Original Article

Nontraditional Lipid Parameters as a Predictor of Cardiovascular Disease Risk in Nepalese Women

Jasper Adhikaree, Ruyusha Shrestha, Prabina Bomjan, Shreya Pokharel, Ashmita Shrestha, Anusha Siwakoti, Rashila Acharya, Roy Rillera Marzo[1], Swosti Acharya[2], Ritesh Pokhrel, Prachand Man Singh Rajbhandari

Department of Medical Biochemistry, Nobel College, Pokhara University, Gandaki, [2]Manmohan Cardiothoracic Vascular and Transplant Center, Institute of Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal, [1]Department of Community Medicine, International Medical School, Management and Science University, Shah Alam, Malaysia

Abstract

Background: The use of nontraditional lipid parameters for assessing clinical conditions is emerging; however, no study has identified thresholds for those parameters for the identification of cardiovascular disease (CVD) risk. The present study aimed to establish the thresholds of nontraditional lipid parameters and test its ability to identify CVD risk factors. **Methodology:** A cross-sectional study in women (n = 369, age: 46 ± 13 years, body mass index (BMI): 26.31 ± 2.54 kg/m^2) was conducted. Blood samples were collected and high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, total cholesterol (TC), and triglycerides (TGs) were estimated. Subsequently, nontraditional lipid parameters were calculated, namely non-HDL-C, Castelli's Risk Index II (CRI-II), CRI-I, lipoprotein combined index (LCI), atherogenic index (AI), and AI of plasma (AIP). **Results:** Based on TC (≥200 mg/dL), the derived thresholds for non-HDL-C, CRI-II, CRI-I, LCI, AI, and AIP were 139 mg/dL, 2.29, 3.689, 58,066, 2.687, and 0.487, respectively. Similarly, based on the threshold of TG (≥150 mg/dL), the derived thresholds for non-HDL-C, CRI-II, CRI-I, LCI, AI, and AIP were 127 mg/dL, 2.3, 3.959, 58,251, 2.959, and 0.467, respectively. Out of considered five risk factors, non-HDL-C, CRI-II, CRI-I, LCI, and AI thresholds were capable in identifying four risk factors (physical activity, blood pressure, BMI, and age) and AIP was able to associate with two risk factors at most (blood pressure and BMI). **Conclusion:** The derived thresholds of nontraditional lipid parameters were capable of differentiating between CVD risk and nonrisk groups suggesting the possible use of these thresholds for studying CVD risk.

Keywords: *Cardiovascular disease risk, nontraditional lipid parameters, traditional lipid parameters*

Submitted: 12-Sep-2023
Revised: 12-Dec-2023
Accepted: 14-Feb-2024
Published: 05-Jul-2024

Introduction

Cardiovascular disease (CVD) is listed as a global burden of disease with a mortality rate of around 31.4% and deaths of around 17.6 million annually.[1] Myocardial infarction and strokes are reported to be the cause of 85% of all deaths reported from CVD. The main cause of CVD is the accumulation of fatty deposits in the arteries (atherosclerosis), which increases the risk of blood clots.[2] Although different risk factors are identified for CVD,[3] dyslipidemia is an ultimate result[4] which is described by the elevated levels of total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), or reduced level of high-density lipoprotein cholesterol (HDL-C) in serum concentration as defined by the established thresholds for those lipid parameters.[5]

The effectiveness of lipid parameter thresholds is based on their discriminating ability for different clinical conditions such as coronary heart diseases, myocardial infarction,

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jomh

DOI: 10.4103/jmh.jmh_179_23

Address for correspondence: Assoc. Prof. Prachand Man Singh Rajbhandari, Department of Medical Biochemistry, Nobel College, Pokhara University, Sinamangal, Kathmandu - 44600, Nepal. E-mail: prachand.rajb@nobelcollege.edu.np

How to cite this article: Adhikaree J, Shrestha R, Bomjan P, Pokharel S, Shrestha A, Siwakoti A, *et al.* Nontraditional lipid parameters as a predictor of cardiovascular disease risk in Nepalese women. J Mid-life Health 2024;15:81-90.

ischemic stroke, congestive heart failure, and particularly the CVD risk. Alteration of these lipid parameters above/below the established thresholds is associated with a high chance of CVD risk, hospitalization, and even mortality.[6,7] Although the lipid parameter thresholds are described as a good indicator for identifying the CVD risk and other clinical conditions, the literature has shown incoherency in the threshold's potential to identify relevant clinical conditions and risk factors.[8] This discrepancy in observations in different populations may be explained by diversity in culture, environment, lifestyle, and included age group.[9,10] Indeed, it should also be noted that studies have reported population-specific thresholds for those lipid parameters.[11,12]

The variable prevalence, ranging from 23% to 30%, for the different lipid abnormalities in the same cohort of the population in the NHANES study comprising 555 individuals has been observed.[13] Traditional lipid parameters are routinely used; however, the idea of nontraditional lipid parameters is emerging in geriatric and therapeutic settings. The use of nontraditional lipid parameters is not mostly adapted due to several reasons, one being the undefined thresholds for those nontraditional lipid parameters for identifying clinical conditions such as CVD risk. These nontraditional lipid parameters are mainly derived as the summation or ratio of the existing traditional lipid parameters. Some of the commonly used lipid indices include non-HDL-C, Castelli's Risk Index-II (CRI-II), CRI-I, lipoprotein combined index (LCI), atherogenic index (AI), and AI of plasma (AIP). The advantage of using nontraditional lipid indices over single lipid parameter thresholds could be further explained by their potential to identify intermediate CVD risk when the traditional parameters failed to identify the CVD risk even within a normal range. This strength of identifying and predicting CVD risk and related adverse events with nontraditional lipid parameters, particularly derived as a ratio of traditional parameters, over a single lipid parameter threshold index, emphasizes the importance of these nontraditional lipid parameters in future clinical studies.[14] Association of non-HDL-C with potential of developing CVD has been well established from existing literature along with its threshold value as non-HDL-C has been strongly been associated with coronary artery disease.[15] However, the determined threshold of non-HDL-C from existing literatures were not based on Nepalese women population. As such, population specific threshold for non-HDL-C should be established. CRI-II, CRI-I and AI have all been associated with atherosclerosis.[16,17] LCI and AIP both has been associated with acute coronary syndrome and coronary artery disease respectively.[17,18] These non-traditional lipid parameters have all been established as good predictor of CVD risk as decrease on the level of these parameters has been associated with reduction in cardiovascular disease outcome. However, the threshold values for these non-traditional lipid parameters has not been established in context to Nepalese women population. Therefore, it is essential to establish the thresholds of these parameters for Nepalese women population.[15-18]

