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Evaluation of risk factors for non-alcoholic fatty liver disease in India: A systematic review and meta-analysis

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Abstract:

INTRODUCTION: NAFLD is emerging as an important cause of liver disease in India. It is estimated that 16-32% of general population in India (nearly 120 million) has NAFLD.

OBJECTIVE: This study aimed to identify the risk factors of NAFLD and to identify the association of lifestyle (dietary and physical activity), genetic, and environmental factors with NAFLD in India.

MATERIALS AND METHODS: A systematic literature search was conducted using an international electronic database: PubMed (MEDLINE) and Google Scholar from the date of inception 31st March 2021 to 28th September 2021. We included studies examining patients with NAFLD: Adults above 18 years of age. Studies with or without a control population were both eligible. The studies with a diagnosis of NAFLD based solely on abnormal liver tests were excluded. We tried to get unpublished data but they were not of the quality of inclusion. Meta-analysis was performed using the software STATA 14.2 (StataCorp, College Station, TX, USA). For each of the studies, the standard error was calculated using the reported number of outcomes and the sample size. A forest plot was used to graphically represent the study-specific and pooled prevalence estimates for overall and subgroup analysis.

RESULTS: In a systematic review and meta-analysis of 8 studies including data from over 1800 individuals, we found that among components of lipid profile, LDL and HDL had a negative effects on NAFLD while triglycerides had a positive effect on NAFLD.

CONCLUSION: Type 2 Diabetes Mellitus, Hypertension, and Obesity were the potential risk factors for NAFLD but the evidence generated was only from single studies.

Keywords:

India, meta-analysis, non-alcoholic fatty liver disease, risk factors, systematic review

Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) is a systemic disorder with complex multifactorial pathogenesis and heterogeneous clinical manifestations. It is a benign form of the disease where the accumulation of fat occurs (steatosis) in >5% of the hepatocytes, with a wide spectrum of presentations ranging from, simple steatosis to non-alcoholic steatohepatitis (NASH) with or without cirrhosis. It is a progressive entitythataffects about 5-7% of the general population and 30-40% of patients present with raised liver enzymes. Around 2 to 5% of adults and up to 20% of those who are obese may develop NASH. Compared with the general population, NAFLD patients are at increased risk of liver-related, cardiovascular, and all-cause mortality.[1,2] Progressive liver disease in

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NAFLD is asymptomatic and usually diagnosed late, at the stage of decompensated cirrhosis, when intervention is less effective and mortality rates are high.[3]

The current annual medical and societal costs of NAFLD are estimated at $292 billion in the United States.[4] The projected cost of caring for patients is expected to increase by 18% from 2000 to 2035 and health-related quality of life of patients with NAFLD is described as declining.[5,6]

NAFLD is estimated to affect around one billion individuals worldwide. NAFLD affects around 20-30% of the population worldwide.[7] NAFLD is emerging as an important cause of liver disease in India.It is estimated that 16-32% of the general population in India (nearly 120 million) has NAFLD. Industrialization, change in lifestyle, diet with less physical activity, and increased calorie-rich food are contributing to the increased prevalence of NAFLD in the Indian population.[8] NAFLD is more common among people who are obese and have conditions related to obesity such as type 2 diabetes.[8] It is also estimated that 63 million Indians are Type 2 diabetic, and among them, 70% are having NAFLD (44 million). Studies are suggesting that Indians are more prone to NAFLD compared to other races due tohigher occurrence of insulin resistance and higher fat levels (triglycerides) in blood.[7] Available literature shows that the majority of Indian patients with NAFLD are obese or overweight but they do not have the kind of morbid obesity that is seen in patients in the West.[9]

The underlying pathophysiology of NAFLD is strongly linked to insulin resistance, aberrant hepatic lipid metabolism, visceral adiposity, and inflammation. However, several other important modulators of disease, such as the environment and diet, can further modify triggers of chronic extra-hepatic and intra-hepatic immune pathways and the pathogenetic roles of the gut. NAFLD is an extremely complex disease that represents the convergence of many pathways, risk factors, and external influences that are not uniform in all the patients. Although many patients with NAFLD have a common metabolic profile (T2DM, hypertension, and obesity, among others), not all patients do.[2]

