

# An Evaluation of Candidate Definitions of the Metabolic Syndrome in Adult Asian Indians

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**OBJECTIVES** — We aimed to evaluate eight candidate definitions of the metabolic syndrome (MS) against the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition as the reference for optimally defining MS in adult Asian Indians.

**RESEARCH DESIGN AND METHODS** — We used clinical and biochemical data from our previous cross-sectional epidemiological studies. Candidate definitions of MS were proposed by modifying the NCEP ATP III definition. These modifications included the following: waist circumference cutoffs as >90 cm in men and >80 cm in women, BMI cutoff as >23 kg/m<sup>2</sup>, and a measure of truncal subcutaneous fat (subscapular skinfold thickness [SST] >18 mm).

**RESULTS** — The highest prevalence (29.9%) of MS was observed by the inclusion of modified cutoffs of waist circumference and BMI and SST in place of the existing cutoffs of waist circumference in the NCEP ATP III criteria. Further, this modified definition showed the maximum absolute gain in the percentage of prevalence of MS over the NCEP ATP III definition, and it was the best predictor for MS in subjects with impaired fasting glucose, type 2 diabetes, and different age-groups. The lowest percentage of prevalence of MS was observed with the definition that excluded biochemical variables and blood pressure.

**CONCLUSIONS** — The criteria for defining MS in adult Asian Indians need revision. Inclusion of modified cutoffs of waist circumference and BMI and measures of truncal subcutaneous fat in the NCEP ATP III definition requires further validation.

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Resistance to insulin-mediated glucose uptake is important for the development of the metabolic syndrome (MS) and subsequently type 2 diabetes. Clustering of clinical and metabolic risk factors, known as “metabolic syndrome,” is defined by criteria laid down by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (1). High predisposition

to the development of type 2 diabetes in certain ethnic groups, such as Asian Indians, necessitates early identification of MS for the purpose of prevention (2).

Doubts have been expressed as to whether the NCEP ATP III definition is appropriate for identifying MS in Asians. Anthropometric parameters of Asians are different than those for white Caucasians and blacks. For example, Asian Indians

have smaller body size, excess body fat, and truncal and abdominal adiposity but lower average waist circumference than white Caucasians (2). The cutoffs of waist circumference to define abdominal obesity by the NCEP ATP III definition underestimate abdominal obesity in adult Asians (3).

Further, application of NCEP ATP III criteria requires the analysis of fasting blood samples for blood glucose, serum triglycerides, and HDL cholesterol levels. The results of these metabolic variables are usually not available on the first clinic visit; and more importantly, the cost of these tests may be prohibitive for economically challenged individuals. Innovative definitions of MS comprised of easy-to-measure relevant anthropometric measures thus need to be evaluated in individuals residing in developing countries.

In the present study, we devised eight candidate definitions of MS by including modified waist circumference and modified BMI cutoffs and subscapular skinfold thickness (SST) as additional defining anthropometric parameters in various combinations with the other defining parameters given by the NCEP ATP III. In the first candidate definition (MS-1), modified waist circumference cutoffs (>90 cm in men and >80 cm in women) were used instead of the waist circumference cutoffs (>102 cm in men and >88 cm in women) proposed by the existing NCEP ATP III definition. This candidate definition (MS-1) has also been used for defining prevalence of MS by other investigators in Asian Indians (3,4). BMI has been a defining parameter in the definition of MS given by the World Health Organization in 1999 (5). Based on reports of excess morbidity risk of Asians at lower BMI values, as compared with other ethnic groups, the cutoff for diagnosis of overweight has been proposed as 23 kg/m<sup>2</sup> (6), which was recently endorsed by the World Health Organization Expert Consultation as a “public health action point” for Asians (7).

