

# Prevalence of asymptomatic nonalcoholic fatty liver disease in nondiabetic participants: a study from south india

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## Background

Nonalcoholic fatty liver disease (NAFLD) is a common chronic disease that is rapidly increasing worldwide.

## Aim

The aim of this study was to investigate the risk factors associated with NAFLD in nondiabetics from South India.

## Participants and methods

We recruited 345 asymptomatic participants consecutively, and the study period was between January 2014 and December 2017. All participants underwent risk factor evaluation, fasting serum lipid profile, C-reactive protein (CRP), hemoglobin A1c, liver function test, and abdominal ultrasound.

## Results

Of 345 participants, men represented 213 (71%). The mean age of the participants was 58.4±11.1 years, with age range from 24–68 years. Prevalence of NAFLD was seen in 22%. On risk factor evaluation, 107 (31%) were hypertensive, 89 (25.7%) smoked, 52 (15%) were overweight, 110 (24.9%) were obese, and 113 (32.7%) had dyslipidemia. The mean CRP was 12.7±9.5 mg/l. High  $\gamma$ -glutamyl transferase levels, elevated CRP levels, obesity (45, 59.2%), high total cholesterol (49, 64.4%), low levels of high-density lipoprotein (28, 36.8%), high levels of low-density lipoprotein (27, 35.5%), and high triglycerides (31, 40.7%) were significantly associated with NAFLD compared with non-NAFLD. After adjustment using multiple regression analysis, obesity (odds ratio: 3.5; 95% CI: 2.18–6.16), high total cholesterol [odds ratio: 4.9; 95% confidence interval (CI): 2.91–9.43], low high-density lipoprotein (odds ratio: 2.3; 95% CI: 1.20–4.47), high low-density lipoprotein (odds ratio: 2.9; 95% CI: 1.58–6.17), high triglycerides (odds ratio: 2.4; 95% CI: 1.33–4.60), and elevated CRP levels (odds ratio: 2.0; 95% CI: 1.21–3.39) were significantly associated with NAFLD.

## Conclusion

Our study established obesity, CRP positivity, and dyslipidemia as independently associated with NAFLD in South Indian patients.

## Keywords:

asymptomatic diseases, C-reactive protein, dyslipidemia, nonalcoholic fatty liver disease, nondiabetics, obesity, South Indian patients

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## Introduction

Nonalcoholic fatty liver disease (NAFLD) is a separate hepatic condition distinguished by abnormal fat deposits in liver cells causing chronic liver disease [1]. NAFLD is now recognized as one of the major chronic liver diseases in industrialized countries [2]. At present, NAFLD is an increasing major health problem worldwide [3]. At the time of diagnosis, most patients with NAFLD have minimal signs and symptoms of liver disease, even though some patients have discomfort or sensation of fullness on the right side of the upper abdomen; there is generalized fatigue with hepatomegaly in most of the patients. Prevalence of NAFLD is 15–40% in Western countries and 9–40% in Asia [4]. Recent studies from the Indian subcontinent recorded a NAFLD prevalence of 9–32% in the general population [5,6]. Studies have

established hypertension, type II diabetes, smoking, obesity, and dyslipidemia to be significantly associated with NAFLD [5,6]. The aim of this study was to investigate NAFLD risk factors among nondiabetics in general population. Limited studies are available on this topic from Indian subcontinent.

## Participants and methods

We recruited consecutively, 345 asymptomatic participants from medical health check-up clinic at

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Yashoda Hospital and Nizam's Institution of Medical Sciences, Hyderabad. The study period was from January 2014 to December 2017, and the study was approved by Institutional Ethics Committee.

