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Association of the CRP–TyG Index with Early Cardiometabolic Risk in Apparently Healthy Young Adults: An Observational Cross-Sectional Study

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Abstract: Background: Early cardiometabolic dysfunction is characterized by alterations in glucose–lipid metabolism, insulin resistance, and chronic low-grade inflammation, often preceding overt metabolic syndrome or cardiovascular disease. Insulin resistance and inflammation are interconnected processes that contribute to endothelial dysfunction, oxidative stress, and progressive vascular injury. The C-reactive protein–triglyceride–glucose (CRP–TyG) index integrates biochemical surrogates of metabolic dysregulation and systemic inflammation. This study evaluated its association with early cardiometabolic abnormalities in apparently healthy young adults and compared its discriminatory performance with the triglyceride–glucose (TyG) index and high-sensitivity C-reactive protein (hs-CRP).Methods: This analytical cross-sectional study included 220 apparently healthy adults aged 18–35 years. The CRP–TyG index was calculated using fasting triglycerides, plasma glucose, and hs-CRP concentrations. Early cardiometabolic abnormalities included central adiposity, elevated blood pressure, and reduced HDL cholesterol, with risk-factor clustering defined as the presence of at least two abnormalities. Multivariable regression and receiver operating characteristic analyses were performed.Results: Risk-factor clustering was observed in 9.5% of participants and increased across CRP–TyG tertiles from 1.4% to 15.1% (p=0.007). Each 1-SD increase in CRP–TyG was associated with greater cardiometabolic risk-factor burden (common OR 1.91, 95% CI 1.36–2.68) and clustering (OR 1.96, 95% CI 1.08–3.53). Associations were particularly evident for central adiposity and reduced HDL cholesterol. Discriminatory performance was moderate for CRP–TyG (AUC 0.705), compared with TyG (AUC 0.728) and hs-CRP (AUC 0.637). CRP–TyG did not significantly outperform TyG (p=0.555).Conclusion: The CRP–TyG index was associated with early cardiometabolic risk-factor burden in apparently healthy young adults, consistent with the biological interrelationship between metabolic dysfunction and low-grade inflammation. However, it did not provide superior discrimination over TyG alone. Further prospective studies are warranted to establish its incremental clinical utility.

Keywords: CRP–TyG index; Insulin resistance; Low-grade inflammation; Cardiometabolic risk; Endothelial dysfunction; Young adults.

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Introduction

Cardiometabolic disorders are a series of metabolic, inflammatory and vascular changes that can occur over a long period of time, even before the clinical diagnosis of metabolic syndrome, type 2 diabetes mellitus or cardiovascular disease. Early cardiometabolic risk involves subtle changes in glucose–lipid metabolism, insulin sensitivity, chronic low-grade systemic inflammation, and early vascular dysfunction. These abnormalities can occur even in people who do not have any apparent signs of health problems before the

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normal diagnostic limits are met. It is therefore crucial to identify these subclinical changes in early adulthood to understand the initial biochemical processes involved in cardiometabolic disease. This is especially important in the South Asian population, such as Indians, who are more prone to cardiometabolic abnormalities at lower BMI levels. This leads to early metabolic dysfunction in these populations, due to greater accumulation of visceral and ectopic fat, changes in adipokine secretion, and an increased propensity for insulin resistance [1]. Rajendran et al. showed that the triglyceride–glucose (TyG) index was significantly associated with metabolic syndrome in Indian young adults, emphasizing the importance of readily available biochemical markers for detecting metabolic abnormalities at an early age [2].

A key pathophysiological link between adiposity, dyslipidaemia, impaired glucose regulation and subsequent cardiovascular complications is insulin resistance. Insulin regulates lipid metabolism, inhibits hepatic glucose production and facilitates peripheral glucose uptake under physiological conditions. These processes are disrupted by impaired insulin action, leading to changes in glucose utilization, increased hepatic lipid synthesis and abnormalities in circulating triglycerides. These metabolic changes can occur before the onset of hyperglycaemia. The TyG index, derived from fasting triglyceride and glucose levels, has been identified as a feasible surrogate marker of insulin resistance. Guerrero-Romero et al. showed its association with insulin sensitivity, assessed with the hyperinsulinaemic–euglycaemic clamp, and thus established its value as a readily available tool to measure metabolic dysfunction [3].

Insulin resistance not only has metabolic effects, but it also affects vascular homeostasis by affecting intracellular signaling. Insulin normally activates the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway, which stimulates endothelial nitric oxide synthase (eNOS) and increases nitric oxide production and endothelial vasodilatation. Insulin-resistant states can cause a decrease in nitric oxide bioavailability while the mitogen-activated protein kinase (MAPK) pathway may be relatively intact, promoting endothelin-1 production and vascular dysfunction. This imbalance is responsible for endothelial activation, oxidative stress and proatherogenic changes. In addition, disturbances in platelet function and inflammatory signaling in the vascular system are associated with these changes and may lead to a prothrombotic state, which could help explain the connection between insulin resistance and cardiovascular damage [4].

