The Metabolic Syndrome, Cardiopulmonary Fitness, and Subcutaneous Trunk Fat as Independent Determinants of Arterial Stiffness

The Amsterdam Growth and Health Longitudinal Study

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Background: The mechanisms that link the metabolic syndrome to increased cardiovascular risk are incompletely understood, especially in young people. We therefore examined whether the metabolic syndrome was associated with arterial stiffness and whether any such associations were independent of cardiopulmonary fitness and subcutaneous trunk fat.

Methods: Cross-sectional analyses of data on 364 men and women aged 36 years from the Amsterdam Growth and Health Longitudinal Study (ninth follow-up measurement, year 2000). The prevalence of the metabolic syndrome was defined by a slightly modified National Cholesterol Education Program (NCEP) definition. Arterial stiffness was ultrasonically estimated by distensibility and compliance of the carotid, femoral, and brachial arteries and by the carotid elastic modulus.

Results: The prevalence of the metabolic syndrome in this young adult population was 18.3% in men and 3.2% in women. Individuals with the syndrome compared with individuals without risk factors had 11.2% and 17.0% less distensibility and 9.0% and 18.2% less compliance of the carotid and femoral arteries, respectively, and 15.9% higher carotid elastic modulus. After adjustment for cardiopulmonary fitness and subcutaneous trunk fat, the metabolic syndrome remained significantly associated with stiffness of the carotid but not the femoral artery. In addition, poor cardiopulmonary fitness and high subcutaneous trunk fat were associated with arterial stiffness, and this was independent of the metabolic syndrome.

Conclusions: A modified NCEP definition of the metabolic syndrome identified young individuals with increased arterial stiffness. The mechanisms that link the metabolic syndrome, poor cardiopulmonary fitness, and high subcutaneous trunk fat to greater arterial stiffness overlap but are partly independent of each other.

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The Metabolic Syndrome is a condition characterized by the clustering of cardiovascular risk factors, notably central obesity, dyslipidemia, elevated blood pressure, and high fasting glucose levels, more than chance alone would dictate.1,2 Insulin resistance emerges as a common pathogenetic denominator that underlies the clustering of these risk factors.3 The metabolic syndrome raises the risk of cardiovascular disease and type 2 diabetes mellitus, thus representing a major health hazard.4,5 Body fatness and a sedentary lifestyle, in the setting of a genetic predisposition, are considered its prime etiologic factors.4,6,8-11 The prevalence of the metabolic syndrome is increasing, particularly in young individuals.12-14 However, how the metabolic syndrome leads to cardiovascular disease is incompletely understood, especially in young people.

The arterial system converts the intermittent flow of blood from the heart to a continuous and steady flow across the arterial tree, thereby reducing the afterload imposed on the heart. Alterations to this cushioning function, because of increases in arterial stiffness, lead to systolic hypertension, left ventricular hypertrophy, and impaired coronary perfusion, increasing cardiovascular risk.15-17 Arterial stiffness (arteriosclerosis) affects the structural elements that are mainly located in the media layer of the arterial wall, whereas the thickening of the intima layer is an early observation of atherosclerosis. The determinants of arterial stiffness have been extensively studied,18-22 but the impact of the metabolic syndrome on arterial stiffness at different sites of the arterial tree in apparently healthy young adults has, to our knowledge, never been addressed. Any such associations can provide further insight into
the pathophysiologic mechanisms that link the metabolic syndrome to the development of cardiovascular disease, so this needs to be further investigated. In addition, because poor cardiopulmonary fitness and high subcutaneous trunk fat deposition are associated with the metabolic syndrome and arterial stiffness, which we have demonstrated previously in the Amsterdam Growth and Health Longitudinal Study (AGAHLS) cohort, the question arises to what extent the metabolic syndrome is a determinant of arterial stiffness independently of cardiopulmonary fitness and subcutaneous trunk fat.