Among the traditional lipid parameters, TG due to its ability to independently associated with CVD risk and TC due to its cost are commonly used indices in geriatric and clinical settings.[19,20] Identification of nontraditional lipid parameter thresholds may be important in the future due to its advantages over the traditional lipid parameter thresholds. However, the importance of traditional lipid parameter thresholds should not be denied while deducting the appropriate nontraditional lipid parameter thresholds. Furthermore, the suitability of the derived thresholds could be justified only in the case when the derived nontraditional lipid parameter thresholds would be able to discriminate the CVD risk factors between the classified CVD risk group and nonrisk groups based on derived thresholds. Establishing the thresholds for these non-traditional lipid parameters could lead to early identification of CVD risk group and thus proper lifestyle modifications on diet, physical activity, and hypertension could be recommended in clinical settings. With these backgrounds, the present study aims to (1) establish the thresholds of nontraditional lipid parameters based on established thresholds of TC and TG and (2) test the ability of derived nontraditional lipid parameter thresholds to identify CVD risk factors.

Methodology

Study design, participant's characteristics, and ethical approval

The current study is cross-sectional, comprising 369 women (range: 19–87 years, mean age: 46 ± 13 years, body mass index [BMI]: 26.31 ± 2.54 kg/m^2). The women were enrolled in 3 months (June 2022–August 2022). At the time of data collection, the participants self-reported that they had no chronic illness and did not have any family history of CVD. In addition, individuals suffering from alcoholism, hyperthyroidism, hypothyroidism, physical disability, mental illness, diabetes, endometrial hyperplasia, heart disease, renal failure, and heavy smokers were excluded. Women who were pregnant, lactating, undergoing estrogen replacement therapy, and having lipid-lowering drugs in the study were also excluded. The study followed the guidelines of the Declaration of Helsinki and ethical approval was taken from the Institutional Review Committee (IRC) at

Nobel College (Ref No.MBIRC005/2022), Sinamangal, Kathmandu. All the data collected were kept confidential, and written consent was taken from individuals included in the study's predata collection.

Anthropometric measurements

Individuals were weighed with light clothing using a weighing scale (OMRON, Omron HN 289). The study participants were instructed to stand against the stadiometer and requested to remove apparel such as shoes, heels, boots, and so on to prevent the assessment of false height, and the height was determined. Following the measurement of weight and height, BMI was computed using the formula weight/height^2 (kg/m^2).

Traditional and nontraditional lipid parameter estimation

Initially, a trained phlebotomist drew overnight fasting blood, approximately 5 mL, using the venipuncture technique. The collected blood was then centrifuged (HERMILE Z326K, China) followed by analysis in a fully automated analyzer (Beckman Coulter A408, USA). The quantification of lipid profile parameters, namely LDL-C, HDL-C, TC, and TG, was performed.

Upon the estimation of traditional lipid parameters, the nontraditional lipid parameters were calculated. Non-HDL-C was calculated as TC-HDL-C, CRI-II was calculated as LDL-C/HDL-C, CRI-I was calculated as TC/HDL-C, LCI as TC*TG*LDL-C/HDL-C, AI as non-HDL-C/HDL-C, and AIP as log (TG/HDL-C).

Cardiovascular disease risk threshold definitions

In the current study, the nontraditional lipid indices were derived based on the established thresholds of TG and TC that discriminated between the non-CVD risk and CVD risk groups. As per the previous literature, CVD risk was defined for individuals with TC ≥200 mg/dL based on the TC threshold;[21] any individuals with TG ≥150 mg/dL were classified in the CVD risk group.[22]

Risk factors

The risk factors for CVD risk were selected based on their extant association with CVD risk in the previous literature. The risk factors considered in our study are blood pressure, age, BMI, diet, physical activity, smoking, and alcoholism.

Individuals with a systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg,[23] or those who have been prescribed anti-hypertensive medication, were classified as having hypertension and grouped into the high blood pressure category.

Participants were classified as ≥55 years or lower. Based on BMI indices, individuals with a BMI of 25.0-29.9 kg/m^2 were categorized as overweight, and with a BMI greater than 30 kg/m^2 were classified as obese, collectively termed the high BMI group. Those with a BMI of 18.5-24.9 kg/m^2 were classified as having a normal BMI. The information on food intake was recorded as an atherogenic and nonatherogenic diet. The information on physical activity was collected and classified as physically active or inactive. For smoking, a person who smoked daily was classified as a smoker and another class as a nonsmoker. A person who consumed 8 or more drinks in a week was classified as an alcoholic.

Statistical analyses

Statistical analyses were performed in SPSS 27.0 (Armonk, NY: IBM Corp.) with significance maintained at $P < 0.05$ for all the analyses. Receiver operating characteristic (ROC) curve analyses were performed for the derivation of thresholds of all nontraditional lipid parameters based on previously established CVD risk thresholds for TC and TG. The thresholds were selected on sensitivity and specificity values that provided high values of Youden's index. The derived discrimination threshold was further utilized to classify the participants into the CVD risk group and nonrisk group. Pearson's Chi-squared test was then performed to investigate the possible associations of considered risk factors (diet, physical activity, blood pressure, BMI, and age) with the CVD risk group as classified by newly derived thresholds. A comparison between the effectiveness of new thresholds was performed based on the number of associations.