Detailed medical history (present and past) was collected from all participants. Standardized questions were adapted from the behavioral risk factor surveillance system prescribed by the Centers for Disease Control and Prevention. All participants underwent glycosylated hemoglobin A1c (HbA1c), lipid profile, C-reactive protein (CRP), ultrasound abdominal and liver function test [alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transferase (GGT), and alkaline phosphatase], and viral screening (HIV and hepatitis B and C). NAFLD was diagnosed based on criteria defined by American Gastroenterology Association [7], and based on the ultrasonography, NAFLD was classified into grade I, grade II, and grade III [8].

#### Including and excluding criteria

Participants older than 18 years were included in the study. If participants having any present or past history of NAFLD; type I or type II diabetes; cardiovascular disease; cerebrovascular disease; other liver diseases like viral hepatitis, primary biliary cirrhosis, drug-induced liver damage, autoimmune hepatitis, biliary obstruction, alcoholic liver disease, and Wilson's disease;  $\alpha_1$ -antitrypsin deficiency; HIV infection; alcohol intake more than 20 g/day; severe end organ damage; malignancy; previous gastrointestinal tract surgery; ingestion of drugs known to produce hepatic steatosis; patients taking corticosteroids, high-dose estrogens, methotrexate, tetracycline hydrochloride, amiodarone, or tamoxifen citrate in the previous 6 months; those who had received any prior therapies that may have been beneficial for NAFLD, such as vitamin E, pentoxifylline, and pioglitazone; and those prescribed diet and exercise for weight loss were excluded from the study.

#### Risk factor assessment

According to Joint National Committee VI–VII, hypertension was defined as a systolic blood pressure more than 140 mmHg and/or a diastolic blood pressure more than 90 mmHg based on the average of the two blood pressure measurements, or a patient's self-reported history of hypertension or antihypertensive use, supported by documents. Diabetes was diagnosed if the patient was on antidiabetic medications. Smokers were defined as those reporting daily smoking, and exsmokers and occasional smokers were classified as nonsmokers. BMI value of 25.1–30 kg/m<sup>2</sup> was

considered overweight and more than 30 kg/m<sup>2</sup> was measured as obese. Dyslipidemia was defined (ATP III) as one or more of the following: total cholesterol more than 200 mg/dl, low-density lipoprotein (LDL) cholesterol more than 130 mg/dl, high-density lipoprotein (HDL) cholesterol below 40 mg/dl, very low-density lipoprotein (VLDL) cholesterol more than 30 mg/dl, and triglycerides more than 150 mg/dl. The CRP was assessed by quantitative analysis, and more than 10.1 mg/l was considered positive [9,10].

#### Statistical analysis

Statistical analysis was performed using statistical package for the social sciences 18.0 Windows Software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented in titer of mean  $\pm$ SD. Categorical variables were expressed as proportions. The Student *t*-test was used to test the differences in continuous variables, and  $\chi^2$ -test was used to study the association in proportions. Multiple logistic regression was performed before and after adjustment for potential confounders. All tests were two sided, and *P* value less than 0.05 was considered statistically significant.

#### Results

Table 1 shows that men represented 213 (71%). The participants' mean age was 58.4 $\pm$ 11.1 years, with age range from 25 to 69 years. Hypertension was observed in 107 (31%), smoking in 89 (25.7%), alcoholism (<20 g/day) in 41 (11.8%), normal weight in 183 (53%), overweight in 52 (15%), and obesity in 110 (24.9%) participants. High total cholesterol levels were seen in 113 (32.7%), low HDL in 67 (19.4%), high LDL in 60 (17.3%), high VLDL in 25 (7.2%), high triglycerides in 83 (24%), and CRP positivity in 125 (36.2%) participants. Mean HbA1c was 5.9 $\pm$ 2.1, mean ALT was 59.4 $\pm$ 12.8 IU/l, mean AST was 40.5 $\pm$ 8.9 IU/l, mean GGT 59.9 $\pm$ 19.4 IU/l, and mean alkaline phosphatase was 98.6 $\pm$ 21.5 IU/l. Prevalence of NAFLD in nondiabetics was seen in 76 (22%) (grade 1 was 11.5%, grade II 7.5%, and grade III 2.8%) (Table 1).