The aim of the present study, therefore, is to investigate (1) the prevalence of the metabolic syndrome in a free-living cohort of apparently healthy 36-year-old adults (the AGAHLS); (2) whether the metabolic syndrome and its components are determinants of carotid, femoral, and brachial artery stiffness estimates; and (3) whether the metabolic syndrome is associated with arterial stiffness independently of cardiopulmonary fitness and subcutaneous trunk fat deposition.

METHODS

PARTICIPANTS AND STUDY DESIGN

The AGAHLS is an observational longitudinal study that started in 1977 with a group of 450 boys and girls. Its initial goal was to describe the natural development of the growth, health, and lifestyle of adolescents and to investigate longitudinal relationships between biological and lifestyle variables. The mean ± SD age of the participants at the beginning of the study was 13.1 ± 0.8 years. Since then, a series of examinations have been performed during a 23-year follow-up period, in which data were collected on anthropometric (body height, weight, and skinfolds), biological (serum lipoprotein levels, blood pressure, and physical fitness), lifestyle (behavioral patterns, smoking behavior, daily physical activity), and psychological variables. In the most recent follow-up measurement (in 2000), when the participants’ mean ± SD age was 36.5 ± 0.6 years, large artery properties as assessed by noninvasive ultrasonography were investigated for the first time; data on 5 risk factors, needed for the identification of the metabolic syndrome according to recent guidelines, were also available for the first time. Analyses reported herein include 364 participants (189 women) for whom complete data on both arterial properties and metabolic syndrome status were available at the age of 36 years. None of the participants used lipid- or blood pressure–lowering medication at the time of the study. The study was approved by the medical ethical committee of the VU University Medical Center, Amsterdam, the Netherlands, and all participants gave their written informed consent.

ARTERIAL PROPERTIES

Arterial properties for the estimation of arterial stiffness were assessed according to guidelines for user procedures and with the use of reproducible and valid methods and devices, as recently recommended. All participants had abstained from smoking and caffeinated beverages on the day the measurements were performed. At the time of the measurements of arterial properties, participants had been resting in a supine position for 15 minutes in a quiet, temperature-controlled room. Properties of the right common carotid and the common femoral and brachial arteries were obtained by I.F. and another trained vascular sonographer with the use of an ultrasound scanner equipped with a 7.5-MHz linear array probe (Pie Medical Imaging, Maastricht, the Netherlands). The ultrasound scanner was connected to a personal computer equipped with an acquisition system and a vessel wall movement detector software system (Wall Track System 2; Pie Medical Imaging). This integrated device enables measurements of arterial diameter, distension, and intima-media thickness (IMT) as described in detail elsewhere. The carotid artery was measured approximately 10 mm proximal to the beginning of the bulb, the femoral artery 20 mm proximal to the flow divider, and the brachial artery approximately 20 mm above the antecubital fossa. The mean diameter, distension, and, for the carotid artery only, IMT of 3 consecutive measurements (each including 3 to 7 heartbeats) were used in the analyses.

Throughout the entire period of ultrasonography, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and resting heart rate were assessed in the left arm at 5-minute intervals with an oscillometric device (model BP-8800; Colin Press-Mate, Komaki-City, Japan; conforms to the American National Standards Institute and the Association for the Advancement of Medical Instrumentation standards). Brachial artery pulse pressure was defined as systolic minus diastolic blood pressure, and pulse pressure at the common carotid and femoral arteries was calculated according to the calibration method first described by Kelly and Fitchett, with the use of distension waveforms as adapted by Van Bortel et al.

STIFFNESS ESTIMATES

The mean diameter (D), distension (ΔD), and local pulse pressure (ΔP) were used to estimate the distensibility (DC) and compliance (CC) coefficients as follows:

$$DC = \frac{(2ΔD × D ÷ ΔD^2)/(ΔD × D^2)}{10^{-3}/kPa}$$

$$CC = \frac{D}{(IMT × DC)}$$

Distensibility reflects the elastic properties, whereas the compliance reflects the buffering capacity of the artery. From carotid IMT, diameter, and the distensibility coefficient, we calculated the carotid Young elastic modulus (Einc), an estimate of the intrinsic elastic properties of the vessel wall, as follows:

$$E_{inc} = D/(IMT × DC)$$

THE METABOLIC SYNDROME

To identify the metabolic syndrome, we used a slightly modified version of the definition proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, namely, when 3 or more of the following 5 risk factors were present: (1) systolic blood pressure of 130 mm Hg or higher and/or diastolic blood pressure of 85 mm Hg or higher; (2) high-density lipoprotein cholesterol levels of less than 40 mg/dL (<1.03 mmol/L) in men and less than 50 mg/dL (<1.29 mmol/L) in women; (3) triglyceride levels of 150 mg/dL or higher (≥1.7 mmol/L); (4) glycated hemoglobin level higher than 6.1% instead of fasting plasma glucose levels of 110 mg/dL or higher (≥6.1 mmol/L); (5) waist circumference greater than 94 cm in men and greater than 80 cm in women, ie, more liberal cutoff values than the originally proposed (≥102 cm in men and ≥88 cm in women), since they may be more appropriate in the identification of individuals at increased risk in young and apparently healthy populations.

Blood pressure was measured on 2 occasions: with the patient in a supine position during the measurement of arterial properties and with the patient in a sitting position before the evaluation of cardiopulmonary fitness levels. The latter was per-
formed on the right arm using a sphygmomanometer (Speidell-Keller, Franken & Itallic, Amsterdam, the Netherlands) after at least 5 minutes of rest; systolic and diastolic blood pressures (Korotkoff phases 1 and 5, respectively) were measured twice, and the lower value was recorded. The systolic and diastolic blood pressures obtained on the 2 occasions were averaged and used in the analyses. Serum high-density lipoprotein cholesterol, total cholesterol, and triglyceride levels were measured by enzymatic techniques (Roche Diagnostics GmbH, Mannheim, Germany). Glycated hemoglobin was measured by ion-exchange high-performance liquid chromatography with a mono-S column (Pharmacia, Uppsala, Sweden). Waist circumference was measured with a flexible steel tape (Martin circum- meter, Franken & Itallic) at the level midway between the lowest rib margin and the iliac crest.

**CARDIOPULMONARY FITNESS AND SUBCUTANEOUS TRUNK FAT**

Cardiopulmonary fitness was measured with a maximal running test on a treadmill (Quinton 18-54; Quinton, Bothell, Wash), with a speed of 8 km/h and increasing slope (every 2 minutes) and with direct measurements of oxygen uptake (Ergoanalyzer; Jaeger, Bunnik, the Netherlands). Maximum oxygen consumption (VO$_2$max) was used as a measure of cardiopulmonary fitness. 23 Biceps, triceps, and subscapular and suprailiac skinfolds were measured to the nearest 0.1 mm with a Harpenden caliper (Holtain, Van Rietshoten and Houwens, Rotterdam, the Netherlands) on the left side of the body. The ratio of subscapular to suprailiac skinfolds ratio to the sum of the 4 skinfolds was used as an estimate of subcutaneous trunk fat.

**OTHER VARIABLES**

Assessment of body height and weight, smoking behavior, alcohol consumption, nutrient intake, and physical activity levels has been described in detail previously. 20,27

**STATISTICAL ANALYSIS**

Participants were classified into 4 groups according to the number of risk factors for the metabolic syndrome: 0, 1, 2, and 3 or more. Multiple linear regression analyses were used to analyze the relationship between the number of risk factors (determinants; 0 risk factors used as reference category) and arterial stiffness estimates (outcomes). These analyses were adjusted for sex, height, smoking behavior, and mean blood pressure (the latter not in analyses with carotid IMT) (model 1). For smoking behavior, participants were categorized as non-smokers, light smokers (defined as below the population’s median value of pack-years, which is 6), and heavy smokers (≥6 pack-years). Next we expanded this model with further adjustments for VO$_2$max and the skinfolds ratio to investigate whether the associations of the metabolic syndrome with arterial stiffness estimates were (wholly or in part) explained by these variables (model 2).