Although many factors have been studied extensively in various parts of the globe, potential risk factors for NAFLD have not undergone a formal evaluation in a representative sample of the general population, especially in low and middle-income countries (LMICs) like India. The fact that a significant proportion of the population already hasrisk factors that can progress into NAFLD and its sequelae of clinical manifestations poses a potential challenge to the healthcare system. In order to develop community-based strategies for earlier, targeted detection of liver disease, a good understanding is needed of metabolic risk factors.In this study, we chose to concentrate on metabolic risk factors, as these have been the subject of minimal attention in global research to date. Ongoing studies are providing evidence for the clinical effectiveness and cost-effectiveness of risk factor-based case finding for NAFLD in unselected populations.[10-12] Thus, evidence from the systematic review can help us identify people with risk factors who might develop NAFLD and other hepatic manifestations and intervene appropriately to halt its progression. Thus we conducted a systematic review of published studies

Objectives: To identify the risk factors of NAFLD in India and to identify the association of lifestyle (dietary and physical activity), genetic, and environmental factors with NAFLD in India

Materials and Methods

This systematic review did not require patient consent or ResearchEthics Committee approval but expedited review was sought.

Search strategy

This study was conducted and reported according tothe PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines[Figure 1].

A systematic literature search was conducted using an international electronic database: PubMed (MEDLINE) and Google Scholar from the date of inception 31st March 2021 to 28th September 2021.The searches used the PICO (P: patient or problems; I: intervention being considered; C: comparison intervention; O: outcome measurements) framework. The search was conducted for studies reporting on patients with risk factors for

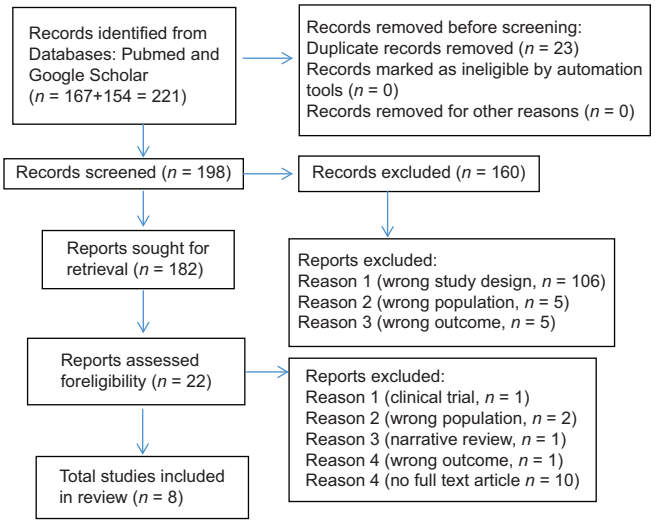

Figure 1: Flow diagram of selection and extraction strategy of data

NAFLD, including synonyms and relevant Medical Subject Headings (MeSH)/Emtree terms such as 'NAFLD', 'non-alcoholic steatohepatitis', 'risk factors', 'determinants', 'causes', 'etiological factors' 'India'. The Boolean operators used for search are as follows -

("Non-alcoholic fatty liver disease"[Title/Abstract] OR "NAFLD"[Title/Abstract]) AND ("India"[Title/Abstract]) AND("prevalence"[Title/Abstract] ORepidemiology"[Title/Abstract] OR "incidence"[Title/Abstract] OR "distribution"[Title/Abstract]) AND ("risk factors"[Title/Abstract] OR "determinants"[Title/Abstract]

Selection criteria

The systematic review included cross-sectional and clinical trials, case-control studies, andcohort studies published inpeer-reviewed journals which follow inclusion criteria. We tried to get unpublished data but they were not of the quality of inclusion.

Inclusion criteria

1. We included studies examiningpatients with NAFLD: adults above 18 years of age.
2. Studies with or without a control population were both eligible. NAFLD was defined as described and diagnosed inindividual studies.
3. Language was restricted to English.
4. No limitations to the year of publication were applied.