Results

Population characteristics and prevalence of cardiovascular disease risk based on total cholesterol and triglyceride thresholds

The general characteristics of the 369 samples included are presented in Table 1. Overall, the prevalence of CVD risk based on TC and TG thresholds was 25.1% and 32.3%, respectively. The group comparison between the non-CVD risk groups and risk group based on TC threshold identified the significant difference among age, height, BMI, lipid profile tests (TC, TG, HDL-C, and LDL-C), and risk factors (low physical activity, high blood pressure, high BMI, and age over 55). Similarly, the TG thresholds identified the significant difference in age, BMI, lipid profile tests (TC, TG, HDL-C, and LDL-C), and risk factors (high blood pressure, high BMI, as well as age over 55) between the non-CVD risk group and the CVD risk group. The pattern of differences among the variables between CVD risk and nonrisk groups with TC and TG-established thresholds is shown in Table 1.

Table 1: Population characteristics and comparison between noncardiovascular disease and cardiovascular disease risk groups

Variables	All participants (*n*=369)	TC			TG		
		Non-CVD risk (*n*=274)	CVD risk (*n*=95)	Percentage difference	Non-CVD risk (*n*=247)	CVD risk (*n*=122)	Percentage difference
Age (years)	46±13	43±13	56±11**	+23.21	44±14	50±12**	+12
Height (m)	1.57±0.06	1.58±0.06	1.55±0.06**	−1.90	1.57±0.07	1.57±0.05	-
Weight (kg)	65±13	64±5	65±6	-	64±5	66±6*	+3.03
BMI (kg/m^2)	26.31±2.54	25.94±2.48	27.39±2.43**	+5.29	26.08±2.59	26.78±2.37*	+2.61
HDL-C (mg/dL)	49±11	48±10	53±12**	+9.43	50±11	47±11*	−6
LDL-C (mg/dL)	105±30	93±20	140±27**	+33.57	101±30	114±29**	+11.40
TC (mg/dL)	174±39	156±24	226±24**	+30.77	167±36	189±40**	+11.64
TG (mg/dL)	145±76	132±65	184±90**	+28.26	106±27	224±81**	+52.67
Non-HDL-C (mg/dL)	125.42±36.91	108.98±24.30	172.84±23.61**	+36.94	117.20±34.10	152.07±36.89**	+22.93
CRI-II	2.22±0.75	2.05±0.67	2.71±0.77**	+24.35	2.08±0.73	2.49±0.73**	+16.46
CRI-I	3.65±0.96	3.40±0.82	4.37±0.97**	+22.19	3.43±0.88	4.10±0.97**	+16.34
LCI	63,707.51±58,190.18	45,319.67±38,419.88	116,741.90±71,701.78**	+61.179	39,086.33±23,305.41	113,555.29±73,832.13**	+65.58
AI	2.65±0.96	2.40±0.82	3.38±0.97**	+28.99	2.43±0.88	3.10±0.96**	+21.61
AIP	0.43±0.23	0.41±0.23	0.50±0.23*	+18	0.32±0.16	0.66±0.18**	+52.51
Atherogenic diet	324 (87.80)	244 (66.12)	80 (21.68)	-	218 (59.07)	106 (28.72)	-
Low physical activity	96 (26.01)	50 (13.55)	36 (9.76)**	-	57 (15.44)	29 (7.85)	-
High blood pressure	70 (18.97)	19 (5.14)	51 (13.82)**	-	36 (9.75)	34 (9.21)*	-
High BMI	282 (76.42)	198 (53.65)	84 (22.76)*	-	179 (48.50)	103 (27.91)*	-
Aged above 55	127 (34.42)	69 (18.69)	58 (15.71)**	-	76 (20.59)	51 (13.82)*	-

* and ** indicate significant difference between two groups at P<0.01–0.05 and P<0.001, respectively. A categorical variable is represented as a *n* (%). The quantitative variable is represented as mean±SD with comparison performed with an independent sample *t*-test. BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TC: Total cholesterol, TG: Triglyceride, CRI-II: Castelli's Risk Index II, CRI-I: Castelli's Risk Index I, LCI: Lipoprotein combined index, AI: Atherogenic index, AIP: Atherogenic index of plasma, SD: Standard deviation, CVD: Cardiovascular disease

Thresholds for nontraditional lipid parameters

Based on the threshold of TC for the CVD risk (≥200 mg/dL), the derived threshold for non-HDL-C was 139 mg/dL, CRI-II was 2.29, CRI-I was 3.687, LCI was 58,066, AI was 2.687, and AIP was 0.487. The corresponding discriminatory ability of the models and the sensitivity and specificity values for these derived thresholds are shown in Table 2.

Similarly, based on the threshold of TG for the CVD risk (≥150 mg/dL), the derived threshold for non-HDL-C was 127 mg/dL, CRI-II was 2.3, CRI-I was 3.959, LCI was 58,251, AI was 2.959, and AIP was 0.467. The corresponding discriminatory ability of the models and the sensitivity and specificity values for these derived thresholds are shown in Table 2.