Another key aspect of early cardiometabolic dysfunction is chronic low-grade inflammation. Immune-cell recruitment and production of proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are stimulated by expansion and metabolic stress of adipose tissue. On the other hand, insulin resistance and changes in lipid metabolism could exacerbate the production of inflammatory mediators and cell stress. This two-way interaction is known as metabolic inflammation or metaflammation, which can lead to a vicious cycle of inflammation and metabolic dysfunction, and may contribute to the progression of vascular dysfunction and cardiometabolic disease [5].

High-sensitivity C-reactive protein (hs-CRP) is an acute-phase protein, mainly synthesized by hepatocytes in response to inflammatory cytokines, especially IL-6, and is a readily available biochemical marker of low-grade systemic inflammation. High levels of hs-CRP have been linked to adiposity, metabolic abnormalities, and cardiovascular risk. It has been shown that CRP is linked to adiposity in youth, while its association with insulin resistance became weaker after adjustment for adiposity, suggesting that there is a relationship between inflammatory and metabolic abnormalities [6]. Moreover, Ridker et al. showed that CRP was linked to metabolic syndrome and future cardiovascular events in initially healthy women, which further emphasizes the importance of inflammatory markers in the assessment of cardiometabolic risk [7].

The metabolic and inflammatory markers can be combined because of their biological connection with insulin resistance and systemic inflammation. The C-reactive protein–triglyceride–glucose (CRP–TyG) index is a combination of the TyG index, which represents glucose–lipid dysregulation and insulin resistance, and a log-transformed CRP component, which represents systemic inflammatory activity. This composite measure may thus reflect a more complete picture of interrelated metabolic and inflammatory abnormalities than either measure alone. In a prospective cohort of middle-aged and older adults, Shan et al. showed that high levels of CRP–TyG were associated with an increased risk of new-onset diabetes, which could be relevant to metabolic risk assessment [8]. The value of adding inflammatory information to TyG in apparently healthy young adults, however, is unclear.

Despite growing interest in integrated metabolic–inflammatory indices, there is limited evidence of the association of CRP–TyG with early cardiometabolic abnormalities in apparently healthy young Indian adults. Central adiposity,

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elevated blood pressure and reduced HDL cholesterol may be early signs of cardiometabolic dysfunction in this population before clinically apparent disease. This study was thus designed to assess the association of the CRP–TyG index with early cardiometabolic risk-factor burden and clustering among healthy adults (18–35 years). In addition, its discriminatory performance was compared to that of TyG and hs-CRP alone to determine if it offers any further information regarding the identification of early cardiometabolic abnormalities.

Materials and Methods

Study design and setting

The study was an analytical cross-sectional observational study carried out at Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha, India from January 2025 to December 2025. Apparently healthy adults aged 18–35 years were recruited to examine the association of the C-reactive protein–triglyceride–glucose (CRP–TyG) index with early cardiometabolic abnormalities. The prespecified target sample size was 220 participants.

Participant selection

Apparently healthy adults aged 18–35 years who were willing to undergo fasting biochemical assessment were considered for inclusion. Participants who had previously been diagnosed with diabetes mellitus, cardiovascular disease or hypertension requiring pharmacological treatment were excluded. Other exclusions included known chronic kidney disease, significant liver disease, acute infection, recent major surgery or trauma, chronic inflammatory or autoimmune disease, active malignancy, current systemic corticosteroid therapy or other medications that significantly affect inflammatory or metabolic markers, and pregnancy or lactation.

Assessment of clinical and lifestyle factors

Demographic and lifestyle information was obtained using a structured assessment. The variables recorded were age, sex, current smoking, regular alcohol consumption, physical activity, sedentary time, dietary pattern and family history of diabetes, hypertension and premature cardiovascular disease.

Standard methods were used to measure body weight and body height, and body mass index (BMI) was computed as weight (kg) divided by height (m^2). A non-stretchable measuring tape was used to measure waist circumference at the abdominal level. Blood pressure was measured in the seated position after a suitable period of rest and repeated measurements were averaged for analysis. Resting heart rate was also recorded.