Exclusion criteria

1. The studies with a diagnosis of NAFLD based solely onabnormal liver tests were excluded. No other restrictions to thetype of diagnostic method were applied.It was mandatory to mention on the description of the exclusion of patients with other causes of hepatic steatosis such as diabetes mellitus, obesity, metabolic syndrome, or liver diseases (e.g. viral hepatitis, alcoholic liver disease).
2. The studies conducted on specific groups like pediatric, non-obese, or euthyroidpopulations were also excluded.
3. Case reports, case series, reviews, posters, abstracts, and descriptive studies were excluded.

Data extraction and quality assessment

Two of the reviewers screened all titles from the searches to exclude studies that were irrelevant. Following this, The Rayyan software was used for a repository of articles during abstract screening. The titles andabstracts were screened using a checklist for inclusion of the article for study bytwo mid-level experienced researchers independently. The full texts of the potentially eligible studies were retrieved for full review and final selection. Two more reviewers did the qualitative critical appraisal of the studies (STROBE guidelines for quality assessment). The weightage for studies and grading of the study was done using the scoring method.

Data for the studies were extracted by2 of the reviewers and verified by the third reviewer, and finally, by the fourth reviewer for accuracyand completeness. Any discrepancies in the extracted data were discussed by all reviewers for a 100% consensus.

Data were extracted based on the following: (a) general information (author, title, citation, and country); (b) study characteristics (study design, number of participants at baseline and follow-up, clinical subgroups, demographic details); and (c) outcome data (baseline and follow-up measure).The common guidefor data extraction included appropriateness of study design to research objective, risk estimate, risk of bias, choice of outcomes, statistical methods employed, quality of reporting, quality of intervention, and generalizability wereincluded.

Data synthesis and analysis

The primary investigator (SK) extracted the following study characteristics required for the current review:

1. General Information: Author, study title, publication year, country.
2. In the Methods section: study design, study period, study setting, study participants, sample size, sampling technique, diagnostic tool, mode of interview, outcome assessment, and statistical tests employed
3. In the Outcome section: mean age, NAFLD prevalence, Clinical features, enzyme levels in cases and controls, scoring criteria used in those studies.

The primary investigator (SK) transferred these data into the software STATA version 14. Data entry was double-checked for correct entry by the co-investigator (RK) through a comparison of data presented in the review and the primary articles.

Risk of bias assessment

Two independent authors (SK and RK) assessed the quality of all the included studies using the Newcastle-Ottawa (NO) scale adapted for cross-sectional studies.[13] Two criteria (selection and outcome) were used to assess the risk of bias. Thefollowing domains were used for assessing the risk of bias under selection criteria: representativeness of the sample, justification of sample size, rate of non-respondents and their characteristics, and use of validated measurement tool. Under Outcome criteria, assessment of outcome through independent blind assessment or record linkage was used to assess the risk of bias. Each of these outcomes was rated as high (1 point) or low (0 points) based on the quality of evidence and availability of information. Studies scoring more than or equal to 3 points were

considered to have a high risk of bias.The risk of bias refers to the potential for systematic errors or deviations from the truth in the results or inferences of a study. Hence ethical concerns are not necessary.

Statistical analysis

Meta-analysis was performed using the software STATA 14.2 (StataCorp, College Station, TX, USA). For each of the studies, the standard error was calculated using the reported number of outcomes and the sample size.A forest plot was used to graphically represent the study-specific and pooled prevalence estimates for overall and subgroup analysis.Publication bias was checked and graphically represented by funnel plot and asymmetry of the plot was tested using Egger's test-value less than 0.10 was considered a statistically significant publication bias.[14]

Results

It was interesting to note that the majority of the studies were cross-sectional analytical [Table 1]and we found 3 Indian studies which were case-control or cohort for all risk factors. Only one clinical trial was done so far.Most of the studies had a sample size of less than 500 except one study. The objective of these studies was to identify the risk factors in India. The second objective of our study with lifestyle, physical activity, and environmental factors had no studies done todate. The studies reviewed had risk factors such as HDL, LDL, Triglycerides, and patients with diabetes and hypertension. All 7 papers spoke on lipid profile and only one paper spoke on hypertension and diabetes among the NAFLD patients.