Truncal subcutaneous fat, as mea-

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**Abbreviations:** MS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; SST, subscapular skinfold thickness.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—NCEP ATP III and candidate definitions of MS

| MS definition         | Parameters included in NCEP ATP III  |                          | Proposed additional anthropometric parameters |            |
|-----------------------|--|--------------------------|---|------------|
|                       | Blood pressure, triglycerides, HDL cholesterol, and fasting blood glucose* | Waist circumference (cm) | BMI >23 kg/m <sup>2</sup>                     | SST >18 mm |
| NCEP ATP III (MS-ATP) | ✓  | Men >102, women >88      | NI  | NI         |
| Candidate definitions |  |                          |   |            |
| MS-1†                 | ✓  | Men >90, women >80       | NI  | NI         |
| MS-2                  | ✓  | Men >90, women >80       | ✓   | NI         |
| MS-3                  | ✓  | Men >90, women >80       | NI  | ✓          |
| MS-4                  | ✓  | Men >90, women >80       | ✓   | ✓          |
| MS-5                  | ✓  | NI                       | ✓   | NI         |
| MS-6                  | ✓  | NI                       | NI  | ✓          |
| MS-7                  | ✓  | NI                       | ✓   | ✓          |
| MS-8                  | NI   | Men >90, women >80       | ✓   | ✓          |

\*Cutoffs according to the NCEP ATP III (MS-ATP) definition (blood pressure  $\geq 130/85$  mmHg; triglycerides  $\geq 150$  mg/dl; HDL cholesterol  $< 40$  mg/dl and  $< 50$  mg/dl in men and women, respectively; and fasting blood glucose  $\geq 110$  mg/dl). †Definition similar to MS-1 has been used by other investigators to define MS in Asian Indians. ✓, Parameter included in definition; NI, parameter not included in the definition. MS-ATP definition and candidate definitions: presence of three or more parameters needed for defining MS.

sured by SST, was also included as a defining anthropometric parameter of MS. The rationale of inclusion of SST in candidate definitions of MS was based on the experience of several investigators, including our group (8–11), that truncal subcutaneous fat is an important determinant of insulin sensitivity in some ethnic groups, particularly in South Asians. Specifically, we recently reported that the influence of excess truncal subcutaneous fat on insulin sensitivity might be similar to that of abdominal obesity (11).

We therefore hypothesized that the NCEP ATP III definition does not appropriately define MS in adult Asian Indians. In the current investigation, we have evaluated eight candidate definitions of MS with the NCEP ATP III definition as a reference. By comparing the prevalence of MS as per these candidate definitions, we aimed to propose a definition based on the criteria and/or a group of anthropometric and biochemical parameters that would optimally define MS in adult Asian Indians.

## RESEARCH DESIGN AND METHODS

We included the subjects from our previous epidemiological studies as the purposive sample for the current study because we had previously demonstrated an inordinately high prevalence of clustering of cardiovascular risk factors in the same population sample (12–14). The epidemiological methods

have been described previously (13). The survey methodology and instruments of measurement were similar in both surveys. For the current investigation, only relevant clinical, anthropometric, and biochemical data were used.

### Anthropometric measurements

Weight, height, waist and hip circumferences, and skinfold thickness measurements at four sites, i.e., the biceps, triceps, subscapular, and suprailiac, were measured as previously described (15).

### Biochemical samples and analysis

Blood glucose and lipids (total cholesterol, triglycerides, very-low-density lipoprotein [VLDL] cholesterol, and HDL cholesterol) were estimated as previously described (13). The value of LDL cholesterol was calculated using Friedewald's equation (16).

### Statistical analysis

The percentage of prevalence and 95% CI of MS by various candidate definitions was computed using STATA 8.0 statistical software. For determining the cutoff of subscapular subcutaneous skinfold thickness, which would have significant effect on insulin sensitivity, we carried out a receiver operating characteristic (ROC) curve analysis. The cutoff value of subcutaneous SST that showed optimal sensitivity and specificity in the ROC curve for the prediction of type 2 diabetes in the

total sample of subjects was  $>18$  mm for both sexes. We used modified cutoffs of waist circumference and BMI, as proposed for Asians (6,7).

Definitions of MS are presented in Table 1. MS is considered to be present if three or more of the defining variables are detected by any of the definitions.