Laboratory investigations

Venous blood samples were collected after an overnight fast of 10-12 hours into separate vacutainers as required for biochemical, haematological and inflammatory investigations. The analysis of serum/plasma was mostly conducted on the same day of blood collection. The routine biochemical investigations involving fasting plasma glucose, serum triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) were done using commercially available kits adapted to Beckman coulter AU480 analyzer. Fasting plasma glucose was measured using hexokinase method, total cholesterol by CHOD-POD method, triglyceride by GPO-PAP method, and HDL by standard enzymatic method. LDL-cholesterol concentration calculation was based on friedewald equation. Glycated haemoglobin (HbA1c) was measured by cation-exchange HPLC method in Bio-Rad D-10 analyzer. Serum high-sensitivity C-reactive protein (hs-CRP) was estimated through immunoturbidimetry assay. For all the tests, validated quality control measures were taken into account. Samples that were stored before testing were run within 2 days meanwhile the storage temperature was maintained at 2-8ºC.

Because hs-CRP may increase substantially during acute inflammatory states, an initial hs-CRP concentration >10 mg/L prompted repeat assessment before the value was used for cardiometabolic evaluation.

Calculation of TyG and CRP–TyG indices

The triglyceride–glucose index was calculated from fasting triglyceride and glucose concentrations as:

TyG index = ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)] / 2

The combined CRP–TyG index was calculated as:

CRP–TyG index = 0.412 × ln [hs-CRP (mg/L)] + TyG index

For descriptive analyses, participants were divided into tertiles of the CRP–TyG index, producing groups of approximately equal size.

Definition of early cardiometaboli cabnormalities

Three early cardiometabolic abnormalities were prespecified:

1. **Central adiposity:** waist circumference ≥ 90 cm in men or ≥ 80 cm in women.
2. **Elevated blood pressure:** systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg.
3. **Reduced HDL cholesterol:** HDL-C < 40 mg/dL in men or < 50 mg/dL in women.

A cardiometabolic risk-factor count ranging from 0 to 3 was calculated by summing these

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abnormalities. **Risk-factor clustering** was defined as the presence of at least two of the three abnormalities.

Study outcomes

The principal exposure was the CRP–TyG index evaluated as both a continuous standardized variable and by tertiles. The principal outcomes were the number of cardiometabolic abnormalities and clustering of at least two risk factors.

Secondary analyses evaluated the association of CRP–TyG with central adiposity, elevated blood pressure, and reduced HDL-C individually. The discriminatory performance of CRP–TyG for identifying risk-factor clustering was compared with that of the TyG index and hs-CRP alone.

Statistical analysis

The relationship between CRP–TyG and risk-factor clustering and with central adiposity, elevated blood pressure and reduced HDL-C was evaluated using binary logistic regression. The models were adjusted for age, sex, current smoking and low physical activity and reported as odds ratios (OR) with 95% confidence intervals (CI).

A sensitivity analysis was also performed to adjust the clustering model for BMI. BMI was not added to the primary model as adiposity was part of the definition of the cardiometabolic outcome. Another sensitivity analysis was performed excluding the participant who had an initial hs-CRP >10 mg/L.

ROC analysis

The ability of the CRP–TyG index, TyG index, and hs-CRP to identify participants with clustering of at least two cardiometabolic abnormalities was assessed using receiver operating characteristic (ROC) analysis. The area under the ROC curve (AUC) with 95% confidence intervals was used to summarize discrimination.

The DeLong method was used to compare AUCs of correlated ROC curves. Sensitivity, specificity, positive predictive value and negative predictive value were calculated using exploratory operating thresholds. Internal validation of discrimination estimates was conducted with 400 bootstrap resamples, and optimism-corrected AUCs were calculated.

All tests were two-sided and $p<0.05$ was considered statistically significant.

RESULTS

Participant characteristics

A total of 220 participants were analyzed. Mean age was 27.0 ± 4.5 years, and 126 (57.3%) were male. The cohort had a mean BMI of 23.9 ± 2.5 kg/m² and mean waist circumference of 79.8 ± 7.2 cm. Demographic, anthropometric, and lifestyle characteristics are summarized in Table 1.

Table 1. Demographic, anthropometric, and lifestyle characteristics of participants

Characteristic	Overall (N=220)
Age, years	27.0 ± 4.5
Male sex	126 (57.3%)
Age group 18–24 years	70 (31.8%)
Age group 25–29 years	81 (36.8%)
Age group 30–35 years	69 (31.4%)
BMI, kg/m²	23.9 ± 2.5
Waist circumference, cm	79.8 ± 7.2
Average systolic BP, mmHg	118.2 ± 7.6
Average diastolic BP, mmHg	76.8 ± 5.4
Resting heart rate, bpm	72.2 ± 6.9
Current smoking	35 (15.9%)
Regular alcohol consumption	19 (8.6%)
Low physical activity	63 (28.6%)
Sedentary time, h/day	6.9 ± 2.0
High-refined-carbohydrate/ultra-processed dietary pattern	77 (35.5%)
Family history of diabetes	71 (32.3%)
Family history of hypertension	74 (33.6%)
Family history of premature CVD	22 (10.0%)

Values are mean ± SD or n (%), as appropriate. Denominators reflect available observations for variables with limited nonessential missingness.

