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ORIGINAL ARTICLE

A Simple Indian Diabetes Risk Score Could Help Identify Nondiabetic Individuals at High Risk of Non-Alcoholic Fatty Liver Disease (CURES-117)

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Abstract

Objective:

We aim to determine whether a simple Indian diabetes risk score (IDRS) is associated with individuals with non-alcoholic fatty liver disease (NAFLD) among nondiabetic Asian Indians.

Methods:

Nondiabetic participants (n = 409) were selected from the Chennai Urban Rural Epidemiology Study. Mean age was 40 ± 11.9 years, mean body mass index was 23.2 ± 3.9 kg/m^2, and 224 (54.8%) were women. The IDRS was classified as high (≥60), medium (30–50), and low (<30) risk. Non-alcoholic fatty liver disease was assessed by high-resolution β mode ultrasonography. To determine the factors associated with NAFLD, a univariate analysis was first done and a stepwise logistic regression analysis was done based on the factors associated with NAFLD. Biochemical and anthropometric measurements were obtained using standardized procedures.

Results:

The overall prevalence of NAFLD was 24.7% (101/409 participants), and it was significantly higher among those with a high (30.4%) and medium IDRS (21%) compared with the low IDRS group (15.8%; trend chi square; p = .022). In stepwise logistic regression, IDRS was associated with NAFLD with an adjusted odds ratio of 1.78 (95% confidence interval 1.04–3.06), even after adjusting for potential confounders.

Conclusions:

The IDRS can be used as the initial step to screen individuals at high risk of NAFLD in the community.

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Abbreviations: (ALT) alanine aminotransferase, (AST) aspartate aminotransferase, (BMI) body mass index, (CURES) Chennai Urban Rural Epidemiology Study, (HbA1c) glycated hemoglobin, (HDL) high-density lipoprotein, (HOMA-IR) homeostasis assessment model for insulin resistance, (IDRS) Indian diabetes risk score, (LDL) low-density lipoprotein, (NAFLD) non-alcoholic fatty liver disease, (NASH) non-alcoholic steatohepatitis, (NCD) noncommunicable disease, (OR) odds ratio

Keywords: Asian Indians, diabetes, Indian diabetes risk score, non-alcoholic fatty liver disease, screening, South Asians

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Introduction

The term non-alcoholic fatty liver disease (NAFLD) includes a wide spectrum of liver disorders ranging from steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis.[1,2] Patients are generally asymptomatic, with mild elevations in liver enzymes.[3] However, many patients can have NASH with normal liver enzymes.[4] Moreover, in developing countries, doing imaging tests or liver enzyme tests on a population basis can prove expensive. Hence there is a need to develop a simple and inexpensive screening tool to identify individuals in the community who may be at high risk of having NAFLD.

India's epidemic of chronic noncommunicable diseases (NCDs) has passed its early stages.[5] The prevalence of NAFLD is also quite high among urban Asian Indians.[6] Non-alcoholic fatty liver disease shares risk factors with other NCDs such as diabetes (e.g., age, physical inactivity, waist circumference, insulin resistance, dyslipidemia, and high blood pressure).[3,7]

The Indian diabetes risk score (IDRS) was derived using four simple parameters, namely, age, abdominal obesity, family history of diabetes, and physical activity. The IDRS was classified as low (<30), medium (30–50), and high (≥60) risk categories, and an IDRS of ≥60 was initially shown to be useful to identify individuals with undiagnosed diabetes in the community.[8] It was subsequently shown to be useful for identifying metabolic syndrome and coronary artery disease.[9] The present study was undertaken to see whether IDRS is associated with individuals at high risk of having NAFLD in the community.

Methods

The Chennai Urban Rural Epidemiology Study (CURES) is a large cross-sectional study done on a representative population of metropolitan city of Chennai (formerly Madras) in Southern India, with a population of approximately 4.3 million people. The detailed study design of CURES is described elsewhere,[10] while the phases of CURES and the subject selection methods for this study are described in **Figure 1**. This study involves phase 5 of CURES, where every fourth participant recruited in phase 3 (n = 588) was invited to participate in studies on NAFLD, which maintained the representativeness of the original CURES sampling frame. A total of 541 individuals participated (response rate 92%); however, we excluded 132 participants who either had diabetes or consumed alcohol.