**RESULTS** — Of a total of 640 subjects, complete clinical and biochemical data were available for 557 and 575 subjects, respectively. The mean age was  $38.9 \pm 14.8$  years. The average values and prevalence of measures of obesity and surrogate markers of insulin resistance are shown in Table 2. Central obesity, as defined by the NCEP ATP III waist circumference cutoffs (1), was present in 3.4% (95% CI 1.1–7.7) and 9% (6.4–12.2) of men and women, respectively. By lowering the waist circumference cutoffs to  $>90$  cm and  $>80$  cm, the prevalence of central obesity in men and women increased to 10.1% (5.7–16.1) and 25.9% (21.7–30.0), respectively. All of the measures of obesity were more prevalent in women than men (Table 2).

Table 3 shows the comparison of candidate definitions of MS with the NCEP ATP III definition (MS-ATP). The overall prevalence of MS by the MS-ATP definition, which was taken as the reference, was 9.2% (95% CI 6.8–12.1). The maximum percentage of prevalence was 29.9% (26.9–34.1), and the maximum

Table 2—Measures of obesity and prevalence of surrogate markers of MS

| Variables  | n   | Men              | n   | Women            |
|--|-----|------------------|-----|------------------|
| Average measures of obesity                                    |     |                  |     |                  |
| Waist circumference (cm)                                       | 149 | 74.2 ± 11.6      | 409 | 72.2 ± 4.5       |
| SST (mm)*  | 168 | 15.6 ± 8.7       | 462 | 16.8 ± 9.5       |
| Suprailiac skinfold thickness (mm)*                            | 168 | 17.6 ± 10.6      | 461 | 19.3 ± 10.6      |
| Biceps skinfold thickness (mm)†                                | 168 | 7.5 ± 5.2        | 463 | 8.0 ± 5.3        |
| Triceps skinfold thickness (mm)†                               | 168 | 13.0 ± 6.9       | 463 | 14.2 ± 8.2       |
| BMI (kg/m <sup>2</sup> )                                       | 168 | 19.9 ± 4.1       | 466 | 20.5 ± 4.6       |
| Prevalence of measures of obesity                              |     |                  |     |                  |
| Waist circumference (men >102 cm, women >88 cm)                | 149 | 3.4 (1.1–7.7)    | 410 | 9.0 (6.4–12.2)   |
| Modified waist circumference (men >90 cm, women >80 cm)        | 149 | 10.1 (5.7–16.1)  | 410 | 25.9 (21.7–30.0) |
| BMI (>23 kg/m <sup>2</sup> )                                   | 168 | 22.6 (16.5–29.7) | 466 | 23.8 (20.0–28.0) |
| SST (>18 mm)   | 168 | 32.7 (25.7–40.4) | 463 | 36.3 (25.7–40.7) |
| Surrogate markers of insulin resistance                        |     |                  |     |                  |
| Impaired fasting blood glucose (≥110 mg/dl <126 mg/dl)         | 170 | 13 (7.7)         | 465 | 30 (6.5)         |
| Diabetes (fasting blood glucose ≥126 mg/dl)                    | 170 | 6 (3.5)          | 464 | 24 (5.2)         |
| Hypertension (blood pressure ≥130/85 mmHg)                     | 168 | 19 (11.3)        | 466 | 75 (16.1)        |
| Hypertriglyceridemia (triglycerides ≥150 mg/dl)                | 167 | 43 (25.8)        | 435 | 111 (25.5)       |
| Low levels of HDL cholesterol (men <40 mg/dl, women <50 mg/dl) | 161 | 64 (39.8)        | 425 | 382 (89.9)       |

Data are means ± SD, % (95% CI), and n (%). \*Central skinfold thickness; †peripheral skinfold thickness.

absolute percentage of gain (20.7%) over the MS-ATP definition of MS was observed by the application of the candidate definition MS-4 in the total population (see Table 1 for description of defini-

tions). Table 4 depicts comparison of overall and sex-specific prevalence of MS, as defined by MS-ATP and the candidate definitions, in the total study sample, in subjects with impaired fasting glucose,

and in patients with type 2 diabetes. The percentage of prevalence of MS by the MS-ATP definition was 35.3% (19.7–53.5) and 43.5% (23.2–65.5) in subjects with impaired fasting glucose and those

