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# Use of plasma triglyceride/high-density lipoprotein cholesterol ratio to identify increased cardio-metabolic risk in young, healthy South Asians

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***Background & objectives*: Prevalence of insulin resistance and associated dyslipidaemia [high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentrations] are increased in South Asian individuals; likely contributing to their increased risk of type-2 diabetes and cardiovascular disease. The plasma concentration ratio of TG/HDL-C has been proposed as a simple way to identify apparently healthy individuals at high cardio-metabolic risk. This study was carried out to compare the cardio-metabolic risk profiles of high-risk South Asian individuals identified by an elevated TG/HDL-C ratio versus those with a diagnosis of the metabolic syndrome.**

***Methods*: Body mass index, waist circumference, blood pressure, and fasting plasma glucose, insulin, TG, and HDL-C concentrations were determined in apparently healthy men (n=498) and women (n=526). The cardio-metabolic risk profile of "high risk" individuals identified by TG/HDL-C ratios in men (≥ 3.5) and women (≥2.5) was compared to those identified by a diagnosis of the metabolic syndrome.**

***Results*: More concentrations of all cardio-metabolic risk factors were significantly higher in "high risk" groups, identified by either the TG/HDL-C ratio or a diagnosis of the metabolic syndrome. TG, HDL-C, and insulin concentrations were not significantly different in "high risk" groups identified by either criterion, whereas plasma glucose and blood pressure were higher in those with the metabolic syndrome.**

***Interpretation & conclusions*: Apparently healthy South Asian individuals at high cardio-metabolic risk can be identified using either the TG/HDL-C ratio or the metabolic syndrome criteria. The TG/HDL-C ratio may be used as a simple marker to identify such individuals.**

**Key words** Cardio-metabolic risk - high-density lipoprotein cholesterol - insulin resistance - metabolic syndrome - South Asian - triglycerides

Individuals of South Asian ancestry tend to be insulin resistant with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentrations[1-4], changes that contribute substantially to their increased risk of type 2 diabetes and cardiovascular disease[2,5-7]. It would, therefore, be of clinical benefit to have a relatively simple way to identify South Asian individuals at high cardio-metabolic risk, while they are still relatively young and apparently healthy. The diagnostic category of the metabolic syndrome (MetS) has been frequently used for this purpose[8-11], but two of its five diagnostic criteria would include subjects with known disease (type-2 diabetes and/or hypertension). In an effort to accomplish the same task, but limited to subjects without known disease, we have explored use of the plasma TG/HDL-C concentration ratio as an alternative mean of identifying patients at high risk to develop cardiovascular disease and type-2 diabetes[12,13]. This lipid ratio specifically was chosen based on prior evidence that this ratio is positively associated with insulin resistance;[14] by contrast, other lipid ratios do not perform as well at identifying insulin resistance[15].

The current study is aimed to extend these observations to individuals of South Asian ancestry, selected because they represent a racial group in which insulin resistance, accompanied by high TG and low HDL-C concentrations, occurs more commonly than in individuals of European ancestry[1,2]. Consequently, sex-specific TG/HDL-C ratio cut-points for men (3.5) and women (2.5), previously established in a population of primarily European ancestry[16], were applied to a relatively younger, apparently healthy group of South Asians. The objectives of this study were to *(i)* determine the cardio-metabolic risk profile of high-risk individuals identified by an elevated TG/HDL-C ratio compared to those diagnosed with the MetS; and *(ii)* determine the ability of the two sets of criteria to identify the presence of insulin resistance in a sample of South Asians residing in the United States (US).

## Material & Methods

*Study subjects*: The study sample consisted of 489 women and 526 men, part of a larger group of volunteers (n = 3314) evaluated for cardio-metabolic risk between May, 2006 and September, 2011 at the South Asian Heart Center; a not-for-profit organization providing cardiovascular disease risk assessment and counselling to South Asians in the San Francisco Bay Area. Participants were recruited by convenience through recruitment at community and workplace events, provider referral, and individual referral. The Institutional Review Board at El Camino Hospital provided a waiver of consent for all participants in the Bay Area South Asian study. All participants were in generally good health and older than 18 years. Individuals taking drugs to lower glucose or lipid concentrations were excluded (n=5). Volunteers whose fasting plasma glucose concentration was ≥ 7.0 mmol/l or self-reported history of diabetes were excluded from analysis (n=52), as were participants with TG > 500mg/dl (n=1), known history of hypertension (n=860), abnormal cholesterol (n=1156), and those missing values for any of the relevant clinical variables included in Table I (n=225).