Diabetes is strongly associated with an IDRS ≥ 60, and as almost half of the diabetes population has NAFLD, this could act as a confounder. Participants with alcohol use were excluded according to our definition of NAFLD. Moreover, individuals were assessed for signs and symptoms of acute liver diseases such as anorexia, nausea, jaundice, fatigue, vomiting, arthralgia, fever, and weight loss. If any of these conditions were present, the individuals were excluded. Thus, the final number of study participants was 409.

Anthropometric measurements were obtained using standardized techniques.[10] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mm Hg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus; Pune, India). Two readings were taken 5 min apart, and the mean was used.

Fasting plasma glucose and 2 h post load (75 g) plasma glucose (glucose oxidase-peroxidase method), serum total cholesterol (cholesterol oxidase-peroxidase amidopyrine method) serum triglycerides (glycerol phosphate oxidase-peroxidase amidopyrine method), high-density lipoprotein cholesterol (HDL, direct method, polyethylene glycol pretreated enzymes), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and gamma-glutamyltranspeptidase were measured using a Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography method using the Variant machine (BIORAD, Hercules, CA). The intra- and inter-assay coefficients of variation were 3.1% to 7.6%.

Serum insulin concentration was estimated using Dako kits (Dako, Glostrup, Denmark).

Insulin resistance was calculated using the homeostasis assessment (HOMA) model: fasting insulin (mIU/ml) × fasting glucose (mmol/liter)/22.5. Those with values above the third quartile for the nondiabetic population (i.e., >2.58) were considered to have insulin resistance (HOMA-IR).[11]

Indian Diabetes Risk Score

The IDRS is a simplified risk score for identifying undiagnosed diabetes subjects derived using simple parameters: age, waist circumference, family history of diabetes, and physical activity.[9] The information for these risk factors was obtained based on four simple questions and one anthropometric measurement, namely, waist circumference. These scores were derived based on the multiple logistic regression model as described elsewhere,[9] and the scoring is shown in **Table 1**. Subjects with an IDRS value of <30 were categorized as low risk, those between 30 and 50 as medium risk, and those with ≥60 as high risk for diabetes. We have previously shown that an IDRS

