Development of Fatness, Fitness, and Lifestyle From Adolescence to the Age of 36 Years

Determinants of the Metabolic Syndrome in Young Adults: The Amsterdam Growth and Health Longitudinal Study

Isabel Ferreira, PhD; Jos W. R. Twisk, PhD; Willem van Mechelen, MD, PhD; Han C. G. Kemper, PhD; Coen D. A. Stehouwer, MD, PhD

Background: Among young adults, the metabolic syndrome is an increasingly frequent risk factor for cardiovascular disease. Its determinants are, however, incompletely understood. We investigated the time course, from adolescence (age, 13 years) to young adulthood (age, 36 years), of important potential determinants (body fatness and fat distribution, cardiopulmonary fitness, and lifestyle) in 364 individuals (189 women).

Methods: Data were derived from the Amsterdam Growth and Health Longitudinal Study and analyzed with the use of generalized estimating equations.

Results: The prevalence of the metabolic syndrome at the age of 36 years, as identified with a modified National Cholesterol Education Program definition of the syndrome, was 10.4%. Subjects with the metabolic syndrome at the age of 36 years, compared with those without the syndrome, had (from adolescence to the age of 36 years) the following: (1) a more marked increase in total body fatness and in subcutaneous trunk fat; (2) a more marked decrease in cardiopulmonary fitness levels; (3) a more marked increase in physical activities of light-to-moderate intensity, but a more marked decrease in hard physical activities; (4) a trend toward a higher energy intake throughout the years; and (5) a decreased likelihood of drinking alcoholic beverages.

Conclusions: Fatness, fitness, and lifestyle are important determinants of the metabolic syndrome in young adults. More important, these associations were independent of each other and, therefore, represent separate potential targets for the prevention of the metabolic syndrome. Our study further suggests that intervening early in life (eg, in the period of transition from adolescence to adulthood) may be a fruitful area for prevention of the metabolic syndrome.

Arch Intern Med. 2005;165:42-48

The metabolic syndrome is an important cause of cardiovascular disease. Its prevalence is increasing, especially in young individuals, and there is evidence that the onset of the metabolic syndrome in adulthood has its roots early in life. Prevention of the metabolic syndrome is an important public health goal, but requires better insight into its determinants and their development over time.

Although the metabolic syndrome is thought to be mainly a consequence of obesity, the mechanisms underlying its onset are not fully understood. Other risk factors may also contribute, notably, poor cardiopulmonary fitness and lifestyle behaviors, such as little physical activity, excessive energy and/or unbalanced nutrient intake, low alcohol intake, and cigarette smoking.

Taken together, these data suggest that the pathogenesis of the metabolic syndrome is multifactorial. However, disentangling the contribution of closely interrelated risk factors, such as weight gain, cardiopulmonary fitness, and lifestyle behaviors, requires repeated observations over an extended period.

See also pages 15, 25, and 35

We examined these issues in a cohort of healthy young individuals who have been followed up from the age of 13 years to the age of 36 years and in whom the prevalence of the metabolic syndrome at the age of 36 years could be determined. Specifically, we analyzed to what extent the longitudinal development of fatness, cardiopulmonary fitness, and lifestyle variables from the age of 13 years to the age of 36 years determined...
the occurrence of the metabolic syndrome at the age of 36 years.

METHODS

STUDY DESIGN AND SUBJECTS

The Amsterdam Growth and Health Longitudinal Study is an observational longitudinal study that started in 1977 with a group of 450 boys and girls. Its initial goals were to describe the natural development of growth, health, and lifestyle of adolescents and to investigate longitudinal relationships between biological and lifestyle variables. The mean (SD) age of the subjects at the beginning of the study was 13.1 (0.8) years. Since then, measurements have been obtained 2 to 8 times (at the ages of 13, 14, 15, 16, 21, 27, 32, and 36 years) during a 24-year follow-up period. At each measurement, anthropometrical (body height, body weight, and skinfolds), biological (serum lipoprotein levels, blood pressure, and physical fitness), lifestyle (nutritional habits, smoking behavior, and daily physical activity), and psychological variables were assessed.29 In the most recent measurement period (in 2000), when the subjects’ mean (SD) age was 36.5 (0.6) years, the 5 risk factors needed for the identification of the metabolic syndrome according to recent guidelines27 were assessed for the first time in 364 individuals (189 women). The study was approved by the medical ethical committee of the VU University Medical Center, and all subjects gave their written informed consent (provided by the parents when subjects were aged 13-16 years).