Comparison of prevalence of cardiovascular disease risks with different derived thresholds of nontraditional lipid parameters

Based on the TC threshold (≥200 mg/dL), the prevalence of the CVD risk following the thresholds derived from ROC analyses for each nontraditional lipid parameter is given in Figure 1. The number of participants under the CVD risk according to threshold values of non-HDL-C, CRI-II, CRI-I, LCI, AI, and AIP was 123, 155, 163, 130, 163, and 128, respectively, among 369 total study participants. In the current population, 57 participants were at risk of CVD according to threshold values of

Table 2: Thresholds of nontraditional lipid parameters based on established thresholds of total cholesterol and triglycerides

Nontraditional parameters	Traditional parameters used to derive thresholds	AUC	*P*	95% CI	Threshold value	Sensitivity	Specificity
Non-HDL-C (mg/dL)	TC	0.986	<0.001	0.978–0.994	139	0.989	0.894
	TG	0.695	<0.001	0.637–0.753	127	0.680	0.648
CRI-II	TC	0.757	<0.001	0.702–0.811	2.29	0.726	0.693
	TG	0.663	<0.001	0.606–0.720	2.3	0.607	0.684
CRI-I	TC	0.799	<0.001	0.749–0.849	3.687	0.821	0.690
	TG	0.711	<0.001	0.656–0.767	3.959	0.615	0.753
LCI	TC	0.871	<0.001	0.833–0.910	58066	0.811	0.807
	TG	0.885	<0.001	0.850–0.919	58251	0.754	0.850
AI	TC	0.799	<0.001	0.7490.849	2.687	0.821	0.690
	TG	0.711	<0.001	0.656–0.767	2.959	0.615	0.753
AIP	TC	0.620	<0.001	0.554–0.687	0.487	0.526	0.715
	TG	0.947	<0.001	0.923–0.970	0.467	0.902	0.874

CRI-II: Castelli's Risk Index II, CRI-I: Castelli's Risk Index I, LCI: Lipoprotein combined index, AI: Atherogenic index, AIP: Atherogenic index of plasma, AUC: Area under curve, TC: Total cholesterol, TG: Triglyceride, CI: Confidence interval, HDL-C: High-density lipoprotein cholesterol

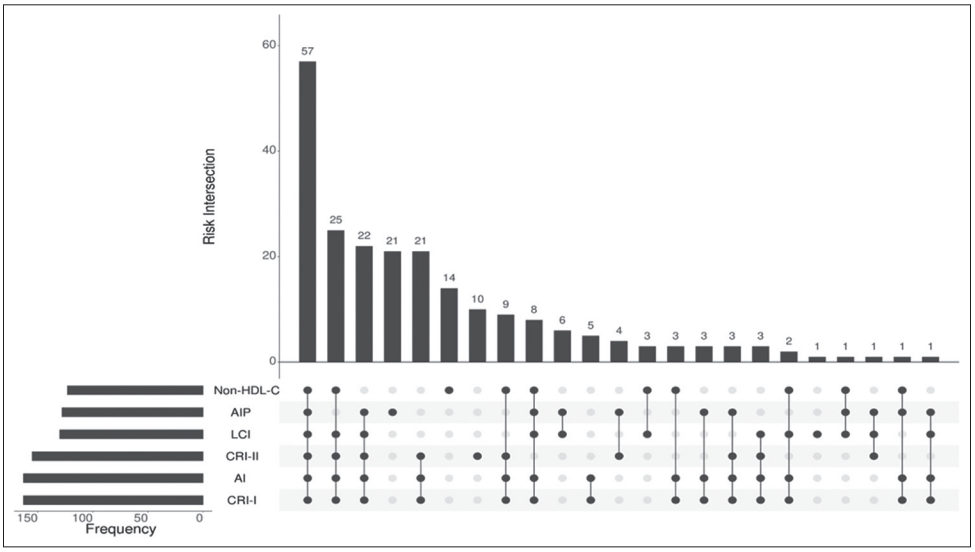

Figure 1: Matrix layout using total cholesterol-derived threshold values for all intersections of nontraditional parameters. The intersection of the several sets is represented by the merging of black circles on the matrix. HDL-C: High-density lipoprotein cholesterol, AIP: Atherogenic index of plasma, LCI: Lipoprotein combined index, CRI-II: Castelli's Risk Index II, AI: Atherogenic index

all nontraditional lipid parameters derived. The number of participants under CVD risk according to various nontraditional lipid parameters and their intersection is given in Figure 1.

The prevalence of CVD risk following the thresholds derived from ROC analyses using established thresholds of TG (≥150 mg/dL) for each nontraditional lipid parameter is shown in Figure 2. Briefly, the number of participants under CVD risk according to threshold values of non-HDL-C, CRI-II, CRI-I, LCI, AI, and AIP was 170, 152, 137, 129, 137, and 142, respectively. Seventy-two participants were at risk of CVD according to threshold values of all nontraditional lipid parameters. The number of participants under CVD risk according to various nontraditional lipid parameters and their interaction is given in Figure 2.

Associations of risk factors with established nontraditional lipid parameter thresholds for cardiovascular disease risk

There was a significant difference in the frequency distribution of individuals between CVD risk and nonrisk groups identified for different considered risk factors in the study for the different thresholds derived for nontraditional lipid parameters using established thresholds of TC and TG. Out of the possible 5 risk factors, the risk factors showing the frequency difference between the CVD risk and nonrisk groups based on the derived thresholds of TC and TG are in the descending order for non-HDL-C, CRI-II, CRI-I, LCI, and AI (physical activity, blood pressure, BMI, and age). AIP thresholds derived from TC and TG showed variable results, where TC-derived thresholds were able to associate with 2 risk factors (blood pressure and BMI) and TG was able to associate with 1 risk factor (blood pressure). The frequency of individuals based on the derived thresholds using risk factor distribution for the nontraditional lipid parameters is shown in Table 3.