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Biochemical profile and cardiometabolic risk

Median hs-CRP was 1.31 [0.76–1.98] mg/L; mean TyG and CRP–TyG indices were 4.563 ± 0.173 and 4.663 ± 0.369, respectively. Central adiposity was identified in 45 (20.5%), elevated blood pressure in 25 (11.4%), and reduced HDL cholesterol in 36 (16.4%) participants. Risk-factor clustering (≥2 abnormalities) was present in 21 (9.5%) participants (Table 2).

Table 2. Biochemical parameters and distribution of cardiometabolic risk factors

Parameter	Overall (N=220)
Fasting plasma glucose, mg/dL	88.0 ± 5.7
Fasting triglycerides, mg/dL	106.0 [83.7–130.2]
Total cholesterol, mg/dL	174.8 ± 18.5
HDL cholesterol, mg/dL	50.9 ± 7.1
LDL cholesterol, mg/dL	101.9 ± 15.9
hs-CRP, mg/L	1.31 [0.76–1.98]
HbA1c, %	5.2 ± 0.2
TyG index	4.563 ± 0.173
CRP–TyG index	4.663 ± 0.369
Initial hs-CRP >10 mg/L requiring repeat testing	1 (0.5%)
Central adiposity	45 (20.5%)
Elevated blood pressure	25 (11.4%)
Reduced HDL cholesterol	36 (16.4%)
Cardiometabolic risk-factor count = 0	139 (63.2%)
Cardiometabolic risk-factor count = 1	60 (27.3%)
Cardiometabolic risk-factor count = 2	17 (7.7%)
Cardiometabolic risk-factor count = 3	4 (1.8%)
Risk-factor clustering (≥2 abnormalities)	21 (9.5%)

Central adiposity: waist circumference ≥ 90 cm in men or ≥ 80 cm in women. Elevated BP: systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg. Reduced HDL-C: < 40 mg/dL in men or <50 mg/dL in women. Clustering denotes ≥ 2 of these three abnormalities.

Association of CRP–TyG with cardiometabolic abnormalities

Increasing CRP–TyG tertiles were accompanied by higher BMI, waist circumference, blood pressure, fasting glucose, triglycerides, and TyG, together with lower HDL cholesterol. Risk-factor clustering increased from 1 (1.4%) in T1 to 9 (12.3%) in T2 and 11 (15.1%) in T3 (trend z=2.69, p=0.007). The full tertile profile is shown in Table 3.

Table 3. Clinical and biochemical characteristics across CRP–TyG index tertiles

Characteristic	T1 (n=74)	T2 (n=73)	T3 (n=73)	Trend statistic	p for trend
Age, years	26.0 ± 4.2	26.8 ± 4.5	28.2 ± 4.6	Spearman ρ=0.201	0.003
BMI, kg/m²	22.1 ± 2.3	24.5 ± 2.2	25.1 ± 2.0	Spearman ρ=0.477	<0.001
Waist circumference, cm	74.6 ± 7.1	80.9 ± 5.8	83.8 ± 5.4	Spearman ρ=0.522	<0.001
Average systolic BP, mmHg	115.7 ± 6.6	118.2 ± 7.9	120.8 ± 7.5	Spearman ρ=0.269	<0.001
Average diastolic BP, mmHg	75.0 ± 5.3	76.5 ± 5.0	78.8 ± 5.2	Spearman ρ=0.285	<0.001
Fasting plasma glucose, mg/dL	85.3 ± 5.8	88.8 ± 4.9	90.0 ± 5.4	Spearman ρ=0.298	<0.001
Fasting triglycerides, mg/dL	83.2 [72.0–103.2]	105.7 [88.4–130.3]	128.0 [113.8–151.5]	Spearman ρ=0.593	<0.001
HDL cholesterol, mg/dL	53.3 ± 5.5	50.9 ± 6.7	48.5 ± 8.0	Spearman ρ=-0.276	<0.001
hs-CRP, mg/L	0.67 [0.49–0.88]	1.34 [1.10–1.67]	2.38 [1.81–3.11]	Spearman ρ=0.847	<0.001
TyG index	4.429 ± 0.143	4.574 ± 0.134	4.690 ± 0.133	Spearman ρ=0.618	<0.001
Cardiometabolic risk-factor count	0.2 ± 0.4	0.6 ± 0.8	0.6 ± 0.8	Spearman ρ=0.280	<0.001
Male sex	37 (50.0%)	37 (50.7%)	52 (71.2%)	z=2.58	0.010
Central adiposity	5 (6.8%)	19 (26.0%)	21 (28.8%)	z=3.22	0.001
Elevated blood pressure	2 (2.7%)	12 (16.4%)	11 (15.1%)	z=2.30	0.021
Reduced HDL cholesterol	6 (8.1%)	15 (20.5%)	15 (20.5%)	z=2.02	0.044
Risk-factor clustering (≥2)	1 (1.4%)	9 (12.3%)	11 (15.1%)	z=2.69	0.007