METABOLIC SYNDROME AND ITS COMPONENTS

The identification of the metabolic syndrome and its components was based on the definition proposed by the National Cholesterol Education Program Adult Treatment Panel III.30 namely, when 3 or more of the following 5 risk factors were present: (1) a systolic blood pressure of 130 mm Hg or higher and/or a diastolic blood pressure of 85 mm Hg or higher; (2) a high-density lipoprotein cholesterol level 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) a triglyceride level of 150 mg/dL or more (≥1.69 mmol/L); (4) a glycated hemoglobin level higher than 6.1%28 because these data were not available in our data set; and (5) a waist circumference of more than 94 cm in men and more than 80 cm in women. Blood pressure was measured on 2 occasions,29,30 in a supine position with an automated device (model BP-8800; Colin Press-Mate, Komaki City, Japan), at 5-minute intervals, for 45 to 60 minutes; and in a sitting position, before the evaluations of cardiopulmonary fitness levels, with a sphygmomanometer (Spedl-Keller; Franken & Itallie, Amsterdam), after at least 5 minutes of rest (this was performed twice, and the lower value was recorded). The systolic and diastolic blood pressure values thus obtained were averaged and used in the analyses. High-density lipoprotein (and total) cholesterol and triglycerides were measured by enzymatic techniques (Roche Diagnostics, Mannheim, Germany), and glycated hemoglobin was determined 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 circumeter; Franken & Itallie) at the level midway between the lowest rib margin and the iliac crest.29

FATNESS, FAT DISTRIBUTION, CARDIOPULMONARY FITNESS, AND LIFESTYLE

From the age of 13 to 36 years, we repeatedly measured estimates of fatness, fat distribution, cardiopulmonary fitness, and lifestyle.29,20,31-34 We measured standing height, body weight, and biceps, triceps, subscapular, and suprailiac skinfolds. We calculated, as indicators of total body fatness, the body mass index (calculated as weight in kilograms divided by the square of height in meters) and the sum of the thickness of the 4 skinfolds. We used the ratio of the subscapular plus the suprailiac to the sum of skinfolds as an estimate of subcutaneous fat.30,33 We used maximal oxygen uptake (measured in milliliters per kilogram per minute) as a measure of cardiopulmonary fitness.30 Daily physical activity was measured by a structured interview that was especially developed for the Amsterdam Growth and Health Longitudinal Study and that has been shown to yield valid estimates of daily physical activity.30,34 Physical activities with a duration shorter than 5 minutes and an intensity of less than 4 times the resting metabolic rate (<4 metabolic equivalents [METs]) were not taken into account. All other physical activities were categorized into light-to-moderate (4-7 METs; eg, walking, gardening, and golf), hard (7-10 METs; eg, skating, tennis, and climbing stairs), and very hard (>10 METs; eg, running, swimming, and rowing).33 The time (calculated in minutes per week) spent in total, light- to-moderate, hard, and very hard activities was calculated and used in the analyses. Nutrient intake was measured with a cross-check dietary interview, in which the subjects were asked to recall their usual dietary intake, during the previous month, by reporting frequency, amounts, and methods of preparation of the foods and drinks consumed.34 We calculated the total energy intake (measured in megajoules [MJ]); the intake of proteins, fats, and carbohydrates (all expressed as percentage of total energy intake); the Keys score, which combines the intakes of saturated fatty acids, polyunsaturated fatty acids, and cholesterol; and alcohol consumption (measured in grams per week). Throughout the longitudinal period, smoking behavior (measured in grams per week) was measured by a separate questionnaire.34