*Anthropometric measurements*: Height and weight were determined with subjects in light clothing and without shoes, and body mass index (BMI) was calculated by dividing weight (kilograms) by height (meter squared). Waist circumference (WC) was measured using the National Health and Nutrition Examination Survey III protocol during normal minimal respiration by placing a measuring tape around the waist just above the uppermost lateral border of the iliac crest[17]. Participants were classified as being normal weight (BMI<25kg/m$^2$), overweight (BMI 25-30kg/m$^2$), or obese (BMI>30kg/m$^2$), and abdominally obese or abdominally normal on the basis of their WC (≥90cm men, ≥80cm women)[17]. Blood pressure was measured with an automatic blood pressure recorder, using an appropriately sized cuff,

**Table I.** Demographic and clinical characteristics of study subjects

| | Men (n = 526) | Women (n = 489) |
|---|---|---|
| Age (yr) | 39 ± 9 | 39 ± 9 |
| BMI (kg/m$^2$) | 25.3 ± 3.6 | 24.9 ± 4.1 |
| Waist circumference (cm) | 90 ± 10 | 81 ± 10$^{**}$ |
| Systolic blood pressure (mmHg) | 121 ± 13 | 111 ± 13$^{**}$ |
| Diastolic blood pressure (mmHg) | 76 ± 8 | 70 ± 9$^{**}$ |
| Triglycerides (mg/dl) | 129 ± 66 | 98 ± 50$^{**}$ |
| HDL-C (mg/dl) | 44 ± 10 | 53 ± 13$^{**}$ |
| TG/HDL-C ratio | 3.2 ± 2.1 | 2.1 ± 1.5$^{**}$ |
| Glucose (mg/dl) | 88 ± 10 | 84 ± 9$^{**}$ |
| Insulin (μU/ml) | 10 ± 6 | 9 ± 5$^{**}$ |
| HOMA-IR | 2.3 ± 1.5 | 1.9 ± 1.1$^{**}$ |

Values are mean ± SD
BMI, body mass index; HOMA-IR, homeostatic model assessment-insulin resistance
$^{**}P$<0.001 compared with men.

with subjects sitting in a chair with feet on the floor and arm supported at heart level.

*Laboratory measurements*: After an overnight fast, blood samples were drawn for measurement of plasma glucose, insulin, TG, and HDL-C concentrations at Berkeley Heart Labs[18]. Specifically, glucose concentrations were measured by enzymatic rate reaction; insulin by electrochemiluminescence immunoassay; TG by blanked enzymatic method; and HDL-C by a homogeneous direct assay. The plasma concentration ratio of TG to HDL-C was calculated, and participants were dichotomized to high TG/HDL-C ratio (> 3.5 men, < 2.5 women) versus normal. HOMA-IR (Homeostatic model assessment-insulin resistance), an estimate of insulin action, was calculated from fasting glucose and insulin concentrations using the formula: [(fasting insulin (μU/ml) x fasting glucose (mmol/l)/22.5][19]. The five criteria for identifying the metabolic syndrome were selected in accordance with the recent consensus guidelines: TG ≥ 150mg/dl, HDL-C < 40mg/dl (men) or < 50mg/dl (women), blood glucose ≥ 100mg/dl, waist circumference ≥ 90cm (men) or ≥ 80cm (women) and blood pressure ≥ 130 mmHg (systolic) or ≥ 85mmHg (diastolic)[8]. The metabolic syndrome was defined by the presence of at least three of five of these criteria.

*Statistical analysis*: Descriptive statistics were used to provide means, ranges, standard deviations, and quartiles. Participants were stratified by sex and quartile for insulin and HOMA-IR. Based on prior evidence showing that non-diabetic individuals in the upper 25$^{th}$ percentile for insulin have significantly greater likelihood of adverse clinical events, and that insulin is almost perfectly correlated with HOMA-IR, we selected this cut-off to define the insulin resistant state[20]. Student's t-test (2-tailed) at the 95% confidence level was used to assess for differences between continuous variables. Sensitivity was calculated as the number with elevated TG/HDL-C ratio or the MetS who were insulin resistant (>75$^{th}$ percentile insulin or >75$^{th}$ percentile HOMA-IR)[20] divided by the total number who were insulin resistant. Specificity was calculated as the total number with normal TG/HDL-C ratio or absence of MetS that were insulin sensitive (insulin ≤75$^{th}$ percentile or HOMA-IR ≤75$^{th}$ percentile) divided by the total number who were insulin sensitive. All statistical tests were performed using STATA version 11 (College Station, TX, USA).