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Continuous-variable trends were assessed using Spearman rank correlation with tertile order; binary-variable trends used logistic regression with tertile coded ordinally. Values are mean ± SD, median [IQR], or n (%), as appropriate.

Multivariable analysis

CRP–TyG correlated positively with the 0–3 cardiometabolic risk-factor count (Spearman ρ=0.315, p<0.001). After adjustment for age, sex, current smoking, and low physical activity, each 1-SD increase in CRP–TyG was associated with higher ordinal risk-factor burden (common OR 1.91, 95% CI 1.36–2.68; z=3.74, p<0.001) and with risk-factor clustering (OR 1.96, 95% CI 1.08–3.53; z=2.23, p=0.026). Additional BMI adjustment attenuated the clustering association (Table 4; Figure 1).

Table 4. Correlations and adjusted associations between CRP–TyG index and cardiometabolic risk indicators

Analysis/outcome	Effect estimate	95% CI	Test statistic	p-value
Spearman association: CRP–TyG vs risk-factor count	ρ=0.315	—	Spearman ρ=0.315	<0.001
Adjusted ordinal model: risk-factor count 0–3, per 1-SD CRP–TyG	common OR=1.91	1.36 to 2.68	z=3.74	<0.001
Proportional-odds approximation (CRP–TyG slope heterogeneity)	—	—	Q=0.55	0.759
Adjusted logistic model: clustering ≥ 2, per 1-SD CRP–TyG	OR=1.96	1.08 to 3.53	z=2.23	0.026
Adjusted logistic model: Central adiposity, per 1-SD CRP–TyG	OR=1.93	1.26 to 2.96	z=3.03	0.002
Adjusted logistic model: Elevated blood pressure, per 1-SD CRP–TyG	OR=1.36	0.85 to 2.18	z=1.26	0.206
Adjusted logistic model: Reduced HDL cholesterol, per 1-SD CRP–TyG	OR=1.64	1.05 to 2.57	z=2.18	0.029
Sensitivity: clustering ≥ 2 additionally adjusted for BMI	OR=1.60	0.84 to 3.07	z=1.42	0.154
Sensitivity: clustering ≥ 2 excluding initial hs-CRP >10 mg/L (n=219)	OR=1.96	1.08 to 3.53	z=2.23	0.026

Adjusted models included age, sex, current smoking, and low physical activity. Effect estimates are per 1-SD increase in CRP–TyG unless otherwise specified. The BMI model was a sensitivity analysis because adiposity contributes to the outcome definition.

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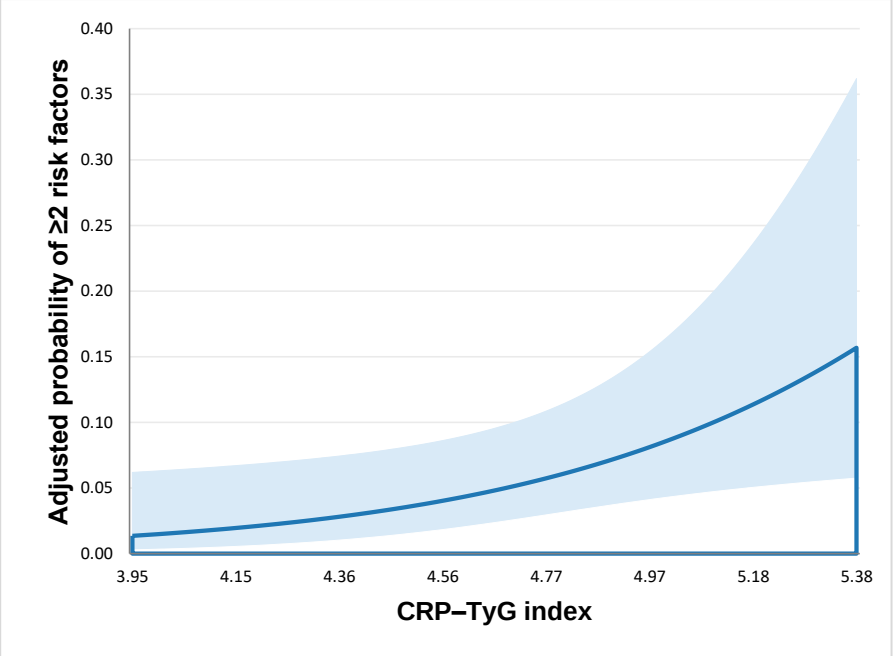


Figure 1. Adjusted probability of cardiometabolic risk-factor clustering across the CRP–TyG index.

