAFLD is actually considered the hepatic manifestation of the metabolic syndrome[58,59]. The pathogenesis of NAFLD and the more severe NASH is yet unclear. So far, it appears multifactorial, with many mechanisms being proposed as possible causes.

Our study attempted to identify some of the emotional, cognitive and behavioral factors associated with the evolution of NAFLD/NASH. The results of our analysis are limited, in part due to the lack of conceptual clarity in some of the studies reviewed, the very diverse samples used and the various methods of collecting and analyzing the resulting data.

Some investigations suggest that emotional factors like anxiety and depression could influence the progression of chronic liver diseases, but further research is needed to establish the type and the causes of such a relationship.

For NAFLD patients, the most relevant areas of investigation for cognitive functioning concern those contents and processes related to the ability to initiate and maintain lifestyle changes. The cognitive mechanisms underlying dietary behaviors and engagement in physical activity are some of the most important targets for further investigation.

Intense physical exercise may act as a protective factor against the debut and aggravation of NAFLD symptoms. In the evolution of NAFLD, poor nutrition seems to play a central role and needs further investigation. Some studies show there is an improvement in insulin resistance and hypertransaminasemia following hypocaloric diets in NAFLD patients[60].

Contrary to the effect of coffee consumption and moderate alcohol drinking, smoking may have a detrimental effect on NAFLD evolution.

In conclusion, some of the factors identified act as protective factors, other as vulnerability factors. NAFLD/NASH may be considered a cognitive-behavioral disease, the most effective management being lifestyle changes, with emphasis on diet and exercise.

Conflict of interest

The Authors declare that they have no conflict of interests.

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