Discussion

The identification of different biomarkers and their derived thresholds for identifying the clinical condition and associated risk is a continuous process. Although the use of nontraditional lipid parameters is novel in lipid-related research, its effectiveness over the existing traditional lipid parameters is emerging. In the current study, our research group identified the thresholds for nontraditional lipid parameters based on previously established TC and TG thresholds and tested the ability of derived thresholds differentiating potential to identify the CVD risk. In brief, we identified the thresholds of non-HDL, CRI-II, CRI-I, LCI, AI, and AIP and observed that non-HDL, CRI-II, CRI-I, LCI, and AI thresholds have been successful in identifying 4 risk factors (physical activity, blood pressure, BMI, and age) and AIP has been successful in identifying 2 risk factors at most (blood pressure and BMI), out of the considered five risk factors in the study. Based on our findings, we conclude that nontraditional lipid parameters are effective in identifying the CVD risk, and we suggest that their use should be tested and expanded in multiple other clinical conditions such as screening and diagnosis indices.

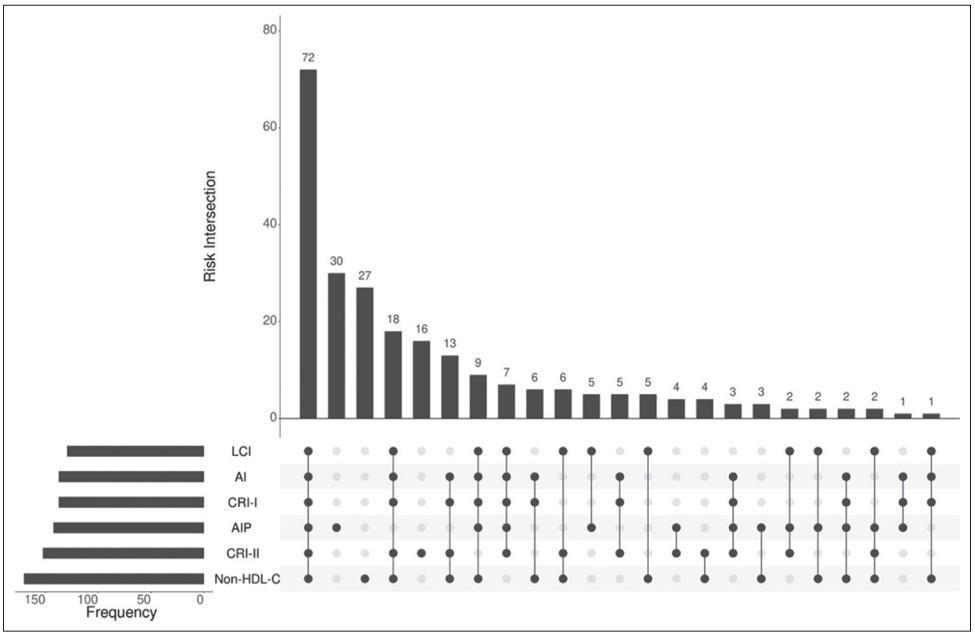

Figure 2: Matrix layout using triglycerides-derived threshold values for all intersections of non-traditional parameters. The intersection of the several sets is represented by the merging of black circles on the matrix. LCI: Lipoprotein combined index, AI: Atherogenic index, CRI-I: Castelli's Risk Index I, AIP: Atherogenic index of plasma, CRI-II: Castelli's Risk Index II, HDL-C: High-density lipoprotein cholesterol

Table 3: Distribution of risk factors for nontraditional lipid parameters based on established threshold values

Traditional parameters used to derive thresholds	Nontraditional parameters	Category	No CVD risk, frequency (%)	CVD risk, frequency (%)	χ^2	*P*
TC	Non-HDL-C	Atherogenic diet	88.20	87.00	0.11	0.736
		Low physical activity	17.90	34.10	12.1	<0.001
		High blood pressure	3.30	50.40	118.61	<0.001
		High BMI	71.10	87.00	11.43	0.001
		Aged above 55	25.20	52.80	27.75	<0.001
	CRI-II	Atherogenic diet	86.00	90.30	1.58	0.208
		Low physical activity	18.70	29.70	6.06	0.014
		High blood pressure	6.10	36.80	55.11	<0.001
		High BMI	70.10	85.20	11.32	0.001
		Aged above 55	29.00	41.90	6.69	0.01
	CRI-I	Atherogenic diet	86.90	89.00	0.36	0.547
		Low physical activity	17.50	30.70	8.86	0.03
		High blood pressure	4.40	37.40	64.68	<0.001
		High BMI	68.40	86.50	16.46	<0.001
		Aged above 55	28.20	42.30	8.10	0.004
	LCI	Atherogenic diet	88.30	86.90	0.14	0.703
		Low physical activity	19.20	30.80	6.25	0.012
		High blood pressure	5.90	43.10	75.88	<0.001
		High BMI	70.30	87.70	14.14	<0.001
		Aged above 55	25	52	28.46	<0.001
	AI	Atherogenic diet	86.90	89.00	0.36	0.547
		Low physical activity	17.50	30.70	8.86	0.003
		High blood pressure	4.40	37.40	64.68	<0.001
		High BMI	68.40	86.50	16.46	<0.001
		Aged above 55	28.20	42.30	8.10	0.004
	AIP	Atherogenic diet	89.20	85.20	1.28	0.257
		Low physical activity	22.00	25.80	0.67	0.412
		High blood pressure	14.50	27.30	8.94	0.003
		High BMI	72.60	83.60	5.59	0.018
		Aged above 55	32.00	39.10	1.87	0.171
TG	Non-HDL-C	Atherogenic diet	88.40	87.10	0.16	0.686
		Low physical activity	19.10	28.20	4.28	0.038
		High blood pressure	1.00	40.00	90.69	<0.001
		High BMI	68.30	85.90	15.65	<0.001
		Aged above 55	23.10	47.60	24.44	<0.001
	CRI-II	Atherogenic diet	86.20	90.10	1.30	0.253
		Low physical activity	19.40	28.90	4.60	0.032
		High blood pressure	6.50	36.80	53.70	<0.001
		High BMI	70.00	85.50	11.88	0.001
		Aged above 55	29.50	41.40	5.65	0.017
	CRI-I	Atherogenic diet	88	88.30	0.05	0.816
		Low physical activity	18.50	31.40	7.96	0.005
		High blood pressure	6.50	40.10	63.56	<0.001
		High BMI	61.80	87.60	15.08	<0.001
		Aged above 55	29.70	42.30	6.05	0.014
	LCI	Atherogenic diet	88.30	86.80	0.17	0.672
		Low physical activity	19.60	30.20	5.32	0.021
		High blood pressure	6.30	42.60	72.26	<0.001
		High BMI	70.40	87.60	13.74	<0.001
		Aged above 55	24.60	52.70	29.41	<0.001

Contd...