Comparative diagnostic discrimination

For identifying clustering of at least two abnormalities, AUCs were 0.705 (95% CI 0.611–0.799) for CRP–TyG, 0.728 (95% CI 0.626–0.829) for TyG, and 0.637 (95% CI 0.538–0.736) for hs-CRP. CRP–TyG did not outperform TyG (DeLong z=−0.59, p=0.555), whereas its AUC exceeded that of hs-CRP (z=2.37, p=0.018). Exploratory operating characteristics and optimism-corrected AUCs are provided in Table 5 and the comparative ROC curves in Figure2.

Table 5. Diagnostic performance for identifying cardiometabolic risk-factor clustering

Marker/ comparison	AUC (95% CI)	Optimism-corrected AUC	Exploratory cut-off	Sensitivity	Specificity	PPV	NPV	Test statistic	p-value
CRP–TyG	0.705 (0.611–0.799)	0.710	4.615	95.2%	44.7%	15.4%	98.9%	—	—
TyG	0.728 (0.626–0.829)	0.730	4.687	61.9%	77.9%	22.8%	95.1%	—	—
hs-CRP	0.637 (0.538–0.736)	0.638	0.840	100.0%	29.6%	13.0%	100.0%	—	—
CRP–TyG vs TyG	ΔAUC=-0.022	—	—	—	—	—	—	z=-0.59	0.555
CRP–TyG vs hs-CRP	ΔAUC=0.068	—	—	—	—	—	—	z=2.37	0.018

Clustering was defined as ≥2 abnormalities. Cut-offs and predictive values are exploratory. AUC confidence intervals and correlated AUC comparisons used DeLong methods; internal validation used 400 bootstrap resamples. AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

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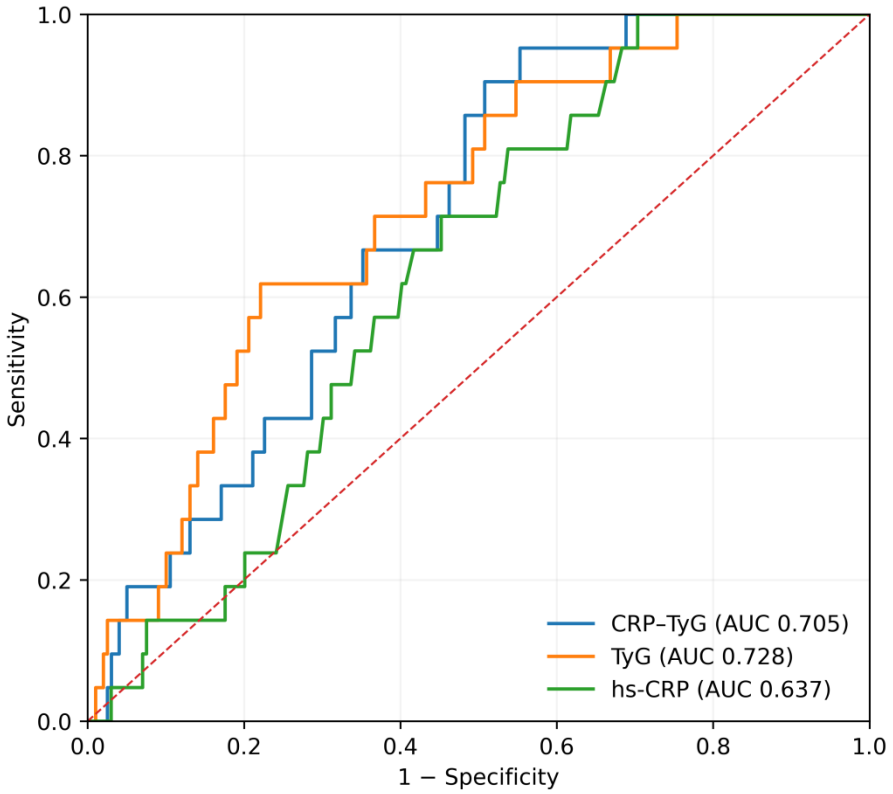


Figure 2. Comparative ROC curves for CRP–TyG, TyG, and hs-CRP for identifying clustering of ≥2 cardiometabolic abnormalities.