Older age (mean age: 59.9 $\pm$ 12.2 years) (*P*=0.043), obesity (45, 59.2%) (*P*<0.0001), high total cholesterol (49, 64.4%) (*P*<0.0001), low HDL levels (28, 36.8%) (*P*<0.0001), high LDL levels (27, 35.5%) (*P*<0.0001), high triglycerides (31, 40.7%) (*P*<0.0001), obesity (45, 59.2%) (*P*<0.0001), elevated mean CRP levels (17.8  $\pm$ 13.9) (*P*<0.0001), elevated mean ALT levels (72.8  $\pm$ 14.8) (*P*<0.0001), AST (47.4 $\pm$ 11.7) (*P*<0.0001) elevated mean GGT (68.4 $\pm$ 12.7) (*P*<0.0001), and

**Table 1 Baseline characteristics**

Parameters	N=345 [n (%)]
Men	213 (71)
Age (mean±SD) (years)	58.4±11.1
Age range (years)	25–69
Hypertension	107 (31)
Smoking	89 (25.7)
Alcoholics (<20g/day)	41 (11.8)
BMI≤24.9 (normal weight) (kg/m <sup>2</sup> )	183 (53)
BMI 25–30 (overweight) (kg/m <sup>2</sup> )	52 (15)
BMI≥30.1 (obesity) (kg/m <sup>2</sup> )	110 (24.9)
High total cholesterol	113 (32.7)
Low HDL	67 (19.4)
High LDL	60 (17.3)
High VLDL	25 (7.2)
High triglycerides	83 (24)
CRP value (mean±SD) (mg/l)	12.7±9.5
HbA1c (mean±SD)	5.4±2.1
Systolic blood pressure (mean±SD) (mmHg)	147.6±29.4
Diastolic blood pressure (mean±SD) (mmHg)	123.7±18.5
Alanine aminotransferase (mean±SD)	59.4±12.8
Aspartate aminotransferase (mean±SD)	40.5±8.9
Alkaline phosphatase (mean±SD)	98.6±21.5
γ-glutamyl transferase (mean±SD)	59.9±19.4
NAFLD	76 (22)
Grade 1 NAFLD	40 (11.5)
Grade II NAFLD	26 (7.5)
Grade III NAFLD	10 (2.8)

CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; VLDL, very low-density lipoprotein.

alkaline phosphatase levels (128.1±13.8) ( $P<0.0001$ ) were significantly associated with NAFLD compared with participants without NAFLD (Table 2).

After adjustment using multiple logistic regression analysis, high total cholesterol levels [odds ratio: 4.9; 95% confidence interval (CI): 2.91–9.43], low HDL levels (odds ratio: 2.3; 95% CI: 1.20–4.47), high LDL levels (odds ratio: 2.9; 95% CI: 1.58–6.17), high triglycerides levels (odds ratio: 2.4; 95% CI: 1.33–4.60), obesity (odds ratio: 3.5; 95% CI: 2.18–6.16), and elevated CRP levels (odds ratio: 2.0; 95% CI: 1.21–3.39) were independently associated with NAFLD (Table 3).

## Discussion

In our study, we found a prevalence of 22% of NAFLD in asymptomatic participants from South India; other studies have found similar findings from 9.3 to 29.5% in Asian countries [11,12], 17.1% in Mexico [13], 30% in Israel [14], 20% in Romania [15], and 22.6% in Italy [16]. Ethnicity and racial differences possibly account for the small changes in the prevalence of NAFLD and less prevalence of NAFLD in African Americans [17].

The difference may be owing to less visceral fat and a different lipoprotein metabolism in African Americans [18].

Recent studies have established increasing prevalence of NAFLD with age [1]. We found our study the mean age (59.9 years) had borderline significant association with NAFLD; other studies have noted slightly lower mean age (49.14±9.65) years [8] and 55.4 years [19].