STATISTICAL ANALYSIS

To investigate the time course of fatness, fitness, and lifestyle in the subjects who were identified with vs those without the metabolic syndrome at the age of 36 years, we used generalized estimating equations (GEEs) on the data available on these subjects from the age of 13 years to the age of 36 years. This method adjusts for the correlation between repeated observations taken in the same subject and has the advantage of handling longitudinal data on subjects with varying number and unequally spaced observations. In all GEE analyses, an exchangeable correlation structure was assumed. To estimate the “true” development from the age of 13 years to the age of 36 years of each variable investigated, time was treated as a categorical variable, and the results obtained were plotted.30 Fatness, fitness, dietary, and physical activity variables were analyzed as continuous variables. Smoking behavior and alcohol consumption were dichotomized (smokers vs nonsmokers and drinkers vs nondrinkers, respectively), and the prevalence of smokers and drinkers was analyzed with the logistic GEE, except that the prevalence of smokers at the ages of 16 and 27 years was too low to be estimated by the GEE models. All analyses were performed for men and women together because no significant interactions with sex were found. All the models were, therefore, adjusted for sex, and further for potential confounding and/or mediating variables. The GEE statistical analyses were performed with a procedure (GENMOD) from SAS statistical software, version 8.0 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

The prevalence of the metabolic syndrome at the age of 36 years in the study population was 10.4% (Table 1).
Subjects with the metabolic syndrome had a more marked increase, from adolescence to adulthood, in body mass index and in the sum of 4 skinfolds compared with those without the metabolic syndrome (Figure, A and B). These differences were significant at the ages of 21, 27, 32, and 36 years. Subjects with the metabolic syndrome, compared with those without the syndrome, had a lower skinfolds ratio at the ages of 13 to 15 years, but a more marked decrease in the skinfolds ratio from this age onward (Figure, C), resulting in significantly higher values at the ages of 21, 27, 32, and 36 years. Adjustments for lifestyle variables did not materially change these results (Table 2, model 2). Further adjustments for maximal oxygen uptake strengthened these differences (data not shown). Subjects with the metabolic syndrome were less likely to drink alcoholic beverages compared with subjects without the syndrome (Figure, M), a pattern that differed significantly at the age of 36 years (odds ratio [95% confidence interval], 0.41 [0.19-0.90]). This difference was independent of other lifestyle variables (odds ratio [95% confidence interval], 0.35 [0.13-0.91]), but decreased after further adjustment for body fatness (odds ratio [95% confidence interval], 0.41 [0.16-1.06]). Finally, the prevalence of smokers did not differ between the subjects with vs those without the metabolic syndrome (Figure, N).

**Table 1. Prevalence of the Metabolic Syndrome and Its Components in the Study Population at the Age of 36 Years**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men (n = 175)</th>
<th>Women (n = 189)</th>
<th>Overall (N = 364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure &gt;130/85 mm Hg</td>
<td>49.1</td>
<td>12.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Triglyceride level &gt;50 mg/dL</td>
<td>33.1</td>
<td>4.2</td>
<td>18.1</td>
</tr>
<tr>
<td>HDL cholesterol level &lt;40 mg/dL</td>
<td>28.0</td>
<td>21.7</td>
<td>24.7</td>
</tr>
<tr>
<td>Waist circumference &gt;94 cm in men</td>
<td>17.1</td>
<td>16.4</td>
<td>16.8</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>18.3</td>
<td>3.2</td>
<td>10.4</td>
</tr>
</tbody>
</table>

*Data are given as percentage of each group.*

**TIME COURSE OF TOTAL FATNESS AND SUBCUTANEOUS TRUNK FAT**

The development over time of fat and carbohydrate intake and the Keys score did not significantly differ between subjects with vs those without the metabolic syndrome at the age of 36 years (Figure, I-K, respectively). However, subjects with the metabolic syndrome had a higher energy intake (Figure, L), although this was statistically significant only at the age of 32 years (mean difference [95% confidence interval], 1.3 MJ [0.1-2.6 MJ]). Adjustments for other lifestyle variables and for body fatness and maximal oxygen uptake strengthened these differences (data not shown). Subjects with the metabolic syndrome were less likely to drink alcoholic beverages compared with subjects without the syndrome (Figure, M), a pattern that differed significantly at the age of 36 years (odds ratio [95% confidence interval], 0.41 [0.19-0.90]). This difference was independent of other lifestyle variables (odds ratio [95% confidence interval], 0.35 [0.13-0.91]), but decreased after further adjustment for body fatness (odds ratio [95% confidence interval], 0.41 [0.16-1.06]). Finally, the prevalence of smokers did not differ between the subjects with vs those without the metabolic syndrome (Figure, N).