We also examined whether there were interactions between the metabolic syndrome, VO$_2$max, and the skinfolds ratio on the one hand and sex on the other, in the associations with stiffness estimates. Because there were no significant interactions (P > .05 for all), data are presented for men and women together. These analyses were performed with SPSS statistical software, version 10.1 for Windows (SPSS Inc, Chicago, Ill).

**RESULTS**

Table 1 gives the general participant characteristics, and Table 2 gives data on large artery properties of the study population.

**PREVALENCE OF THE METABOLIC SYNDROME AND ITS COMPONENTS**

The overall prevalence of the metabolic syndrome in the study population was 10.4%. The metabolic syndrome and its components were much more common in men (18.3%) than in women (3.2%) (Figure 1). Elevated blood pressure was the most prevalent risk factor in men, whereas low high-density lipoprotein cholesterol level
Participants with the metabolic syndrome (men and women combined), compared with those without risk factors, had greater arterial stiffness of the carotid, femoral, and brachial arteries, as shown by lower distensibility and compliance and higher elastic modulus (Table 3). These differences were statistically significant for the carotid and femoral arteries and resulted mainly from a decrease in distension. The adverse association of the metabolic syndrome with arterial distensibility and compliance was more marked in the femoral artery than in the other arteries (Figure 2).

THE METABOLIC SYNDROME, CARDIOPULMONARY FITNESS, AND SUBCUTANEOUS TRUNK FAT AS DETERMINANTS OF ARTERIAL STIFFNESS

Adjustment for $V_{O2}$max and the skinfolds ratio in general decreased the strength of the associations of the metabolic syndrome with arterial stiffness, but the metabolic syndrome remained significantly associated with carotid (distensibility and elastic modulus) and femoral (compliance) artery stiffness estimates (Table 4). Conversely, after adjustment for the metabolic syndrome and for each other, $V_{O2}$max and the skinfolds ratio remained significantly associated with arterial stiffness. Specifically, $V_{O2}$max was positively associated with carotid distensibility and compliance and femoral compliance and positively associated with carotid elastic modulus. These associations resulted mainly from strong associations of $V_{O2}$max with carotid and femoral distension and femoral diameter and from strong associations between the skinfolds ratio and carotid diameter and femoral diameter and distension. Additional adjustments for resting heart rate, alcohol consumption, physical activity, and nutrient intake did not materially alter these associations (data not shown).

## Table 2. Large Artery Properties of Participants 36 Years Old*

<table>
<thead>
<tr>
<th>Artery Property</th>
<th>Men ($n = 175$)</th>
<th>Women ($n = 189$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carotid artery</td>
<td>Femoral artery</td>
</tr>
<tr>
<td>Distensibility coeff.</td>
<td>26.1 ± 5.3</td>
<td>6.0 ± 3.0</td>
</tr>
<tr>
<td>$10^{-3}$/kPa</td>
<td>27.0 ± 6.7</td>
<td>8.3 ± 4.2</td>
</tr>
<tr>
<td>Compliance coeff.</td>
<td>1.07 ± 0.26</td>
<td>0.52 ± 0.24</td>
</tr>
<tr>
<td>$mm^2$/kPa</td>
<td>0.92 ± 0.26</td>
<td>0.51 ± 0.23</td>
</tr>
<tr>
<td>Elastic modulus</td>
<td>0.47 ± 0.12</td>
<td>13.0 ± 9.1</td>
</tr>
<tr>
<td>$10^{-3}$/kPa</td>
<td>0.42 ± 0.12</td>
<td>16.0 ± 9.0</td>
</tr>
<tr>
<td>Diameter, mm</td>
<td>7.19 ± 0.51</td>
<td>6.58 ± 0.51</td>
</tr>
<tr>
<td>Distension, µm</td>
<td>629 ± 138</td>
<td>512 ± 118</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>52.9 ± 6.3</td>
<td>45.8 ± 7.7</td>
</tr>
<tr>
<td>Intima-media thickness, mm</td>
<td>0.63 ± 0.10</td>
<td>0.63 ± 0.10</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.