Fatty liver occurs in all age groups. The liver regulates alcohol metabolism, and as the body ages, toxicity elevates owing to increased organ damage. These developments are related to a mitochondrial transport flaw rising with age and decrease in the smooth endoplasmic reticulum and metabolism of CYP2E1-dependent microsomal ethanol oxidation functions [20].

In our study, we noted that among patients with NAFLD, 43 (56.5%) were men, whereas other studies have noted in 53.3% of men [21]. Our study established no significant association between men and women with NAFLD. However, some studies have noted NAFLD being more predominant in women [1].

We found hypertension in 22 (28.9%) patients with NAFLD, with no significant association with NAFLD. However, some studies have found a significant association with NAFLD [22,23].

This study found smoking was seen in 21 (27.6%) of patients with NAFLD, with no significant association with NAFLD. In contrast, other studies have noted smoking was association with NAFLD [24].

This study found obesity was present in 45 (59.2%) of patients with NAFLD, with a significant association with NAFLD. Our findings were advocated by other studies, which showed the prevalence ranges from 22–74% in obese children and adults [25,26]. De Sousa *et al.* [26] found in a population-based study, central obesity was seen in 50.5% of men and 38.9% of women, and it had an independent association with NAFLD. Cotrim *et al.* showed in their study, 44.7% of patients with NAFLD had obesity [21]. Kim *et al.* [27] noted in his study 34.4% had NAFLD in the overweight group. Kalra *et al.* [1] noted in their study 54.9% of female patients with NAFLD had obesity.

Asian participants have a higher ratio of visceral fat and a minor lean body mass than Caucasian participants

**Table 2 Comparison between nonalcoholic fatty liver disease and non-nonalcoholic fatty liver disease**

	NAFLD (n=76) [n (%)]	Non-NAFLD (n=269) [n (%)]	P value
Men	43 (56.5)	170 (63.1)	0.3
Women	33 (43.4)	99 (36.8)	0.3
Age (mean±SD) (years)	59.9±12.2	56.9±11.4	0.043
Age range	35–69	25–69	
Hypertension	22 (28.9)	85 (31.5)	0.7
Smoking	21 (27.6)	68 (33.6)	0.7
Alcoholics (<20 g/day)	11 (14.4)	30 (14.8)	0.9
Normal weight	24 (31.5)	159 (59.1)	<0.0001
Overweight	7 (9.2)	45 (16.7)	0.1
Obesity	45 (59.2)	65 (24.1)	<0.0001
High total cholesterol	49 (64.4)	64 (31.6)	<0.0001
Low HDL	28 (36.8)	39 (14.4)	<0.0001
High LDL	27 (35.5)	33 (12.2)	<0.0001
High VLDL	5 (5.7)	20 (7.4)	0.5
High triglycerides	31 (40.7)	52 (19.3)	=0.001
CRP value (mean±SD) (mg/l)	17.8±13.9	11.2±7.2	<0.0001
Alanine aminotransferase (mean±SD)	72.8±14.8	48.7±9.8	<0.0001
Aspartate aminotransferase (mean±SD)	47.4±11.7	39.4±8.4	<0.0001
Alkaline phosphatase (mean±SD)	128.1±13.8	90.7±9.7	<0.0001
γ-glutamyl transferase (mean±SD) (U/l)	68.4±12.7	43.7±10.4	<0.0001
Glycosylated HbA1c levels (mean±SD)	5.2±2.4	5.46±4.4	0.7

CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; VLDL, very low-density lipoprotein.