Table 3: Contd...

Traditional parameters used to derive thresholds	Nontraditional parameters	Category	No CVD risk, frequency (%)	CVD risk, frequency (%)	χ^2	*P*
	AI	Atherogenic diet	88	88.30	0.05	0.816
		Low physical activity	18.50	31.40	7.96	0.005
		High blood pressure	6.50	40.10	63.56	<0.001
		High BMI	69.80	87.60	15.08	<0.001
		Aged above 55	29.70	42.30	6.05	0.014
	AIP	Atherogenic diet	88.50	86.60	0.30	0.582
		Low physical activity	21.10	26.80	1.54	0.214
		High blood pressure	14.50	26	7.54	0.006
		High BMI	73.10	81.70	3.55	0.059
		Aged above 55	32.60	37.30	0.86	0.353

CRI-II: Castelli's Risk Index II, CRI-I: Castelli's Risk Index I, LCI: Lipoprotein combined index, AI: Atherogenic index, AIP: Atherogenic index of plasma, BMI: Body mass index, TC: Total cholesterol, TG: Triglyceride, CVD: Cardiovascular disease, HDL-C: High-density lipoprotein cholesterol

The categorization of CVD in a list of the global burden of diseases and its contribution to high mortality[1] has alarmed the health system of low- and middle-income countries to advanced economies and emphasizes the need for its appropriate management. This has resulted in many studies focusing on minimizing CVD-related risks from a different perspective including the identification and screening tool for its control and treatment. As the identification of a new screening tool for the clinical condition from the existing screening tool[24] is a continuous process, the current study also considered the validated thresholds of TC and TG for the derivation of nontraditional lipid parameter thresholds for identifying CVD risk. The use of TC and TG thresholds in the current study is grounded in previous literatures which have demonstrated their potential to identify CVD risk, intercranial atherosclerotic stenosis,[25] insulin resistance,[26] nonalcoholic fatty liver disease,[27] and metabolic syndrome.[28] In the present study, ROC analyses were performed to identify the thresholds of new parameters, the techniques that have been widely adopted when there are two (binary) possible outcome measures.[24,29] Nontraditional lipid parameters have been used to understand the different phenomena in several populations such as Chinese Han population,[30] Northeast Indian population,[31] and Japanese population.[32] The ability to identify CVD risk may be advantageous in lipid-related research and can add to the growing number of literature.

To the knowledge of current authors, this is the first study that has attempted to identify multiple nontraditional lipid parameter thresholds to identify the risk factors for CVD risk. In the present included population, we identified thresholds of non-HDL-C as 139 mg/dL and 127 mg/dL, CRI-II as 2.29 and 2.3, CRI-I as 3.687 and 3.959, LCI as 58,066 and 58,251, AI as 2.687 and 2.959, and AIP as 0.487 and 0.467 as per the TC and TG established thresholds, respectively. A comparison between our derived thresholds and previous literature has shown a high concordance between the values. For example, the derived threshold of non-HDL-C in the current population is close to 130 mg/dL observed in the Thai population for the prediction of acute myocardial infarction.[33] Similarly, the derived threshold of CRI-II in the current study is close to another study conducted in the Japanese population that showed a value of 2.4 for dyslipidemia and 10 years of incidence of diabetes.[34] Comparing our findings with the study conducted in Turkey in coronary artery disease patients, the values for AI and AIP are close, while their threshold for LCI is quite higher (78,830) than ours (58,251). Indeed, previous literature has shown that the values of CRI-II, CRI-I, AI, and AIP are greater in the CVD risk compared to nonrisk groups.[30]

We observed the prevalence of dyslipidemia as 25.1% and 32.3% with TC and TG thresholds, respectively. This variable difference in the prevalence of dyslipidemia based on TC and TG is like other studies conducted in different populations. For example, a study conducted on 727 Jordanian females observed the prevalence of dyslipidemia as 6.7% and 16.6% as per the TC and TG thresholds, respectively.[35] A study conducted in the Chinese population has shown the prevalence of dyslipidemia as 14.7% and 44.2% based on thresholds of TC and TG, respectively.[36] In the current population, we observed similar kinds of associations with the possible risk factors for CVD risk as described by the previous literature.[37-41] The comparison was done for the derived thresholds for nontraditional lipid parameters. Given the higher number of overlaps of the same individuals (n = 72) in the CVD risk group as categorized by derived thresholds, the similar findings observed for most of the thresholds are not surprising. The derivation of thresholds for nontraditional lipid parameters based on established thresholds of TC and TG in our study also

adds to the literature that physical inactivity, high blood pressure, high BMI, and older age are the risk factors for CVD. We did not observe a significant difference in frequency distribution for diet and smoking/alcoholism between CVD risk and nonrisk group. Although previous studies have reported alcoholism/smoking as a risk factor for CVD,[42] we need to acknowledge that the study was conducted in the Nepalese female population, where females are mostly reluctant to state their smoking/alcoholism habit despite they are following those habits.[43] This may result in bias in data collection and thus may interfere with the results. However, the observation of no difference in dietary habits may be explained by the small number of participants reporting a nonatherogenic diet. Overall, our observation using the nontraditional lipid parameters indices showed that all the indices are effective in identifying the already established CVD risk factors to a larger extent.