**TIME COURSE OF CARDIOPULMONARY FITNESS AND PHYSICAL ACTIVITY**

We addressed the time course, from adolescence to adulthood, of potential determinants of the metabolic syndrome. The prevalence of the metabolic syndrome in this population of healthy 36-year-old subjects was 18.3% among men and 3.2% among women, a sex difference (ie, a higher prevalence in white men than in white women) that is consistent with other studies.\(^3,8,24\) We show that, compared with individuals without the metabolic syndrome at the age of 36 years, those with the syndrome are characterized, from the age of 13 years to the age of 36 years, by a greater increase in total and subcutaneous trunk fatness and a greater decrease in cardiopulmonary fitness. More important, these associations were independent of each other and, therefore, represent separate potential targets for the prevention of the metabolic syndrome. With regard to the (self-reported) lifestyle variables, a less consistent different pattern between those with vs those without the syndrome was found, with the exception of the time course of time spent in very hard-intensity physical activities, which decreased to a greater extent in those with the syndrome. Finally, these results suggest that the observed prevalence of the metabolic syndrome in young adults has its roots in the period of transition from
adolescence to adulthood. To our knowledge, this is the first study to comprehensively address these issues with a longitudinal design in young adults.

Body fatness, in particular, central fatness, is a well-recognized trigger of the syndrome, and is strongly associated with insulin resistance/hyperinsulinemia, dyslipid-
emia, and hypertension, even though the mechanisms linking fatness to these disorders are incompletely understood.\textsuperscript{14,15} Our data suggest that the increase in total and central fatness from adolescence to young adulthood may be critical for the development of the metabolic syndrome. Therefore, efforts to prevent the metabolic syndrome may most usefully be targeted at the prevention of excessive weight gain and central fat deposition in this period.

Table 2. Differences in Body Fatness and Subcutaneous Trunk Fat From Adolescence to Adulthood Between Subjects With vs Those Without the Metabolic Syndrome at the Age of 36 Years*\textsuperscript{a}

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Model</th>
<th>Body Mass Index\textsuperscript{a}</th>
<th>Sum of 4 Skinfolds, mm</th>
<th>Skinfolds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>1</td>
<td>-0.01 (-0.93 to 0.92)</td>
<td>2.11 (1.38 to 2.85)</td>
<td>0.55 (0.09 to 1.00)</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>0.10 (-0.78 to 0.99)</td>
<td>2.28 (1.50 to 3.06)</td>
<td>0.61 (0.22 to 1.01)</td>
</tr>
<tr>
<td>27</td>
<td>3</td>
<td>0.22 (-0.65 to 1.09)</td>
<td>2.10 (1.26 to 2.93)</td>
<td>0.62 (0.23 to 1.01)</td>
</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
<td>2.74 (1.63 to 3.85)</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td>3.53 (2.54 to 4.51)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Data are given as differences (95% confidence intervals) as estimated by generalized estimating equations.

*Model 1 is adjusted for sex; model 2, adjusted for sex plus lifestyle variables (total energy intake, relative intake of fat and carbohydrates, Keys score, total time spent in physical activities, being a drinker, and being a smoker); model 3, adjusted for the variables in model 2 plus maximal oxygen uptake.

†Calculated as weight in kilograms divided by the square of height in meters.