**Table 3 Predictors of nonalcoholic fatty liver disease (before and after adjustment in stepwise method)**

	Before adjustment		After adjustment	
	Odds ratio	95% CI	Odds ratio	95% CI
Hypertension	0.8	0.49–1.50	0.3	0.20–0.77
Smoking	1.1	0.63–2.0	0.5	0.31–1.12
Alcoholics	1.34	0.64–2.83	0.9	0.41–1.51
Obesity	4.7	2.75–8.04	3.5	2.18–6.16
High total cholesterol	5.8	3.36–10.0	4.9	2.91–9.43
Low HDL	3.4	1.93–6.12	2.3	1.20–4.47
High LDL	3.9	2.17–7.14	2.9	1.58–6.17
High triglycerides	2.9	1.71–5.13	2.4	1.33–4.60
Positive CRP	2.8	1.66–4.72	2.0	1.21–3.39

CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

with the same BMI. Central obesity is an important factor for insulin resistance, and an increased visceral adiposity may cause pathogenesis of NAFLD. Visceral adipose tissue is strongly associated with insulin resistant and produces more free fatty acid than accomplish adipose tissue in other sites. In liver deposited of undeveloped lipogenesis causing to NAFLD [27].

Studies have reported that obesity is a major risk factor for NAFLD [27]. In our study, after adjustment of logistic regression analysis, obesity was an independent risk factor for NAFLD (odds ratio: 3.5; 95% CI: 2.18–6.16). Our findings were advocated by de Sousa and colleagues [26–28].

Studies have noted the prevalence of 20–92% of patients having dyslipidemia with NAFLD [29]. Amarapurkar *et al.* [3] found in their study the prevalence of NAFLD among patients with dyslipidemia ranges between 25 and 60% in reports from the Asia–Pacific region. In our study, we showed hypercholesterolemia in 64.4%, high LDL in 35.5%, high triglycerides in 31 (40.7%), and low HDL in 36.8% in patients with NAFLD. Our findings were supported by other studies [8,30–32]. Jali *et al.* [31] noted in their study, 52% of the patients with NAFLD had hypercholesterolemia, 27% had low HDL, 59% had high levels of LDL, and 67% had high levels of triglycerides. Mahaling *et al.* [8] found in their study hypertriglycerides in 67.1%, hypercholesterolemia in



45.7%, high LDL in 34.2%, and high VLDL in 25.7%. Agrawal *et al.* [32] showed in his study, 21.8% had hypercholesterolemia, 45.16% had low HDL, 25% had high LDL, 56.5% had elevated VLDL, and 63.7% had hypertriglyceridemia, and obesity association with NAFLD. Marchsini *et al.* [33] noted in their study, hypertriglyceridemia is present in 64% of patients with hepatic steatosis and 30–42% of HDL low levels. Cotrim *et al.* [21] reported the presence of hyperlipidemia in 66.8% of patients with NAFLD. Duseja *et al.* [34] found hypercholesterolemia in 32% of patients and hypertriglyceridemia 79 (63.7%) patients.

Differences in body fat distribution of patients with NAFLD may have a genetic predisposition. Deposits of lipids within hepatocytes, in the form of triglycerides, can lead to development of NAFLD. The primary metabolic abnormalities leading to lipid accumulation are not properly understood, but they may consist of alterations in the pathways of uptake, synthesis, degradation or secretion in hepatic lipid metabolism and finally from insulin resistance. Insulin resistance is one of the factors for development of NAFLD [8]. The pathophysiology of NAFLD is still incompletely understood. Storage of triglycerides in hepatocytes due to oxidative stress, lipid peroxidation, and proinflammatory cytokines [e.g. tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL-6)]. Animal studies have shown elevated fatty acids in the liver, and it may cause higher levels of TNF- $\alpha$ . When hepatocytes get damaged, liver-specific macrophages (Kupffer cells) are activated and produce more TNF- $\alpha$  and IL-6 into the blood stream, which leads to the production of the acute-phase protein high-sensitivity CRP [35].