Table 3—Comparison of candidate definitions of MS with the NCEP ATP III definition (MS-ATP) as reference

| MS definitions        | Prevalence | Absolute gain |   | True positive | True negative | Percentage agreement |
|-----------------------|------------|---------------|---|---------------|---------------|----------------------|
|                       |            | %*            | Attributed to†  |               |               |                      |
| MS-ATP (a + b)        | 9.2        | —             | —   | —             | —             | —                    |
| Candidate definitions |            |               |   |               |               |                      |
| MS-1 (a + b)‡         | 10.6       | 1.4           | MWC instead of WC   | 100.0         | 98.5          | 98.6                 |
| MS-2 (a + b‡ + c)     | 18.6       | 9.4           | MWC and BMI instead of WC   | 100.0         | 89.8          | 90.7                 |
| MS-3 (a + b‡ + d)     | 21.6       | 12.4          | MWC and SST instead of WC   | 100.0         | 86.4          | 87.7                 |
| MS-4 (a + b‡ + c + d) | 29.9       | 20.7          | MWC, SST, and BMI instead of WC   | 100.0         | 77.4          | 78.5                 |
| MS-5 (a + c)          | 11.0       | 1.8           | BMI instead of WC   | 95.6          | 96.7          | 96.6                 |
| MS-6 (a + d)          | 16.6       | 7.4           | SST instead of WC   | 89.1          | 90.2          | 90.1                 |
| MS-7 (a + c + d)      | 23.1       | 13.9          | SST and BMI instead of WC   | 100.0         | 84.3          | 85.8                 |
| MS-8 (c + d + b‡)     | 5.7        | –3.8          | SST, MWC, and BMI instead of blood pressure, triglyceride, HDL cholesterol, and fasting blood glucose cutoffs according to MS-ATP definition and WC | 15.2          | 97.9          | 90.2                 |

\*Absolute gain in % prevalence of the metabolic syndrome = % prevalence by candidate definition – % prevalence by MS-ATP. †Modification of the MS-ATP definition. a: Blood pressure, triglycerides, HDL cholesterol, and fasting blood glucose cutoffs according to the MS-ATP definition. b: Waist circumference (WC) cutoffs according to the MS-ATP definition. b‡: Modified waist circumference (MWC) cutoffs (men >90 cm and women >80 cm). c: BMI >23 kg/m<sup>2</sup>. d: SST >18 mm.

with type 2 diabetes, respectively. The candidate definition MS-4 was the best predictor of MS in subjects with impaired fasting glucose and in patients with type 2 diabetes (Table 4). Further, on stratification by age-groups, the MS-4 definition was found to be the best predictor of MS in the total study population and in subgroups (Table 5).

**CONCLUSIONS**— Our data show that the candidate definition MS-4, which included modified cutoffs of waist circumference and BMI and SST (as a measure of truncal subcutaneous fat) in addition to the criteria given by the MS-ATP definition, demonstrated the maximum percentage of prevalence and gain in prevalence (Table 3) of MS over the MS-ATP definition. Interestingly, the MS-8 definition, which includes only anthropometric criteria (modified waist circumference, SST, and BMI) showed poor predictability for MS against the MS-ATP definition, indicating that biochemical criteria and blood pressure are important for defining MS in Asian Indians.

Our investigation was a preliminary study to investigate and explore candidate definitions of MS in adult Asian Indians who, along with the other Asian ethnic groups, have different anthropometric characteristics in comparison with white Caucasians and blacks. Metabolic abnormalities contributing to cardiovascular risk factors are detectable at a lower waist circumference in Asians in comparison with Caucasians, suggesting that NCEP ATP III criteria might underestimate the prevalence of MS in Asians. Tan et al. (3) tested the adequacy of the NCEP ATP III definition to predict MS in Asians, including Asian Indians residing in Singapore, using modified cutoffs for waist circumference (same as in definition MS-1 of the present study). With use of the revised definition, they demonstrated that the crude prevalence of MS in Asian Indians increased from 20.4 to 28.8% and that in men and women it increased from 21.7 to 32.4% and 19.3 to 25.8%, respectively (3). In contrast, in the current investigation, using definition MS-1, only a slight increase in the prevalence rates of MS in women and none in men was observed. This difference may be due to different body composition characteristics of migrant Asian Indians in comparison with Asian Indians residing in India (2). Despite these differences, the higher preva-