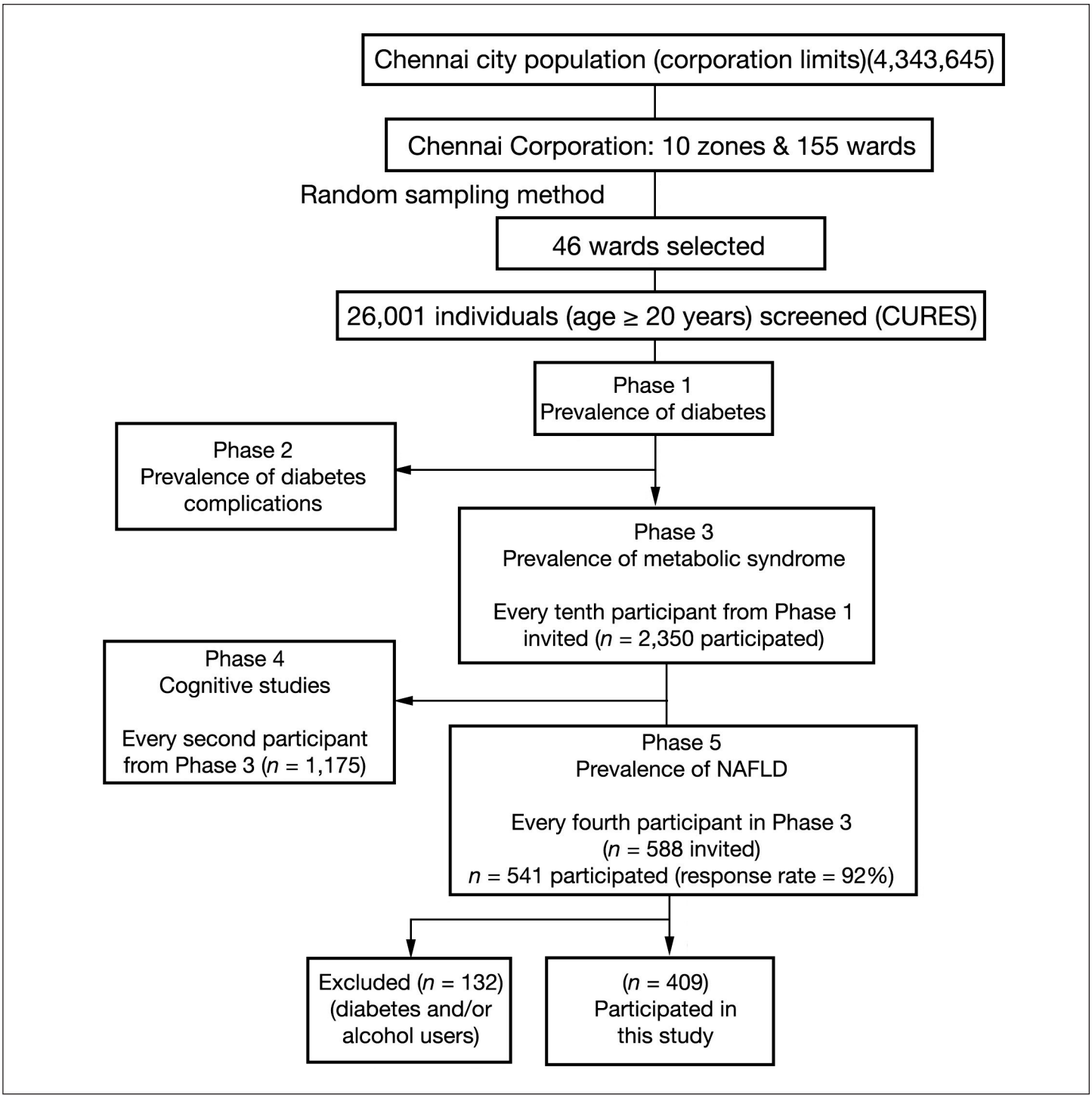

Figure 1. Phases of Chennai Urban Rural Epidemiology Study (CURES) showing selection of study participants.

of 60 has 72.5% sensitivity, 60.1% specificity, 17.0% positive predictive value, 95.1% negative predictive value, and 61.3% accuracy for detecting undiagnosed diabetes.[9]

Non-Alcoholic Fatty Liver Disease

Using a high-resolution B-mode ultrasonogram (Logic 400; GE, Milwaukee, WI), fatty liver was defined as the presence of "bright liver," with evident contrast between hepatic and renal parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins in the absence of chronic liver disease findings.[12,13] Repeat measurements in a random subgroup of 20 participants gave intraobserver and interobserver coefficients of variation of <5%.

Statistics

All statistical analyses were performed using SAS version 9.1. Differences between the risk groups of IDRS were tested using the chi square test and analysis of variance. Kruskal–Wallis test was used for nonparametric variables. Univariate analysis was first done to see the factors associated with NAFLD and then stepwise logistic regression analysis was performed by introducing these factors one by one into the model. A p value < .05 was considered to be significant.

Results

Table 2 presents the clinical and biochemical characteristics of the study participants stratified according to the IDRS. With increasing IDRS, there was a significant increase in BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, 2 h plasma glucose, HbA1c, HOMA-IR, total serum cholesterol, LDL cholesterol, ALT, and alkaline phosphatase.

Overall, 101/409 participants had NAFLD (24.7%). **Table 2** shows that the prevalence of NAFLD was significantly higher among participants with a high IDRS (30.4%) and a medium IDRS (21%) compared with those with a low IDRS (15.8%), and the trend was significant (p = .022).

Table 3 presents the univariate analysis of various factors associated with NAFLD. Not surprisingly, the ALT/AST ratio had the highest odds ratio (OR) for NAFLD followed by HbA1c, IDRS, and several other factors. A stepwise multiple logistic regression analysis was then done using NAFLD as the dependent variable and the various risk factors as independent variables, and the parameters that remained significant in the final model are shown in **Table 4**. It is seen that only the ALT/AST ratio, HbA1c, and IDRS remained in the model as being significantly associated with NAFLD in the model.

Table 1.
Indian Diabetes Risk Score Developed Based on Multiple Logistic Regression Analysis Derived from CURES[9,a]

Particulars	Score
Age	
<35 years	0
35–49 years	20
≥50 years	30
Waist circumference	
Waist < 80 cm (female), <90 cm (male)	0
Waist ≥ 80–89 cm (female), ≥90–99 cm (male)	10
Waist ≥ 90 cm (female), ≥100 cm (male)	20
Physical activity	
Vigorous exercise (regular) or strenuous (manual) work at home/work	0
Moderate exercise (regular) or moderate physical activity at home/work	10
Mild exercise (regular) or mild physical activity at home/work	20
No exercise and sedentary activities at home/work	30
Family history of diabetes	
No diabetes in parents	0
One parent has diabetes	10
Both parents have diabetes	20
Maximum score possible	100

[a] The IDRS is classified by low risk (≤30), medium risk (40–50), and high risk (≥60) categories.