In our study, we established that elevated total cholesterol (odds ratio: 4.9; 95% CI: 2.91–9.43), LDL (odds ratio: 3.0; 95% CI: 1.55–6.07) triglycerides (odds ratio: 2.4; 95% CI: 1.33–4.60), and low HDL (odds ratio: 2.3; 95% CI: 1.20–4.47) are independent associations with NAFLD; our findings are supported by Amirkalali *et al.* [36]. In our study, we found elevated CRP levels were significantly associated with NAFLD compared with non-NAFLD, and our findings are supported by Nigam *et al.* [35]. Very few studies have found elevated CRP levels are a useful diagnostic marker for NAFLD [37,38]. Studies have noted CRP levels were higher in Asians Indians than Caucasians [39]. Park *et al.* [40] showed in their study that elevated high-sensitivity CRP level was associated with NAFLD in nonobese healthy men. The proposed mechanism between CRP and NAFLD is the rise in acute-phase cytokines. IL-6 is a strong booster and elevates CRP levels.

This study established elevated CRP levels as an independent risk factor for NAFLD (odds ratio: 2.1; 95% CI: 1.21–3.39), and these findings were advocated by Assy *et al.* [41].

Our study found that elevated ALT (72.8 $\pm$ 14.8 IU/l), AST (47.4 $\pm$ 11.7 IU/l), and alkaline phosphatase (128.1 $\pm$ 13.8 IU/l) are significantly associated with NAFLD compared with without NAFLD. A similar finding was noted by Agrawal *et al.* [32], who noted in their study ALT had a mean value of 97.0 $\pm$ 56.0 IU/l, AST had a mean value of 75.0 $\pm$ 50 IU/l, and alkaline phosphatase had a mean value of 216.0 $\pm$ 77 IU/l. Jali *et al.* [31] noted elevated levels of AST (30%) and ALT (22%) in NAFLD. Amirkalali *et al.* [36] showed in their study very low prevalence of AST (3.9%) and ALT (10.4%) in NAFLD. However, some studies have found no significant association AST and ALT with NAFLD [42,43]. Studies have established GGT levels were significantly associated with NAFLD [44,45]. Our study showed elevated GGT levels were significantly associated with NAFLD when compared with non-NAFLD; our findings are advocated by Saxena and colleagues [44,45].

#### Limitations of study

The main drawback of the study was that we were unable to examine insulin resistance in our participants. The second drawback was that we were unable to analyze grade I to grade III with multiple logistic regression owing to small number. In our study, all asymptomatic participants underwent for one laboratory examination at the time of recruitment. Some studies have found liver biopsy as a gold standard for NAFLD diagnosis, but it is an invasiveness and painful procedure with complications, and sometimes, mortality also occurs. In this study, we performed ultrasonography, which is a noninvasiveness procedure and a promising tool for NAFLD in asymptomatic participants, and it also cost-effective. Ultrasonography has a sensitivity of 60–94% and specificity of 88–95% [46]. In our study, we assessed the relationship between CRP and NAFLD and analyzed multiple logistic regressions for potential risk factors to NAFLD.

#### Conclusion

In this study, we established dyslipidemia, obesity, and CRP positivity as independent risk factors for NAFLD in asymptomatic nondiabetic South Indian participants. We need long-term follow-up studies from India on patients with NAFLD to understand the temporal evolution of NAFLD, metabolic syndrome, and

coronary artery disease in our population. From our results, we suggest that every asymptomatic participant older than 40 years should undergo ultrasonography screening. Further studies should explore these findings.

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VCS Srinivasarao Bandaru was involved in data collection and manuscript writing; Jaydip R. Chaudhury in manuscript review and data analysis; Palle L. Reddy in manuscript writing and interpretation of data; Somala N. Reddy in data collection and statistical analysis; Pradeep K. Misra in manuscript review and data collection; Banda Balaraju in manuscript review and interpretation of data; and Kandadai R. Mridula in study design, manuscript preparation, data review, manuscript review, and statistical analysis. All authors have read the manuscript and approved it for submission.

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### Conflicts of interest

There are no conflicts of interest.

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