Figure 1. Prevalence of the metabolic syndrome (MetS) and its components. BP indicates blood pressure of 130/85 mm Hg or higher; TRIG, triglyceride level of 150.58 mg/dL ($>1.70$ mmol/L); HDL-C, high-density lipoprotein cholesterol level of less than 39.83 mg/dL ($<0.95$ mmol/L) (men) and less than 49.88 mg/dL ($<1.29$ mmol/L) (women); HbA1c, glycated hemoglobin level greater than 6.1%; WC, waist circumference greater than 94 cm (men) and greater than 80 cm (women).

The central new finding of this study is that the metabolic syndrome is associated with large artery stiffness in apparently healthy 36-year-old men and women. Specifically, individuals with the metabolic syndrome had significantly increased stiffness of the elastic carotid and even more of the muscular femoral artery, and these adverse associations were, at least partially, independent of poor cardiopulmonary fitness and high subcutaneous trunk fat, which themselves were independent determinants of arterial stiffness. These findings therefore suggest that the mechanisms that link the metabolic syndrome, poor cardiopulmonary fitness, and high subcutaneous trunk fat to greater arterial stiffness overlap in part but not completely.

How the metabolic syndrome increases risk of cardiovascular disease is incompletely understood. Our study suggests that increased arterial stiffness may be in-
Table 3. The Metabolic Syndrome and Its Components as Determinants of Large Artery Stiffness

<table>
<thead>
<tr>
<th>Outcome and No. of Risk Factors</th>
<th>Stiffness Estimates</th>
<th>Carotid Artery</th>
<th>Femoral Artery</th>
<th>Brachial Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distensibility</td>
<td>β (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−1.17</td>
<td>(−2.58 to −0.24)</td>
<td>(−1.84 to −0.04)</td>
<td>(−1.99 to 2.68)</td>
</tr>
<tr>
<td>2</td>
<td>−1.11</td>
<td>(−3.08 to 0.85)</td>
<td>(−2.77 to −0.30)</td>
<td>(−2.53 to 3.85)</td>
</tr>
<tr>
<td>≥3 (MetS)</td>
<td>−3.06†</td>
<td>(−5.20 to −0.93)</td>
<td>(−2.68 to −0.00)</td>
<td>(−4.29 to 2.65)</td>
</tr>
<tr>
<td>Compliance</td>
<td>β (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−5.36</td>
<td>(−12.24 to 0.35)</td>
<td>(−10.41 to 1.18)</td>
<td>(−1.30 to 3.28)</td>
</tr>
<tr>
<td>2</td>
<td>−5.28</td>
<td>(−12.82 to 2.68)</td>
<td>(−18.39 to 2.51)</td>
<td>(−2.85 to 3.41)</td>
</tr>
<tr>
<td>≥3 (MetS)</td>
<td>−9.24†</td>
<td>(−18.48 to 0.00)</td>
<td>(−18.68 to −1.34)</td>
<td>(−4.19 to 2.62)</td>
</tr>
<tr>
<td>Young elastic modulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.21</td>
<td>(−2.68 to 3.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.00</td>
<td>(−5.03 to 3.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 (MetS)</td>
<td>6.80‡</td>
<td>(2.43 to 11.17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individual Elements of Stiffness Estimates