Comparing the derived thresholds and their ability to discriminate the risk factors for CVD in current data, the present authors suggest that nontraditional lipid parameter thresholds are also effective in studying CVD risk. While few studies have utilized the nontraditional lipid parameters,[30,44] the derivation of specific thresholds to explore the clinical condition of CVD in the current study is very scarce. To extend the validity of the currently derived thresholds, we suggest that further research in different clinical conditions and populations is warranted. Our study benefits from being cross-sectional, having a good sample size, using acceptable analytical procedures, and being generalizable to other demographic study contexts. However, this study is not untouched by the limitations. First, we collected the data on risk factors using a self-designed questionnaire. There is a high chance of bias in the data collection when using the questionnaire.[45] There could be also a chance of data collection biasness due to the cultural practices in the Nepalese context. For instance, Nepalese females are less open to questions about smoking and drinking, as those practices among females are considered to be taboo in Nepal.[43] A single center is taken in this study; therefore, the inclusion of many centers may provide more generalizable results.

Conclusion

The use of nontraditional lipid parameters is emerging and its potential for adoption in clinical practice can be justified by its effectiveness in discriminating against several conditions such as CVD. Our study identified thresholds of multiple nontraditional lipid parameters for the CVD risk and observed the good discriminatory ability for association with CVD-related risk factors as described by the previous studies. Based on our findings, we suggest that the use of nontraditional lipid parameters in lipid-related research for studying CVD-related events in the future can be expanded. Furthermore, we also emphasize the necessity of nontraditional lipid parameters in other clinical conditions that are particularly related to lipid parameters.

Financial support and sponsorship

There was no external funding for this study.

Conflicts of interest

There are no conflicts of interest.

References

1. McAloon CJ, Boylan LM, Hamborg T, Stallard N, Osman F, Lim PB, *et al.* The changing face of cardiovascular disease 2000-2012: An analysis of the world health organisation global health estimates data. Int J Cardiol 2016;224:256-64.
2. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Med 2013;11:117.
3. Mohammadnezhad M, Mangum T, May W, Jeffrey Lucas J, Ailson S. Common modifiable and non-modifiable risk factors of cardiovascular disease (CVD) among pacific countries. World J Cardiovasc Surg 2016;6:153-70.
4. Lin HQ, Wu JY, Chen ML, Chen FQ, Liao YJ, Wu YT, *et al.* Prevalence of dyslipidemia and prediction of 10-year CVD risk among older adults living in Southeast coastal regions in China: A cross-sectional study. Clin Interv Aging 2019;14:1119-29.
5. Hedayatnia M, Asadi Z, Zare Feyzabadi R, Yaghooti Khorasani M, Ghazizadeh H, Ghaffarian Zirak R, *et al.* Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids Health Dis 2020;19:42.
6. Meyer FA, von Känel R, Saner H, Schmid JP, Stauber S. Positive affect moderates the effect of negative affect on cardiovascular disease-related hospitalizations and all-cause mortality after cardiac rehabilitation. Eur J Prev Cardiol 2015;22:1247-53.
7. Orozco Beltran D, Gil Guillen VF, Redon J, Martin Moreno JM, Pallares Carratala V, Navarro Perez J, *et al.* Lipid profile, cardiovascular disease and mortality in a mediterranean high-risk population: The escarval-risk study. PLoS One 2017;12:e0186196.
8. Dong J, Yang S, Zhuang Q, Sun J, Wei P, Zhao X, *et al*. The associations of lipid profiles with cardiovascular diseases and death in a 10-year prospective cohort study. Frontiers in Cardiovascular Med 2021;8:745539.
9. Dekker LH, Snijder MB, Beukers MH, de Vries JH, Brants HA, de Boer EJ, *et al*. A prospective cohort study of dietary patterns of non-Western migrants in the Netherlands in relation to risk factors for cardiovascular diseases: HELIUS-dietary patterns. BMC Public Health 2011;11:441.
10. Etzel RA. Foreword: A review on the genetic, environmental, and lifestyle aspects of the early-life origins of cardiovascular disease. Curr Probl Pediatr Adolesc Health Care 2014;44:53.
11. Jeong SM, Choi S, Kim K, Kim SM, Lee G, Park SY, *et al.* Effect of change in total cholesterol levels on cardiovascular disease among young adults. J Am Heart Assoc 2018;7:e008819.
12. Aberra T, Peterson ED, Pagidipati NJ, Mulder H, Wojdyla DM, Philip S, *et al.* The association between triglycerides and incident cardiovascular disease: What is "optimal"? J Clin Lipidol 2020;14:438-47.e3.
13. Tóth PP, Potter D, Ming EE. Prevalence of lipid abnormalities in the United States: The National Health and Nutrition Examination Survey 2003-2006. J Clin Lipidol 2012;6:325-30.