The results of the lipid profile as per all the studies no effect of high LDL [Figure 2]. Though 4 studies have found that LDL increases the risk of NAFLD, overall the effect is almost nullified to say the effect runs fromnegative to positive. The weightage of all studies is almost equal and we don't find any study having more than 20%. More studies with positive and only two studies with the negative effect of LDL was found.

The results of the lipid profile as per all the studies no effect of high HDL [Figure 3]. Though 3 studies have found that low HDL increases the risk of NAFLD, overall the effect is almost nullified to say the effect runs fromnegative to positive. The weightage of all studies is almost equal except for one study where it is 6.13% weightage also we don't find any study having more than 20%. More studies with negative effect and only two studies with the positive effect of high HDL was found.

The results of the lipid profile as per all the studies positive effect of high triglycerides [Figure 4]. Though 1 study hasfound that high triglyceridelower the risk of NAFLD.Overall the effect is positive at31.60 and the confidence interval is 16.69 to 46.91. The weightage of all studies wasall different one study with a negative effect but the weightage of the study wastoo low and is just 7.37%. Weightage of all studies is low below 20%.We don't find any study having more than 20%. The systematic review todate speaks only those high triglycerides alone have a positive causal effect on NAFLD.

The gender distribution was seen in studies which showed-Males- 58.1%; Females- 56%in Bhat G *et al*.[19] and 60% in males and 40% in females in Sanjay Kalra *et al*.[18] study and both were almost the same.

The OR of diabetes and hypertension was seen in only one study done by Agarwal AK *et al*.[16] and diabetes was2.5 times the risk for NAFLD cases. Hypertension had 4 times more risk for NAFLD. But this was from only one study. BMI: 27.2 in NAFLD vs. 21.7 in Non-NAFLD; $P < 0.001$) was found in a study done by Bhat G *et al*.[19] Poor glycemic control -(HbA1c >7%): 69.1%inNAFLD vs. 54.7% in non-NAFLD (OR 1.8) was seen in Bhat G *et al*.[19] Waist circumference risk OR- 5.7 (2.8-11.3) $P < 0.001$ was found in Anido