## Results

Demographic and clinical characteristics are shown in Table I. The mean age was similar (39 ± 9 yr), and BMI was not significantly different, but the remainder of the demographic and metabolic characteristics differed substantially as a function of sex. Of particular relevance to this study was that the men had higher TG (129 ± 66 vs. 98 ± 50, $P < 0.001$) and lower HDL-C concentrations (44 ± 10 vs. 53 ± 13, $P<0.001$) and were more insulin resistant as seen in the higher values for both HOMA-IR (2.3 ± 1.5 vs. 1.9 ± 1.1, $P<0.001$) and fasting plasma insulin concentration (10 ± 6 vs. 9 ± 5, $P<0.001$). Men had greater abdominally adiposity by WC (90 ± 10 vs. 81 ± 10, $P<0.001$), but were not more overweight/obese by BMI.

Table II presents the cardio-metabolic risk profile of men and women divided into those with an elevated TG/HDL-C ratio (>3.5 men, >2.5 women) versus individuals whose ratios were below this cut point. The ages of the four groups were identical. With the exception of systolic blood pressure in men, the cardio-metabolic risk profile was substantially worse (in most cases with a $P$ value <0.001) in both men and women whose plasma TG/HDL-C concentration ratios were greater than 3.5 (men) or 2.5 (women).

Table III compares the cardio-metabolic risk profile of men and women with an elevated TG/HDL-C ratio to men and women with a diagnosis of MetS. These results showed that more men had a high TG/HDL-C ratio than the MetS (33 vs. 21%), and this was also the case in women (25 vs. 12%). A diagnosis of MetS identified individuals who were somewhat older with higher values for BMI, WC, blood pressure, and fasting glucose concentrations as compared to those with an elevated TG/HDL-C ratio. There was no significant difference in plasma concentrations of TG and HDL-C, or the TG/HDL-C ratio between the two diagnostic criteria, and this was true for both men and women. Finally, men with the MetS have somewhat higher values for fasting plasma insulin and HOMA-IR, whereas there was no difference in either of these variables in women.

Table IV compares the sensitivity and specificity with which the TG/HDL-C ratio and MetS identify individuals with >75$^{th}$percentile of fasting plasma insulin concentration and HOMA-IR. The results were very similar, whether plasma insulin concentration or HOMA-IR was used as the marker of insulin resistance. In men, the TG/HDL-C concentration identified the

**Table II.** Comparison of cardio-metabolicrisk factors with triglyceride/HDL-C ratio >3.5 (men) or >2.5 (women) compared to ≤3.5 (men) or ≤2.5 (women)

| | TG/HDL-C ratio | | | | | |
|---|---|---|---|---|---|---|
| | Men | | | Women | | |
| | ≤3.5 (n = 352) | >3.5 (n = 174) | *P* value | ≤2.5 (n = 369) | >2.5 (n = 120) | *P* value |
| Age (yr) | 39 ± 9 | 38 ± 7 | 0.3 | 39 ± 9 | 39 ± 8 | 0.7 |
| BMI (kg/m$^2$) | 24.8 ± 3.5 | 26.4 ± 3.7 | <0.001 | 24.1 ± 3.6 | 27.2 ± 4.5 | <0.001 |
| Waist circumference (cm) | 88 ± 10 | 93 ± 9 | <0.001 | 79 ± 9 | 87 ± 9 | <0.001 |
| Systolic blood pressure (mmHg) | 120 ± 13 | 122 ± 12 | 0.1 | 110 ± 12 | 115 ± 15 | <0.001 |
| Diastolic blood pressure (mmHg) | 75 ± 8 | 77 ± 8 | <0.05 | 69 ± 8 | 72 ± 9 | <0.001 |
| HDL-C (mg/dl) | 47 ± 9 | 37 ± 6 | <0.001 | 57 ± 13 | 42 ± 8 | <0.001 |
| Triglycerides (mg/dl) | 95 ± 30 | 197 ± 65 | <0.001 | 76 ± 24 | 164 ± 51 | <0.001 |
| TG/HDL-C ratio | 2.1 ± 0.8 | 5.5 ± 2.1 | <0.001 | 1.4 ± 0.5 | 4.1 ± 1.7 | <0.001 |
| Glucose (mg/dl) | 87 ± 10 | 89 ± 10 | <0.05 | 83 ± 9 | 85 ± 9 | <0.05 |
| Insulin (µU/ml) | 9.1 ± 5.5 | 12.9 ± 6.8 | <0.001 | 7.9 ± 3.8 | 12.4 ± 6.1 | <0.001 |
| HOMA-IR | 2 ± 1.3 | 2.9 ± 1.6 | <0.001 | 1.6 ± 0.8 | 2.6 ± 1.4 | <0.001 |