14. Abid H, Abid Z, Abid S. Atherogenic indices in clinical practice and biomedical research: A short review. Baghdad J Biochem Appl Biol Sci 2021;2:60-70.
15. Brunner FJ, Waldeyer C, Ojeda F, Salomaa V, Kee F, Sans S, *et al*.; Multinational Cardiovascular Risk Consortium. Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the multinational cardiovascular risk consortium. Lancet 2019;394:2173-83.
16. Yıldız A, Seçen Ö, Yıldız C, Çiçekçi M. Relationship between breast arterial calcification and lipid profile, plasma atherogenic index, Castelli's risk index and atherogenic coefficient in premenopausal women. IJC Metab Endocr 2016;11:19-22.
17. Çelik E, Çora AR, Karadem KB. The Effect of untraditional lipid parameters in the development of coronary artery disease: Atherogenic index of plasma, atherogenic coefficient and lipoprotein combined index. J Saudi Heart Assoc 2021;33:244-50.
18. Wu TT, Gao Y, Zheng YY, Ma YT, Xie X. Atherogenic index of plasma (AIP): a novel predictive indicator for the coronary artery disease in postmenopausal women. Lipids Health Dis 2018;17:197.
19. Nantsupawat N, Booncharoen A, Wisetborisut A, Jiraporncharoen W, Pinyopornpanish K, Chutarattanakul L, *et al.* Appropriate total cholesterol cut-offs for detection of abnormal LDL cholesterol and non-HDL cholesterol among low cardiovascular risk population. Lipids Health Dis 2019;18:28.
20. Kim EH, Lee JB, Kim SH, Jo MW, Hwang JY, Bae SJ, *et al.* Serum triglyceride levels and cardiovascular disease events in Koreans. Cardiology 2015;131:228-35.
21. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. Circulation 2002;106:3143-421.
22. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, *et al.* Evaluation and treatment of hypertriglyceridemia: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2969-89.
23. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, *et al.* Effect of systolic and diastolic blood pressure on cardiovascular outcomes. N Engl J Med 2019;381:243-51.
24. Khanal P, He L, Stebbings GK, Onambele Pearson GL, Degens H, Williams AG, *et al.* Static one-leg standing balance test as a screening tool for low muscle mass in healthy elderly women. Aging Clin Exp Res 2021;33:1831-9.
25. Yang WS, Li R, Shen YQ, Wang XC, Liu QJ, Wang HY, *et al.* Importance of lipid ratios for predicting intracranial atherosclerotic stenosis. Lipids Health Dis 2020;19:160.
26. Zhang L, Chen S, Deng A, Liu X, Liang Y, Shao X, *et al.* Association between lipid ratios and insulin resistance in a Chinese population. PLoS One 2015;10:e0116110.
27. Lu S, Kuang M, Yue J, Hu C, Sheng G, Zou Y. Utility of traditional and non-traditional lipid indicators in the diagnosis of nonalcoholic fatty liver disease in a Japanese population. Lipids Health Dis 2022;21:95.
28. Paredes S, Fonseca L, Ribeiro L, Ramos H, Oliveira JC, Palma I. Novel and traditional lipid profiles in metabolic syndrome reveal a high atherogenicity. Sci Rep 2019;9:11792.
29. Khanal P, He L, Degens H, Stebbings GK, Onambele Pearson GL, Williams AG, *et al.* Dietary protein requirement threshold and micronutrients profile in healthy older women based on relative Skeletal muscle mass. Nutrients 2021;13:3076.
30. Zhu L, Lu Z, Zhu L, Ouyang X, Yang Y, He W, *et al.* Lipoprotein ratios are better than conventional lipid parameters in predicting coronary heart disease in Chinese Han people. Kardiol Pol 2015;73:931-8.
31. Bora K, Pathak MS, Borah P, Hussain MI, Das D. Association of the apolipoprotein A-I gene polymorphisms with cardiovascular disease risk factors and atherogenic indices in patients from Assam, Northeast India. Balkan J Med Genet 2017;20:59-70.
32. Nagayama D, Watanabe Y, Saiki A, Shirai K, Tatsuno I. Lipid parameters are independently associated with Cardio-ankle vascular index (CAVI) in healthy Japanese subjects. J Atheroscler Thromb 2018;25:621-33.
33. Wongcharoen W, Sutthiwutthichai S, Gunaparn S, Phrommintikul A. Is non-HDL-cholesterol a better predictor of long-term outcome in patients after acute myocardial infarction compared to LDL-cholesterol? A retrospective study. BMC Cardiovasc Disord 2017;17:10.
34. Kobayashi G, Okada H, Hamaguchi M, Kurogi K, Murata H, Ito M, *et al.* Dyslipidemia and 10-year diabetes incidence in Japanese people: Population-based panasonic cohort study 9. Front Endocrinol (Lausanne) 2022;13:957728.
35. Khader YS, Batieha A, El-Khateeb M, Al-Omari M, Ajlouni K. Prevalence of dyslipidemia and its associated factors among Jordanian adults. J Clin Lipidol 2010;4:53-8.
36. Qi L, Ding X, Tang W, Li Q, Mao D, Wang Y. Prevalence and risk factors associated with dyslipidemia in Chongqing, China. Int J Environ Res Public Health 2015;12:13455-65.
37. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol 2019;74:2529-32.
38. Nangia R, Singh H, Kaur K. Prevalence of cardiovascular disease (CVD) risk factors. Med J Armed Forces India 2016;72:315-9.
39. Prasad DS, Kabir Z, Dash AK, Das BC. Cardiovascular risk factors in developing countries: A review of clinico-epidemiological evidence. CVD Prev Control 2010;5:115-23.
40. Batacan RB Jr., Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of light intensity activity on CVD risk factors: A systematic review of intervention studies. Biomed Res Int 2015;2015:596367.
41. Michas G, Karvelas G, Trikas A. Cardiovascular disease in Greece; the latest evidence on risk factors. Hellenic J Cardiol 2019;60:271-5.
42. Li XX, Zhao Y, Huang LX, Xu HX, Liu XY, Yang JJ, *et al.* Effects of smoking and alcohol consumption on lipid profile in male adults in Northwest rural China. Public Health 2018;157:7-13.
43. Aryal UR, Petzold M, Bondjers G, Krettek A. Correlates of smoking susceptibility among adolescents in a peri-urban area of Nepal: A population-based cross-sectional study in the Jhaukhel-Duwakot health demographic surveillance site. Glob Health Action 2014;7:24488.
44. Sheng G, Kuang M, Yang R, Zhong Y, Zhang S, Zou Y. Evaluation of the value of conventional and unconventional lipid parameters for predicting the risk of diabetes in a non-diabetic population. J Transl Med 2022;20:266.
45. Choi BC, Pak AW. A catalog of biases in questionnaires. Prev Chronic Dis 2005;2:A13.