Discussion

The results of this study of apparently healthy adults (18–35 years) showed that higher CRP–TyG values were correlated with increased burden of early cardiometabolic abnormalities despite the lack of established cardiometabolic disease. Risk-factor clustering was found to be 1.4% in the lowest CRP–TyG tertile and 15.1% in the highest CRP–TyG tertile, while waist circumference, blood pressure, fasting glucose, triglycerides and BMI were found to increase progressively, and HDL cholesterol decreased. Each 1-SD increment in CRP–TyG was linked to almost double the odds of clustered risk factors and an increased ordinal cardiometabolic-risk burden after controlling for age, sex, smoking and low physical activity. The association was highest for central adiposity and low HDL cholesterol, while the adjusted association with high blood pressure was not significant.

The present results are in line with ongoing longitudinal data indicating that simultaneous metabolic and inflammatory dysfunction could be used to identify patients with an unfavorable cardiometabolic phenotype. In the study by Wang et al., 8,487 adults ≥ 45 years of age were followed for 9 years, with 1,030 cases of cardiometabolic multimorbidity recorded. Both TyG and CRP–TyG were associated with subsequent multimorbidity, with unadjusted hazard ratios of 1.89 and 1.83, respectively, and the associations remained after multivariable adjustment. They found that CRP–TyG was better than TyG for predicting established multimorbidity in their ROC analyses [9]. However, in our very young low-risk population, there was no difference between CRP–TyG and TyG. This disparity could suggest that the extra inflammatory data that comes with CRP becomes more informative as the burden of cardiometabolic disease and age grow.

Similar evidence was reported by Lin et al. using several population cohorts. Of the 10,863 CHARLS participants who did not have cardiometabolic multimorbidity at baseline, 1,698 developed cardiometabolic multimorbidity over the course of about nine years of follow-up. The adjusted risk increased by 71% for every one-unit increase in baseline CRP–TyG, and the inclusion of the index with conventional risk factors led to an increase in the AUC for four-year prediction from 0.753 to 0.778. For external ELSA validation, participants in the highest CRP–TyG quartile were more than twice as likely to develop multimorbidity as those in the lowest quartile [10]. While these outcomes are significantly more advanced than the early abnormalities assessed in our study, the dose-response pattern is consistent with our finding of an increase in cardiometabolic-

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risk count across the tertiles of CRP–TyG.

One aspect that is worth highlighting is the link with blood pressure. Yang et al. tracked 6,435 adults without hypertension for about nine years and noted 1,705 new cases of hypertension. The risk of hypertension was 18% higher per one-unit increase in CRP–TyG, and the hazard ratio was 1.41 in those in the highest quartile compared with the lowest quartile of CRP–TyG among participants with prediabetes. No significant associations were seen in the normal-glucose-regulation subgroup [11], however. This could be one of the reasons why our adjusted association with elevated blood pressure was less than that of adiposity and HDL cholesterol. We had a younger population, with normal mean fasting glucose, and only 25 of our participants had elevated blood pressure according to the definition, which reduced accumulated exposure and statistical power.

Evidence based on TyG alone, however, indicates that metabolic disturbance can occur before the onset of hypertension. Lee et al. examined 15,721 adults who had no known cardiometabolic disease and found that both systolic and diastolic blood pressure increased with each TyG quartile. The highest quartile of TyG was associated with adjusted odds ratios of 1.52, 2.22 and 4.24 for elevated blood pressure, prehypertension and hypertension, respectively, compared with the lowest quartile, with the associations particularly evident in those < 50 years of age [12]. Although the dichotomous adjusted blood-pressure outcome was not significant, these data are consistent with the upward trend in blood pressure across the tertiles of CRP–TyG in our cohort.

The relationship between adiposity seems to be a significant modifier of these relationships. In a prospective study of 4,866 adults who were not hypertensive at baseline in China, Yang et al. found 1,256 new cases of hypertension over 6 years. The highest TyG quartile had an adjusted odds ratio of 1.49 compared with the lowest quartile. Indices combining TyG and anthropometric measures performed better, with TyG-waist-to-height ratio having an AUC of 0.628 compared with 0.583 for TyG alone, and TyG-waist circumference performing similarly well [13]. This observation is important for our sensitivity analysis, where adding an adjustment for BMI reduced the association between CRP–TyG and clustered risk factors from an OR of 1.96 to 1.60 and made it statistically insignificant. The CRP–TyG signal in young adults may therefore partly reflect the close interrelationship between adiposity, insulin resistance and inflammation.