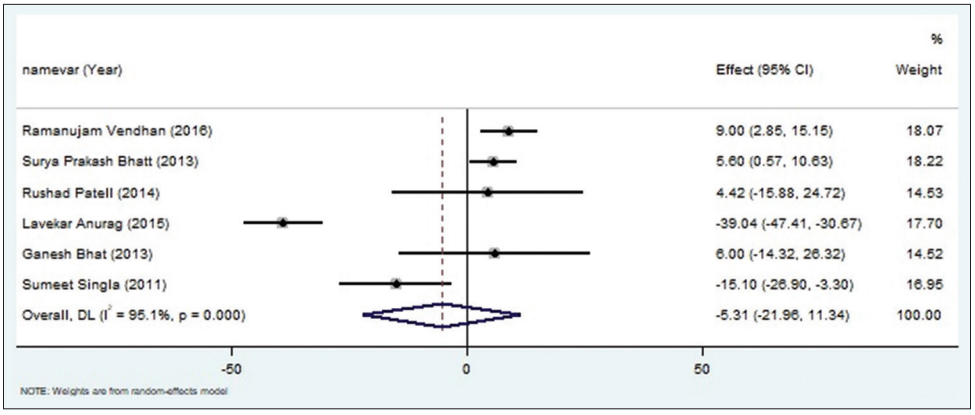

Figure 2: The forest plot of LDL risk factor for NAFLD

Table 1: Description of the studies reviewed

Authors	Type of study	Sample size	Time Period	Methods used	Outcomes assessed
Bhatt SP *et al*.[15]	Case control Study	335	5 years	Study setting: Hospital Sampling: Not mentioned Study Population: Non-diabetic Asian Indians with NAFLD	Two prediction equations were developed; Clinical [Indian Fatty Liver Index-Clinical; IFLIC]: 1(double chin) +15.5 (systolic blood pressure) +13.8 (buffalo hump); andIFLI-Clinical and Biochemical (CB): serum triglycerides +12 (insulin) +1(systolic blood pressure) +18 (buffalo hump).
Agarwal AK *et al*.[16]	Case control study	124	Not mentioned	Study setting : R.M.L.Hospital, Delhi India Sampling: Not mentioned Study Population: Asian Indians with NAFLD	NAFLD had high incidence of diabetes, hypertension
Majumdar A *et al*.[17]	Cross sectional study	176	3 years	Study setting : Rural Haryana Sampling: Not mentioned Study Population Rural Indians with NAFLD	Prevalence of NAFLD
Sanjay Kalra *et al*.[18]	Cross-sectional, multi-center study	924	4 months	Study setting : Routine diabetic clinics Sampling: Consecutive Study Population: All eligible patients cross 101 cities in India included in the study	Elevation in AST and ALT levels, based on NHANES III criteria, were employed to estimate and characterize the prevalence of NAFLD
Ganesh Bhat *et al*.[19]	Prospective study	Not mentioned	Not mentioned	Study setting : Patients attending the liver clinic at the selected center Sampling: Not mentioned Study population: Eligible patients attending one centre only	Clinical and Anthropometric (Body Mass Index, Waist and Hip circumference) Metabolic syndromedefined according to the National Cholesterol Education Program (NCEP) adult treatment panel III (ATP III) guidelines; Insulin resistance based onhomeostasis model of Insulin resistance and metabolic syndrome 19 assessment for insulin resistance (HOMA-IR)
Avica Atri *et al*.[20]	Cross-sectional Study	106	18 months	Study setting: Hospital Sampling: Random Study population: Women	Nearly three-quarters[73.6%] of the 106 morbidly obese participants were found to have NAFLD. Waist circumference, body mass index and waist–height ratio to be most useful in distinguishing between patients with and without NAFLD, and found waist–height ratio was the best screening tool for diagnosing NAFLD
Charu Arora *et al*.[21]	Clinical trial	140	18 months	Study setting: Hospital Sampling: Random Study population: Patients with NAFLD	No significant association was found between grade of fatty liver and diet quality (p=0.197) or between grade of fatty liver with level of physical activity (p=0.615).
Rina Mohanty, *et al*.[22]	Cross-sectional Study	100	Not mentioned	Study setting: Hospital Sampling: Not clear Study population: Not clear	Out of total NAFLD cases, majority 13 (43.3%) were of USG grade II. (P=1.685)

Manjumdar *et al*.[17] In another study by Suryaprakash Bhatt *et al*.[15] spoke of a double chin (risk ratio 2.2), buffalo hump (risk ratio), and hypertension (3.3risk ratio), but this study's risk ratio crosses over one and is insignificant.

We tried to notice the difference in obese and nonobese individuals and the review could get only one such study which speaks as 80% of patients were overweight/obese among patients with NAFLD according to the Asia Pacific criteria, 5% had central obesity whereas 15% patients were lean NAFLD patients (normal BMI and WC). The results of the above were in the Bhat G *et al*. study.[19]

Discussion

In a systematic review of 8 studies including data from over 1800 individuals, we found thatamong components of lipid profile, LDL and HDL had a negative effects