As IDRS was significantly associated with NAFLD (OR 1.78; 95% confidence interval 1.04–3.06; p = .035), we next looked at individual components of IDRS to see which of these contributed most to the association with NAFLD. The unadjusted OR for age was 1.01 (95% confidence interval 0.99–1.03), p = .232; waist circumference was 1.06 (1.04–1.08), $p \leq .001$; family history of diabetes was 1.00 (0.60–1.69), p = .988; and physical activity as 0.98 (0.20–4.95), p = .984. Thus, it can be seen that the composite effect of all four factors, i.e., IDRS, has a higher OR for NAFLD.

Discussion

The main findings of this study are as follows: (1) the prevalence of NAFLD was significantly higher in the

Table 2.
Bioclinical Characteristics of Study Participants in Relation to Different Risk Categories Based on Indian Diabetes Risk Score

Parameters	IDRS < 30 (*n* = 19)	IDRS 30–50 (*n* = 219)	IDRS ≥ 60 (*n* = 171)	*p* value for trend
BMI (kg/m²)[a]	21.6 ± 3.5	22.3 ± 3.5	23.8 ± 3.8[b,c]	<.001
Systolic blood pressure (mmHg)[a]	112 ± 14	115 ± 14	126 ± 17[b,c]	<.001
Diastolic blood pressure (mmHg)[a]	71 ± 10	72 ± 11	78 ± 9	<.001
Fasting plasma glucose (mg/dl)[a]	93 ± 9	92 ± 9	95 ± 10	<.001
2 h plasma glucose (mg/dl)[a]	105 ± 23	107 ± 26	127 ± 31[b,c]	<.001
HbA1c (%)[a]	5.3 ± 0.4	5.6 ± 0.5	5.9 ± 0.9	<.001
HOMA-IR[d]	1.39 (0.38–2.96)	1.24 (0.39–6.32)	1.64 (0.36–6.68)[c]	.014
Total serum cholesterol (mg/dl)[a]	155 ± 25	180 ± 38	182 ± 33[b]	.004
HDL cholesterol (mg/dl)[a]	44 ± 8	44 ± 11	45 ± 10	.992
LDL cholesterol (mg/dl)[a]	89 ± 23	113 ± 32[b]	113 ± 28[b,c]	.004
Serum triglycerides (mg/dl)[d]	98 (52–238)	96 (32–378)	108 (46–355)	.051
AST (IU/liter)[a]	26 ± 9	22 ± 7	22 ± 8	.318
ALT (IU/liter)[d]	26 (17–106)	19 (10–154)[b]	19 (10–89)[b]	.001
Alkaline phosphatase (IU/liter)[a]	212 ± 46	192 ± 63	214 ± 66[c]	.002
Gamma-glutamyltranspeptidase (IU/liter)[d]	19 (14–48)	19 (8–142)	22 (6–157)	.331
Prevalence of NAFLD (*n* [%])[e]	3 (15.8)	46 (21)	52 (30.4)	.022

[a] Analysis of variance was done for normally distributed variables represented as mean and standard deviation.
[b] Significantly different compared with IDRS < 30.
[c] Significantly different compared with IDRS 30–50.
[d] Kruskal–Wallis test was done for non-normally distributed variables represented in median and range.
[e] Chi square test was done for the categorical variables.

Table 3.
Univariate Analysis Using Non-Alcoholic Fatty Liver Disease as a Dependent Variable and Other Covariates as Independent Variables

Variables	Odds ratio	Confidence interval	*p* value
ALT/AST ratio	4.88	2.47–9.68	<.001
HbA1c	2.07	1.33–3.23	.001
IDRS	1.61	1.07–2.41	.022
HOMA-IR	1.29	1.07–1.54	.006
BMI	1.16	1.09–1.24	<.001
ALT	1.04	1.02–1.06	<.001
AST	1.04	1.01–1.07	.016
Systolic blood pressure	1.02	1.00–1.03	.022
2 h plasma glucose	1.01	1.00–1.02	.002
Serum LDL cholesterol	1.01	1.00–1.02	.006
Serum total cholesterol	1.01	1.00–1.015	.004
Alkaline phosphatase	1.01	1.00–1.01	.001
Serum triglycerides	1.03	1.00–1.01	.006
Serum HDL cholesterol	0.97	0.95–0.99	.021

high-risk IDRS group compared with participants with a medium- and low-risk IDRS and (2) IDRS is independently associated with NAFLD even after adjusting for various metabolic risk factors.