The good performance of TyG in our ROC analysis is also consistent with pooled evidence. Nabipoorashrafi et al. reviewed 13 observational studies that included 49,325 adults, and the average TyG was 0.83 units higher in those with metabolic syndrome. The pooled sensitivity and specificity for the diagnosis of metabolic syndrome were 80% and 81%, respectively, and summary ROC AUC was 0.87 [14]. It is not surprising that the lower AUC of 0.728 was seen in our study as we had a deliberately early phenotype (clustering of central adiposity, elevated blood pressure and reduced HDL cholesterol) and only 9.5% of participants fulfilled the clustering definition. The result that TyG was slightly higher than CRP–TyG indicates that triglyceride–glucose metabolism may already reflect a large proportion of the detectable signal of risk at this early stage.

Although the inflammatory component has less discrimination alone, it is biologically relevant. The NHANES sample included 5,728 participants, with 34% having metabolic syndrome and 32% having elevated hs-CRP. The odds of elevated hs-CRP were approximately 2.4, 3.3, 5.1, 10.7, and 11.1 times higher in people with 1, 2, 3, 4, and 5 metabolic-syndrome components, respectively, compared with those without any of the components, indicating a strong dose-response relationship between inflammatory burden and the number of metabolic abnormalities [15]. This is consistent with our finding that CRP–TyG correlated with the 0–3 risk-factor count, albeit with only modest discrimination for clustering (AUC 0.637) when using hs-CRP alone.

The relationship between inflammation and adiposity is especially pertinent in an Indian population. Mahajan et al. analyzed 9,517 urban Indians, of whom 4,066 had metabolic syndrome. Among the components of metabolic syndrome, waist circumference had the highest correlation with hs-CRP (r=0.28) and hs-CRP >3 mg/L increased the odds of metabolic syndrome by 65%. They also showed a progressive increase in the risk of metabolic syndrome with increasing hs-CRP levels, along with increasing BMI and insulin resistance [16]. These results are similar to the significant gradient in waist circumference among the tertiles of CRP–TyG in our cohort, and suggest a possible explanation for the attenuation of the association between CRP–TyG and clustered risk factors after BMI adjustment.

Comparative ROC results should be taken with a grain of salt. For clustered cardiometabolic abnormalities, CRP–TyG was moderately discriminatory with an AUC of 0.705, and was significantly better than hs-CRP alone. Its AUC was not significantly different from TyG and was numerically lower, however. Therefore, the combined index showed a strong epidemiological

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relationship with the risk-factor burden but did not add to the discrimination of the simpler TyG index in this population. It is important to note that this association/discrimination distinction does not imply that a marker cannot be independently associated with risk, but that such association does not necessarily provide meaningful classification of individuals.

It is important to note that the low prevalence of clustered abnormalities is associated with the very high sensitivity and negative predictive value of the exploratory CRP–TyG threshold. The specificity and positive predictive value were low, suggesting that the index might be better at excluding significant early risk than confirming it. These operating characteristics must be validated externally before proposing any clinical threshold.

There are a number of strengths of the present study that should be noted. The study specifically targeted young adults aged 18–35 years who were not diagnosed with any major cardiometabolic disease, in whom conventional clinical risk scores may not offer much distinction. Metabolic and inflammatory markers were evaluated as a whole and the risk-factor burden was evaluated ordinally and dichotomously, and the discrimination of CRP–TyG was directly compared with its individual components. This analysis was further strengthened by the use of multivariable adjustment, BMI sensitivity analysis, exclusion of an initially very high hs-CRP value and bootstrap correction of AUC estimates.

There are also some limitations to the study. It is cross-sectional in design, so the temporality and causality of the findings cannot be determined, and the sample from a single centre may not be generalizable. Only 21 participants had clustering of at least two abnormalities, resulting in relatively wide confidence intervals for logistic estimates and ROC measures. There is potential for residual confounding due to dietary quality, sleep, psychosocial stress, visceral adiposity and unmeasured inflammatory conditions. CRP is not a static value and one measurement cannot be used as a marker for chronic inflammatory exposure. Lastly, associations with metabolic phenotypes are in part due to the mathematical structure of the indices, as both TyG and CRP–TyG are mathematically composed of triglycerides and glucose.

Overall, the results indicate that CRP–TyG reflects an early adverse metabolic-inflammatory phenotype in apparently healthy young adults, especially one involving central adiposity and reduced HDL cholesterol. Its association with a rise in cardiometabolic-risk burden warrants further prospective study, but because there is no evidence of greater discrimination than TyG, its incremental clinical utility in young low-risk populations is still unclear.

Conclusion

Early cardiometabolic risk-factor burden was positively associated with the CRP–TyG index in apparently healthy young adults, especially central adiposity and reduced HDL cholesterol. CRP–TyG was a better discriminator than hs-CRP alone but did not outperform the TyG index for the identification of clustered cardiometabolic abnormalities. These results suggest that CRP–TyG could be used as an early marker of metabolic-inflammatory risk, and that its incremental clinical utility over TyG needs to be further validated in prospective studies.

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