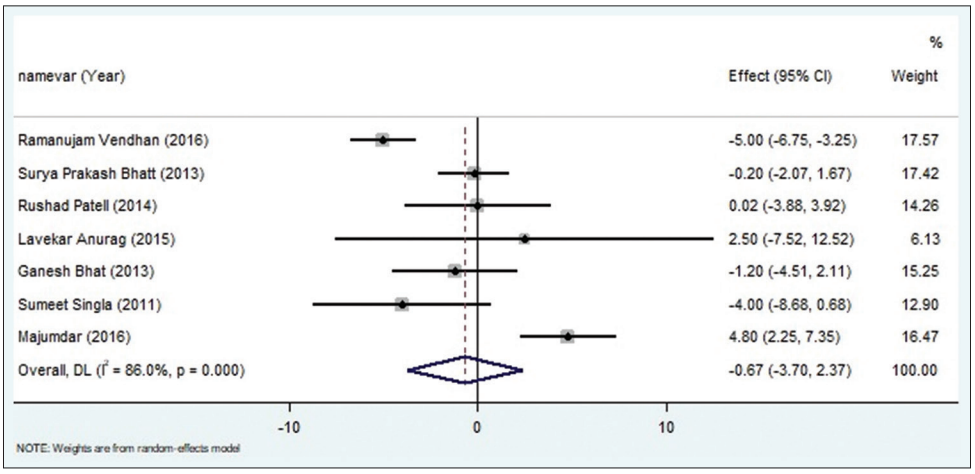

Figure 3: The forest plot of HDL risk factor for NAFLD

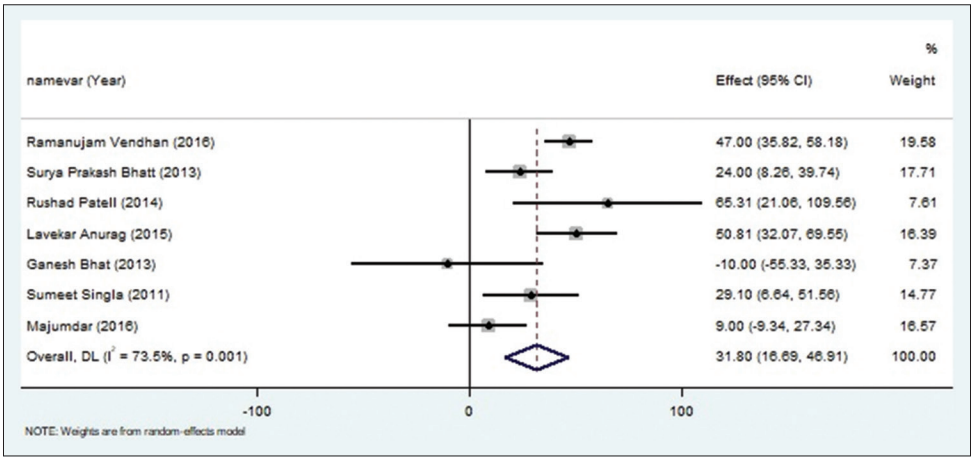

Figure 4: The forest plot of Triglyceride risk factor for NAFLD

on NAFLD while triglycerides had a positive effect on NAFLD.T2DM, HTN, and Obesity were the potential risk factors for NAFLD but the evidence generated was only from single studies.

General interpretation of review in the context of other evidence

The published literature so far focuses on metabolic risk factors for NAFLD and also NAFLD and cirrhosis or NAFLD and Hepatocellular carcinoma combined. Most of the studies were conducted in the western population and followed a cohort design and T2DM, Obesity, and BMI were risk factors of interest, while few studies focused on components of lipid profile and HTN. Few cross-sectional and case-control studies were conducted among the Asian population while evidence from large population-based studies is lacking.[23,24] There is also great variability in the time of progression from NAFLD to cirrhosis (via NASH), ~11% of patients progress over a 15-year period.Equally ~7% of cirrhotic patients progress to HCC over a 6.5-year period.[25]

In a systematic review of 22 studies, conducted by Jarvis H *et al*.,[3] it was found that T2DM was significantly associated with incident liver disease among NAFLD patients (random-effects HR2.25, 95% CI 1.83–2.76, $P < 0.001$, I 2 99%). This finding is inconsistent with our study.The risk factors for diabetes such as a sedentary lifestyle, and moving away from traditional diets might be risk factors for NAFLD as well. A large study conducted in Sweden with over 1,00,000 subjects reports that low HDL and high triglycerides are also potential risk factors for NAFLD. This is similar to our study where high triglycerides had a significant effect on NAFLD but in contrast, HDL had no effect.[26] However previous literature suggests that Asian patients are more likely to have "lean" or "non-obese" NAFLD, potentially representing a pathophysiolocally different group of patients from those seen in Western countries. A cohort study conducted among 84, 523 subjects in Australia found that hypercholesteremia and BMI were associated with greater odds of developing NAFLD.[22]