**Table 4—Percentage prevalence (95% CI) of MS by the NCEP ATP III (MS-ATP) and candidate definitions (MS-1 through MS-11)**

| MS definition         | Total population |                  |                  | Subjects with impaired fasting glucose (FBG $\geq$ 110 mg/dl and $<$ 126 mg/dl) |                  |                  | Subjects with diabetes (FBG $\geq$ 126 mg/dl) |                  |                  |
|-----------------------|------------------|------------------|------------------|---|------------------|------------------|---|------------------|------------------|
|                       | Overall          | Men              | Women            | Overall   | Men              | Women            | Overall                                       | Men              | Women            |
| MS-ATP                | 9.2 (6.8–12.1)   | 11.0 (6.3–17.4)  | 8.5 (5.9–11.9)   | 35.3 (19.7–53.5)  | 60.0 (26.2–87.8) | 25.0 (9.8–46.7)  | 43.5 (23.2–65.5)                              | 66.7 (9.4–99.2)  | 40.0 (19.1–63.9) |
| Candidate definitions |                  |                  |                  |   |                  |                  |   |                  |                  |
| MS-1                  | 10.6 (8.0–13.6)  | 11.0 (6.3–17.4)  | 10.5 (7.5–14.1)  | 38.2 (22.2–56.4)  | 60.0 (26.2–87.8) | 29.2 (12.6–51.1) | 47.8 (26.8–69.4)                              | 66.7 (9.4–99.2)  | 45.0 (23.1–68.5) |
| MS-2                  | 18.6 (15.2–22.2) | 15.6 (9.9–22.8)  | 19.7 (15.7–24.1) | 47.1 (29.8–64.8)  | 60.0 (26.2–87.8) | 41.7 (22.1–63.3) | 56.5 (34.5–76.8)                              | 66.7 (9.4–99.2)  | 55.0 (31.5–76.9) |
| MS-3                  | 21.6 (18.0–25.5) | 20.6 (14.1–28.4) | 21.9 (17.8–26.6) | 46.9 (29.1–65.3)  | 66.7 (30.0–92.5) | 39.1 (19.7–61.5) | 69.6 (47.1–86.8)                              | 66.7 (9.4–99.2)  | 70.0 (45.7–88.1) |
| MS-4                  | 29.9 (25.9–34.1) | 26.8 (19.6–35.2) | 31.0 (26.2–36.1) | 53.1 (36.0–72.7)  | 66.7 (29.9–92.5) | 47.8 (28.6–69.4) | 78.3 (56.3–92.5)                              | 66.7 (9.4–99.2)  | 80.0 (56.3–94.3) |
| MS-5                  | 11.0 (8.6–13.8)  | 11.5 (7.0–14.2)  | 10.8 (8.0–14.1)  | 40.0 (24.8–56.7)  | 46.2 (19.2–74.9) | 37.0 (19.4–74.9) | 50.0 (30.0–70.1)                              | 80.0 (28.4–99.5) | 42.9 (21.8–66.0) |
| MS-6                  | 16.6 (13.6–20.0) | 19.8 (13.8–26.8) | 15.4 (12.0–19.3) | 44.7 (28.6–61.7)  | 58.3 (27.7–84.8) | 38.5 (20.2–59.4) | 69.2 (48.2–85.7)                              | 80.0 (28.4–99.5) | 66.7 (43.0–85.4) |
| MS-7                  | 23.1 (15.1–32.9) | 25.2 (16.9–35.2) | 22.3 (14.2–31.8) | 47.4 (31.0–64.2)  | 58.3 (27.7–84.8) | 42.3 (23.4–63.1) | 76.0 (65.9–84.0)                              | 80.0 (28.4–99.5) | 75.0 (64.8–83.0) |
| MS-8                  | 5.7 (1.7–11.9)   | 2.1 (0.3–7.4)    | 6.9 (3.0–14.6)   | 5.7 (0.7–19.2)  | 0.0              | 7.7 (0.9–25.1)   | 7.7 (3.0–14.6)                                | 0.0              | 9.1 (4.4–17.2)   |

See text for description of MS-ATP and candidate definitions MS-1 through MS-8. FBG, fasting blood glucose.