We have previously reported that a third of the general population and half of diabetes population in Chennai city, which is representative of urban India, have NAFLD.[6] Even assuming a lower prevalence of NAFLD in rural India, and using conservative estimates, this would translate to nearly 200–300 million people in India having NAFLD.[6] It may be argued that the high frequency of NAFLD in this study reflects other tropical liver diseases such as parasitic liver infections. While this possibility exists, it is unlikely due to strict exclusion criteria for liver diseases that were followed in the study. Non-alcoholic fatty liver disease is known to be associated with many cardiometabolic risk factors such as obesity, diabetes, dyslipidemia, hypertension, and insulin resistance.[14–17] Moreover, progression of the disease to hepatic fibrosis and cirrhosis is seen in 26–37% and to hepatocellular carcinoma in approximately 0–0.5% of patients with NAFLD.[18,19]

Although there are some clinical scoring systems for NAFLD, they are mostly used to identify different stages of disease.[20–23] Our study shows that a simple clinical risk score originally developed to identify undiagnosed type 2 diabetes in the population may help to identify individuals at high risk of NAFLD. We have shown that the IDRS also helps to identify metabolic syndrome and cardiovascular disease in our population,[9] and it costs virtually nothing, as it requires only three questions and a waist measurement. Since NAFLD is associated with several metabolic abnormalities,[14–17] we controlled for most of these risk factors in the logistic regression. However, the IDRS was still seen to be significantly associated with NAFLD. We propose that, among Asian Indians, the IDRS could be used as an initial inexpensive screening tool to identify individuals at high risk of NAFLD in the community. As biochemical tests such as ALT/AST are expensive to do in mass, community-based screening programs, those with high IDRS scores could be referred for ALT/AST estimation or for ultrasonography or other imaging techniques for more definitive assessment of NAFLD.

Non-alcoholic fatty liver disease is an independent risk factor of type 2 diabetes[18] and could have a significant impact in terms of patient health, health-related quality of life, and health care economics.[24,25] Evidence-based practical guidelines for diabetes prevention have been published, derived from a large European initiative.[26] Furthermore, there was a review summarizing risk factors for diabetes risk.[27] Such tools are extremely important for the prevention of diabetes, but their applicability in Asian Indian populations needs to be studied. Similar tools also need to be developed for NAFLD. Thus the prevention of NAFLD requires a multistage approach that begins with identification of high-risk individuals with a noninvasive risk score, confirmation with a diagnostic test, and implementation of evidence-based strategies, including nonpharmacological interventions and active partnerships across all different levels of public health.

Table 4.
Multiple Logistic Regression Analysis of Non-Alcoholic Fatty Liver Disease Using Stepwise Model[a]

Independent variables	Odds ratio	95% confidence interval	*p* value
ALT/AST	5.74	2.46–13.06	<.001
HbA1c	1.85	1.05–3.28	.033
IDRS	1.78	1.04–3.06	.035

[a] Metabolic risk factors such as fasting plasma glucose, 2 h post-load plasma glucose, HbA1c, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, AST, ALT, AST/ALT ratio, alkaline phosphate, gamma-glutamyltranspeptidase, insulin resistance, systolic blood pressure, diastolic blood pressure, and IDRS were included in the model. The variables which remained significantly associated with NAFLD are shown in this model.

The strengths of the study are that it is population based with a good response rate in an ethnic group where such studies are limited. One of the limitations is that we have used a simple ultrasound measure to diagnose NAFLD, which has both false positives and false negatives.[12] However, doing a liver biopsy, which is the gold standard for diagnosis of NAFLD, is neither feasible nor ethical in large-scale epidemiological studies. Another limitation is that the cross-sectional nature of the design does not allow for cause–effect relationships, and thus prospective studies are needed to validate the use of the IDRS in predicting development of NAFLD.

In summary, we report that a simple diabetes risk score could be used as an initial screening tool to identify subjects at high risk of NAFLD, particularly in developing countries where resources are limited. Those with high risk scores could then to be subjected to more expensive or definitive tests to confirm the presence of NAFLD.

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