In a systematic review and meta-analysis conducted by Gerui Li *et al*.,[27] a meta-analysis of 11 observational cohort studies, found that the presence of NAFLD is significantly associated with a higher risk of incident HTN (HR 1.55, 95% CI:.29–1.87; I2 = 80.5%; n = 9 studies, 46,487 participants). On the other hand, the presence of HTN was significantly associated with a higher incidence of NAFLD (HR 1.63, 95%CI: 1.41–1.88; I2 = 37.6%; n = 4 studies, 25,260 participants) indicating that association is bidirectional. The reason for this is due to dysregulation ofglucose and lipid metabolism, disturbance of immunologichomeostasis, and increased release of cytokines, hepatokines, and oxidants and also activation of the Renin Angotensin Activation System. However, a cross-sectional study conducted in Bangladesh by Alam *et al*.,[28] found that HTN wasnot an independent predictor of NAFLD while early to midlife adults; diabetic, overweight, and obeseindividuals; rural women; and married individuals are at a greaterrisk of developing NAFLD than others. The study also found that young and non-obese individuals can also be affected by NAFLD but the risk is lesser compared to obese individuals. Abdominal/central obesity could be a risk factor for NAFLD as in lean individuals fat is stored in the liver but not in adipose tissue.[24] Waist circumference could be a better risk factor in such individuals for the development of NAFLD.

Limitations of evidence included in the review

A systematic review of observational studies by the same author[29] also found that Lean and non-lean NAFLD patients are metabolically similarand share common risk factors.An increased uric acid (UA) level was found to be associated with thepresence of NAFLD among lean. Our study could not capture this important aspect of obesityvs lean as a risk factor for NAFLD which can be considered as a limitation. Our study could not include the socioeconomic status as a risk factor for NAFLD. A study conducted by Zhu *et al*.[30] suggested that countries withhigher economic status tend to present a higher prevalence of NAFLD. Although the objective was to identify risk factors for NAFLD that included genetic, environmental, and metabolic, socio-demographic and genetic factors were not taken into account. This could be consideredan important limitation as gender differences, socio-economic status, and rural/urban divide can influence the lifestyle which inturn can affect the occurrence of NAFLD

Limitations of the review processes

We could not get more data and grey data was not available. The studies which we reviewed were not good for inclusion criteria. The risk factors for NAFLD were not commonly done and we couldn't find the diet factor in our review. There could have been missed grey materials from the review.

Implications of the results for practice, policy, and future research

This study demonstrates important associationsbetween the individual metabolic syndrome components with odds of developing NAFLD. The existing division of risk factors as modifiable and non – modifiable for Non Communicable diseases can be applied for NAFLD as well for designing community-based programs. Annual health checkups whose trend is increasing nowadays can also be used as starting point for diagnosis of NAFLD and to prevent its progression to more aggressive forms of nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis, end-stageliver disease, and eventually hepatocellular carcinoma. Since ultrasonography cannot detect fatty infiltration of less than 30%, biopsy is considereda gold standard for diagnosis of NAFLD, and using this test in a large population is not practical, hence preventive approach should be the focus, and management of metabolic riskfactors could be the initial step in stopping further progression to cirrhosis or carcinomas.

Generating evidence through large population-based studies in India can throw light on genetic factors, environmental factors, and metabolic risk factors as well as for making informed decisions.Data from annual health check-ups can also be used to understand the correlation between socio-demographic and metabolic risk factors with NAFLD. There is a need for future research on which combination of metabolic risk factors can predict the occurrence of NAFLD and also its progression to severe forms and also an association of NAFLD in individuals without metabolic risk factors. NAFLD is considered adisease of higher income groups or developed countries. More evidence is required from studies involving low-socioeconomic groups. Our findings also suggest a risk-factor-based approach for the management of patients progressing to NAFLD.

Abbreviation

- NAFLD - Non-alcoholic Fatty Liver Disease
- T2DM – Type 2 Diabetes Mellitus
- HTN- Hypertension
- LDL – Low-Density Lipoprotein

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Conflicts of interest

There are no conflicts of interest.

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