Table 5—Percentage of prevalence (95% CI) of MS stratified according to age-groups

| MS definitions        | Age-groups (years) |                  |                  |                  |                   |
|-----------------------|--------------------|------------------|------------------|------------------|-------------------|
|                       | 18–29              | 30–39            | 40–49            | 50–59            | ≥60               |
| NCEP ATP III (MS-ATP) | 5.9 (2.6–11.3)     | 5.9 (2.5–11.3)   | 13.9 (7.8–22.2)  | 12.3 (5.5–22.8)  | 12.7 (5.6–23.5)   |
| Modified MS-ATP*      | 2.1                | 4.5              | 10.7             | 22.1             | 25.0              |
| Candidate definitions |                    |                  |                  |                  |                   |
| MS-1                  | 5.9 (2.6–11.3)     | 7.4 (3.6–13.2)   | 15.8 (9.3–24.4)  | 15.4 (7.6–26.5)  | 14.3 (6.7–25.4)   |
| MS-4                  | 22.7 (15.1–32.9)   | 26.5 (17.8–36.4) | 38.0 (28.1–47.4) | 36.9 (27.1–47.4) | 31.75 (22.4–41.9) |

\*Data from Tan et al. (3), who studied Asian Indians residing in Singapore using modified waist circumference cutoffs: men >90 cm and women >80 cm instead of the currently accepted cutoffs in the MS-ATP definition. This definition is the same as candidate definition MS-1 used in the current study.

lence of MS and the greater increase in the percentage of prevalence in women with the use of candidate definitions are interesting observations. Higher prevalence of MS in women as compared with men is also in line with observations in the urban South Indian population (4) and our previous studies (11–13). Use of the modified NCEP ATP III definition, which is similar to the MS-1 candidate definition, in urban Asian Indians residing in South India showed the prevalence of MS as 41%; however, these data were not compared with the NCEP ATP III definition (4).

Importance of truncal subcutaneous fat as a contributory factor for the development of insulin resistance has been emphasized by several investigators. Haffner et al. (8) stressed that the ratio of subscapular to triceps skinfold and abdominal obesity may be independently associated with type 2 diabetes and surrogate markers of insulin resistance in Hispanic populations. Further, truncal skinfold thickness independently predicts cardiovascular risk (17) and type 2 diabetes in adults (18). Adult South Asians and post-pubertal children have thicker truncal skinfolds than similar populations of white Caucasians (9–11). Moreover, at similar values of BMI, greater truncal skinfold thickness in adult migrant Asian Indians has been shown to be associated with a higher degree of hyperinsulinemia than white Caucasians (10). In a recent study, we have shown that increasing tertiles of truncal skinfold thickness were associated with higher fasting insulin concentrations than those recorded at any tertile of peripheral skinfold thickness, total body fat, and waist circumference (11). Thicker truncal subcutaneous fat patterning in Asian Indians with higher serum insulin levels in comparison with white Caucasians is evident at birth (19).

Thus, it appears that excess truncal subcutaneous adipose tissue is an important determinant of insulin resistance in Asian Indians. These data justify inclusion of measures of truncal subcutaneous adiposity for devising candidate definitions of MS for South Asians.

The present study could have been improved by comparing the candidate definitions against insulin resistance, as measured ideally by hyperinsulinemic-euglycemic clamp technique and cardiovascular end points. The modified waist circumference cutoffs need to be confirmed by gathering more representative data from Asian ethnic groups. The cutoffs of SST should be validated by other investigators. Further, we did not test the hypothesis that insulin resistance in Asian Indians may occur de novo and independent of obesity. Finally, the definition of MS by the World Health Organization was not tested, since it is not always possible to estimate fasting serum insulin levels and microalbuminuria in a resource-constrained population.

Based on the observations of the present study, and those from other investigators, we suggest that, similar to diagnostic criteria of obesity, criteria for the diagnosis of MS need to be revised in Asian Indians and other Asian ethnic groups. Inclusion of modified waist circumference and BMI cutoffs and SST may be considered as defining variables of MS in the future studies on Asian Indians and other Asian ethnic groups.

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