Values are mean ± SD

**Table III.** Cardio-metabolic risk factors with triglyceride/HDL-C ratio >3.5 (men) or >2.5 (women) compared to presence of the metabolic syndrome

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | TG/HDL-C>3.5 (n = 174) | Metabolic syndrome (n = 111) | *P* value | TG/HDL-C>2.5 (n = 120) | Metabolic syndrome (n = 60) | *P* value |
| Age (yr) | 38 ± 7 | 40 ± 8 | <0.05 | 39 ± 8 | 41 ± 8 | 0.1 |
| BMI (kg/m$^2$) | 26.4 ± 3.7 | 28.3 ± 3.9 | <0.001 | 27.2 ± 4.5 | 28.6 ± 4.2 | <0.05 |
| Waist circumference (cm) | 93 ± 9 | 98 ± 9 | <0.001 | 87 ± 9 | 91 ± 7 | <0.05 |
| Systolic blood pressure (mmHg) | 122 ± 12 | 129 ± 13 | <0.001 | 115 ± 15 | 122 ± 19 | <0.05 |
| Diastolic blood pressure (mmHg) | 77 ± 8 | 80 ± 9 | <0.05 | 72 ± 9 | 76 ± 11 | <0.05 |
| HDL-C (mg/dl) | 37 ± 6 | 38 ± 7 | 0.2 | 42 ± 8 | 42 ± 8 | 1.0 |
| Triglycerides (mg/dl) | 197 ± 65 | 190 ± 78 | 0.4 | 164 ± 51 | 179 ± 62 | 0.09 |
| TG/HDL-C ratio | 5.5 ± 2.1 | 5.3 ± 2.6 | 0.5 | 4.1 ± 1.7 | 4.5 ± 2.1 | 0.2 |
| Glucose (mg/dl) | 89 ± 10 | 93 ± 11 | <0.05 | 85 ± 9 | 88 ± 10 | <0.05 |
| Insulin (mg/dl) | 12.9 ± 6.8 | 14.5 ± 7.5 | 0.06 | 12.4 ± 6.1 | 13.2 ± 6.4 | 0.4 |
| HOMA-IR | 2.9 ± 1.6 | 3.4 ± 1.8 | <0.05 | 2.6 ± 1.4 | 2.9 ± 1.5 | 0.2 |

Values are mean ± SD
Metabolic syndrome defined by the presence of ≥ 3 of the following:
Elevated triglycerides (≥150 mg/dl)
Low HDL-C (<40mg/dl in men, <50 mg/dl in women)
Elevated blood glucose (≥100 mg/dl)
Abdominal adiposity (waist circumference ≥ 90 cm in men, ≥80 cm in women)
Elevated blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg)

markers of insulin resistance with greater sensitivity, but less specificity than a diagnosis of the MetS. The same general trend was seen in women, but the increased sensitivity using the TG/HDL-C ratio was accentuated, and the greater degree in specificity using MetS was attenuated. The odds of insulin resistance in the presence of elevated TG/HDL-C ratio after controlling for age, sex, systolic blood pressure, diastolic blood pressure, WC, and BMI were 2.9 (2.1, 4.1) for insulin >75$^{th}$ percentile and 2.4 (1.7, 3.3) for HOMA-IR >75$^{th}$

**Table IV**. Per cent sensitivity (true positives/all positives) and specificity (true negatives/all negatives) of insulin >75th percentile and HOMA-IR >75th percentile for triglyceride/HDL-C ratio > 3.5 (men) or > 2.5 (women) and metabolic syndrome

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | TG/HDL-C ratio > 3.5 | | Metabolic syndrome | | TG/HDL-C ratio > 2.5 | | Metabolic syndrome | |
| | Sensitivity | Specificity | Sensitivity | Specificity | Sensitivity | Specificity | Sensitivity | Specificity |
| Insulin > 75th percentile | 51 (91/168) | 77 (275/358) | 42 (71/168) | 89 (318/358) | 51 (56/109) | 83 (316/380) | 31 (34/109) | 93 (354/380) |
| HOMA-IR > 75th percentile | 51 (99/193) | 77 (258/333) | 41 (79/193) | 90 (301/333) | 46 (56/123) | 83 (302/366) | 29 (36/123) | 93 (342/366) |

Metabolic syndrome defined by the presence of ≥ 3 of the following:
Elevated triglycerides (≥150mg/dl)
Low HDL-C (<40mg/dl in men, <50mg/dl in women)
Elevated blood glucose (≥100mg/dl)
Abdominal adiposity (waist circumference ≥ 90cm in men, ≥80 cm in women)
Elevated blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg)

percentile. The odds of insulin resistance in the presence of metabolic syndrome after controlling for age, sex, systolic blood pressure, diastolic blood pressure, WC, and BMI were 2.7 (1.7, 4.0) for insulin >75th percentile and 2.6 (1.7, 3.9) for HOMA-IR>75th percentile. When both TG/HDL-C ratio and MetS were added to the same model, only TG/HDL-C ratio remained significant [OR 2.5 (1.7, 3.6)] for insulin>75th percentile.