| Diameter                      | β (95% CI)          |                |                |
| 1                             | −0.04               | (−0.17 to 0.09) | (−0.01 to 0.52) | (−0.13 to 0.13) |
| 2                             | −0.05               | (−0.23 to 0.13) | (−0.27 to 0.45) | (−0.23 to 0.13) |
| ≥3 (MetS)                     | 0.12                | (−0.08 to 0.31) | (−0.32 to 0.46) | (0.00 to 0.39)  |
| Distension                    | β (95% CI)          |                |                |
| 1                             | −19.51              | (−50.43 to 11.43) | (−51.84 to −1.36) | (−12.04 to 37.60) |
| 2                             | 3.89                | (−39.29 to 47.06) | (−75.55 to −6.58) | (−19.68 to 48.20) |
| ≥3 (MetS)                     | −50.96†             | (−97.81 to −4.11) | (−82.34 to −41.59) | (32.21) |
| Pulse pressure                | β (95% CI)          |                |                |
| 1                             | 0.31                | (−1.66 to 2.27)  | (−3.05 to 1.45)  | (−0.59 to 2.38)  |
| 2                             | 2.13                | (−0.61 to 4.87)  | (−1.74 to 4.41)  | (0.75 to 4.82)  |
| ≥3 (MetS)                     | 0.08                | (−2.90 to 3.05)  | (−3.96 to 2.75)  | (−0.11 to 4.31)  |
| Intima-media thickness        | β (95% CI)          |                |                |
| 1                             | 16.01               | (−8.24 to 40.27) |                |                |
| 2                             | 29.29               | (−3.52 to 62.10) |                |                |
| ≥3 (MetS)                     | −2.80               | (−39.18 to 35.57) |                |                |

Abbreviations: CI, confidence interval; MetS, metabolic syndrome.
*All analyses were adjusted for sex, height, smoking status, and mean arterial pressure (model 1). The regression coefficient (β) for MetS indicates difference in arterial property compared with participants without risk factors of the syndrome.
†P<.05.
‡P<.01.

Figure 2. Change in arterial stiffness estimates according to number of risk factors (RFs) compared with no risk factors for distensibility (A), compliance (B), and Young elastic modulus (C). MetS indicates metabolic syndrome.
Because poor cardiopulmonary fitness and greater subcutaneous trunk fat cluster with the metabolic syndrome and are associated with greater arterial stiffness, arterial stiffening in individuals with the metabolic syndrome will often be more pronounced than predicted by the presence of the metabolic syndrome per se. In addition, since individuals with the metabolic syndrome are at increased risk for the development of type 2 diabetes mellitus, these findings support the view that the clock starts “ticking” for arterial stiffness long before the overt onset of type 2 diabetes mellitus.

Both the elastic carotid and especially the muscular femoral artery were considerably stiffer in individuals with the metabolic syndrome. Elastic and muscular arteries respond differently to aging, drugs, and other factors, and the present study suggests that the effects of the metabolic syndrome, although adverse throughout, also were not uniform along the arterial tree. These findings agree with those previously reported by the Hoorn Study cohort: compared with individuals with normal glucose metabolism, those with impaired glucose metabolism and type 2 diabetes mellitus had considerably higher arterial stiffness, which was more marked in the femoral than the carotid artery (and central arterial segments).

In the absence of a shift in the genetic pool, the high prevalence of the metabolic syndrome we observed is likely triggered by environmental factors. These factors include lack of physical activity and excessive caloric intake, which in turn lead to poor cardiopulmonary fitness and obesity. Obesity, in particular central obesity, is a well-recognized trigger of the syndrome, and therefore waist circumference measurements have been included in the NCEP definition of the metabolic syndrome. In analyses that focus on each separate risk factor included in the syndrome, abdominal obesity was the only feature independently associated with arterial stiffness estimates (data not shown). Nonetheless, the presence of the metabolic syndrome was more strongly associated with arterial stiffness than abdominal obesity, which suggests that abdominal obesity alone cannot fully explain the association of the metabolic syndrome with arterial stiffness. Although visceral fat (commonly assessed by the waist circumference) is thought to be the major determinant of the metabolic complications of central obesity, subcutaneous trunk fat is also strongly correlated with insulin sensitivity. In this context, we have previously shown in the same (young) cohort that not only abdominal adiposity (as expressed by the waist circumference) but also subcutaneous trunk fat (as expressed by the skinfolds ratio) is associated with greater carotid and femoral stiffness.

Regardless of the compartment involved, important mechanisms that are thought to relate excess upper-body adiposity to cardiovascular risk include excessive release of free fatty acids and glycerol into the circulation, which in turn leads to insulin resistance and hyperinsulinemia. Alternatively, secretion of mediators by adipose tissue that affect vascular structure and function, such as angiotensin, interleukin 6, tumor necrosis factor alpha, plasminogen activator inhibitor 1, leptin, and adiponectin, may constitute another potential mechanism.