## Discussion

It has been previously shown in a population of primarily European ancestry that sex-specific ratios of the plasma concentration ratio of TG/HDL-C are able to identify individuals who are insulin resistant and at increased cardio-metabolic risk to a comparable degree as a diagnosis of the MetS[16]. The goal of this study was to see if applying these same cut points to a young, apparently healthy South Asian population would be similarly effective, and to compare the TG/HDL-C ratio to the diagnosis of the MetS to identify insulin resistant individuals.

The results showed that approximately 33 per cent of the men and 25 per cent of the women had an elevated TG/HDL-C ratio using the sex-specific cut points of 3.5 (men) and 2.5 (women). By this metric, the data demonstrated that the cardio-metabolic risk profile of these individuals was significantly adverse relative to men and women with a lower TG/HDL-C ratio. Use of the same criteria in a population primarily of European ancestry showed that the prevalence of an elevated TG/HDL-C ratio was similar between men (25%) and women (24%)[16].

Significantly fewer men (22%) and women (12%) met the diagnostic criteria for the MetS compared to those who had an elevated TG/HDL-C ratio. Men and women with the MetS were more overweight/obese and had higher blood pressure and glucose concentrations than those with elevated TG/HDL-C concentration. However, insulin, TG and HDL-C concentrations were not different in either group. After controlling for potential co-variates, the relationship between TG/HDL-C ratio and MetS with both measures of insulin resistance remained significant.

The sensitivity with which both the MetS and elevated TG/HDL-C ratio identified subjects classified as being insulin resistant was modest, ranging from about 30 per cent for MetS in women to 50 for elevated TG/HDL-C ratio. The specificity was greater, ranging from >75 to > 90 per cent, and these findings were also comparable to those reported in a study of individuals of European ancestry[16]. Compared to MetS, the TG/HDL-C ratio offered improved sensitivity with very little loss of specificity in this South Asian sample. These findings suggest that, within the parameters of commonly measured clinical risk factors, the TG/HDL-C ratio might offer slightly improved diagnostic properties compared to MetS for South Asians.

To summarize, application of sex-specific cut points developed in a population of European ancestry to identify individuals at higher vs. lower cardio-metabolic risk seems to perform equally well in South Asian men and women. Specifically, the cardio-metabolic risk profile was significantly worse in South

Asian men and women whose plasma TG/HDL-C concentrations were above the cut point. In addition, an elevated TG/HDL-C concentration identified more individuals as high risk than did a diagnosis of the MetS, with a cardio-metabolic risk profile that seemed comparable to that of individuals with the MetS. Also an elevated TG/HDL-C ratio and a diagnosis of the MetS identified insulin resistant individuals with reasonably similar sensitivity and specificity. In this context, it should be noted that fasting plasma insulin concentration and HOMA-IR in non-diabetic South Asians provide similar estimates of insulin resistance[21].

In conclusion, determination of the TG/HDL-C concentration in South Asians provided clinical information approximately as useful as that obtained with the more complicated use of the MetS diagnostic criteria. On the other hand, although our findings suggest that TG/HDL-C cut points derived from a European population identify South Asian men and women at increased cardio-metabolic risk, caution should be exercised in generalizing from these data. First, the South Asians enrolled in this study reside in a relatively affluent region of Northern California, and they may not be representative of the global South Asian population. In addition, the notion that the TG/HDL-C ratio is as clinically useful as the MetS should be tempered by the fact that a diagnosis of the MetS has been shown in large population-based studies to predict incident type-2 diabetes and cardiovascular disease[9-11], whereas there are relatively little data as to the prediction of incident disease from the TG/HDL-C ratio[22-24]. The use of the top 25$^{th}$ percentile of insulin and HOMA-IR is not a true gold-standard for assessment of insulin resistance, however, among the available estimates of insulin resistance, these measures have the highest correlations with the gold-standard euglycaemic clamp test[25]. We hope that the findings in this study will encourage investigators with databases of large South Asian populations, including clinical outcomes, to evaluate the ability of the plasma TG/HDL-C concentration ratio to identify apparently healthy individuals of South Asian ancestry who are at risk for developing type-2 diabetes and cardiovascular disease.

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