<table>
<thead>
<tr>
<th>Table 4. The Metabolic Syndrome, Cardiopulmonary Fitness, and Subcutaneous Trunk Fat as Determinants of Large Artery Stiffness*</th>
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</thead>
<tbody>
<tr>
<td><strong>β (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Outcome and Determinant</strong></td>
</tr>
<tr>
<td>Distensibility</td>
</tr>
<tr>
<td>MetS</td>
</tr>
<tr>
<td>V̇O₂max</td>
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<tr>
<td>Skinfolds ratio</td>
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<tr>
<td>Compliance</td>
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<tr>
<td>MetS</td>
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<td>V̇O₂max</td>
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<td>Skinfolds ratio</td>
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<tr>
<td><strong>Individual Elements of Stiffness Estimates</strong></td>
</tr>
<tr>
<td>Diameter</td>
</tr>
<tr>
<td>MetS</td>
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<tr>
<td>V̇O₂max</td>
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<tr>
<td>Skinfolds ratio</td>
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<tr>
<td>Distension</td>
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<tr>
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<tr>
<td>V̇O₂max</td>
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<td>Skinfolds ratio</td>
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<tr>
<td>Pulse pressure</td>
</tr>
<tr>
<td>MetS</td>
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<tr>
<td>V̇O₂max</td>
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<td>Skinfolds ratio</td>
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<tr>
<td>Intima-media thickness</td>
</tr>
<tr>
<td>MetS</td>
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<tr>
<td>V̇O₂max</td>
</tr>
<tr>
<td>Skinfolds ratio</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MetS, metabolic syndrome; V̇O₂max, maximum oxygen consumption.

*Results presented herein are those obtained in a multivariable model, including sex, height, smoking status, mean arterial pressure, metabolic syndrome, cardiopulmonary fitness (V̇O₂max), and subcutaneous trunk fat (model 2). The regression coefficient (β) for MetS indicates difference in arterial property compared with participants without risk factors of the syndrome; for V̇O₂max and skinfolds ratio, the regression coefficient represents difference in arterial property per 1-SD increase in these variables.

†P<.05
‡P<.01
§P<.001
Cardiopulmonary fitness is a potent determinant of the metabolic syndrome and arterial stiffness, and we have now shown this to be independent of the metabolic syndrome (and subcutaneous trunk fat). This suggests that the mechanisms that link the metabolic syndrome and cardiopulmonary fitness to arterial stiffness may differ. Adaptation to intermittent shear stress forces and changes in vascular smooth muscle tone have been the specific mechanisms proposed to explain the changes in large artery structural and functional properties that occur as a consequence of changes in cardiopulmonary fitness. However, because the associations between the metabolic syndrome and arterial stiffness decreased after adjustment for cardiopulmonary fitness levels (and subcutaneous trunk fat), these variables may share mechanisms that lead to arterial stiffness. Cardiopulmonary fitness is associated with insulin sensitivity ($r=0.44$ in men and $0.32$ in women)

and inflammatory activity

and could constitute such common pathways.

Our study had several limitations. Its cross-sectional design does not allow us to draw conclusions in terms of causality. Our results were obtained in a young adult, white, and apparently healthy population, and therefore inferences to older individuals, other ethnicities, and high-risk populations should be made with caution. Finally, the low prevalence of the metabolic syndrome in women (only $3.2\%$) did not allow a proper analysis of whether the associations investigated were similar or differ between men and women.

In conclusion, our study demonstrated that healthy 36-year-old individuals with the metabolic syndrome had greater arterial stiffness than those without it. In addition, poor cardiopulmonary fitness levels and high subcutaneous trunk fat, although associated with the metabolic syndrome, were independent determinants of arterial stiffness. These findings suggest that prevention of the metabolic syndrome should start early in life. Regular physical activity and prudent eating are key lifestyle measures to maintain good cardiovascular fitness and avoid obesity, thereby preventing the development of the metabolic syndrome and arterial stiffness.

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