Table 3. Differences in Cardiopulmonary Fitness and Physical Activity Variables From Adolescence to Adulthood Between Subjects With vs Those Without the Metabolic Syndrome at the Age of 36 Years*\textsuperscript{a}

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Model</th>
<th>Maximal Oxygen Uptake, mL/kg per min</th>
<th>Total Physical Activity, min</th>
<th>Light-to-Moderate Activities, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>1</td>
<td>-0.25 (-3.98 to 3.47)</td>
<td>174 (4 to 346)</td>
<td>133 (-6 to 273)</td>
</tr>
<tr>
<td>27</td>
<td>2</td>
<td>-1.43 (-4.25 to 1.39)</td>
<td>380 (77 to 723)</td>
<td>107 (-27 to 240)</td>
</tr>
<tr>
<td>32</td>
<td>3</td>
<td>0.55 (-2.29 to 3.39)</td>
<td>390 (127 to 723)</td>
<td>118 (-56 to 252)</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td>369 (-121 to 197)</td>
<td>139 (-21 to 299)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Data are given as differences (95% confidence intervals) as estimated by generalized estimating equations.

*Model 1 is adjusted for sex; model 2, adjusted for sex, relative intake of fat and carbohydrates, Keys score, being a drinker and being a smoker; model 3, adjusted for the variables in model 2 plus the sum of 4 skinfolds; model 4, adjusted for the variables in model 2 plus maximal oxygen uptake; and model 5, adjusted for the variables in model 2, the sum of 4 skinfolds, and maximal oxygen uptake.

†Also adjusted for total time spent in physical activities.

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A greater decrease in cardiopulmonary fitness from adolescence to adulthood was also a characteristic of individuals with the metabolic syndrome, and this was in part independent of the increase in body fatness. This suggests that poor cardiopulmonary fitness may be associated with metabolic abnormalities characteristic of the metabolic syndrome partly because of its associations with body fatness and also because of other mechanisms that, again, are poorly understood but may involve insulin resistance, inflammation, thrombogenicity, and arterial stiffness, or a common genetic background that predisposes to low cardiopulmonary fitness and the metabolic syndrome.

With aging, individuals with vs those without the metabolic syndrome tended to spend more time being physically active, but this time was mainly in light-to-moderate intensity activities, whereas the time spent in very hard activities was considerably lower as early as at the age of 27 years. This suggests that individuals with the metabolic syndrome had a greater shift from very hard-intensity to light-to-moderate intensity activities than did those without the syndrome. Part of the association between lack of very hard physical activity and the metabolic syndrome seemed mediated through body fatness and even more through cardiopulmonary fitness. Fatness and fitness are pathways via which these kinds of activities impact favorably on the metabolic syndrome and cardiovascular health. Other studies have also shown physical activity, in particular, vigorous activity, to be inversely associated with the metabolic syndrome, but activities with an intensity as low as 4.5 METs also had beneficial effects. Our study, however, does not necessarily contradict those findings, which were obtained in older populations. Taken together, this may indicate that, with aging, physical activity of any intensity may be beneficial with regard to the prevention of the metabolic syndrome, and this again through mechanisms other than body fatness and cardiopulmonary fitness (eg, by reducing arterial stiffness, inflammation, and thrombogenicity). As such, promotion of (any kind) of physical activity remains a potential prevention target.

Individuals with the metabolic syndrome at the age of 36 years, compared with those without the syndrome, did not differ with regard to the relative contribution of macronutrients to their diet, but were characterized by greater energy intake in prior years. It is likely that this contributed to their increase in body fatness and prevalence of the metabolic syndrome. To further substantiate this conclusion, and because individuals with the metabolic syndrome also spent more time being physically active, we also calculated the energy balance, ie, the ratio between energy in (as estimated by dietary intake) and energy out (as estimated by the time and intensity of physical activities). This showed that, throughout the longitudinal period, a positive energy balance was in fact independent of the increase in body fatness in these individuals (β = 0.36; 95% confidence interval, −0.03 to 0.75), ie, an increase of 1 U/y in energy balance resulted in a 0.36-mm/y increase in the sum of skinfolds.

Drinking alcoholic beverages seemed to protect from the development of the metabolic syndrome, which is in agreement with others. Interestingly, this favorable association was independent of other lifestyle variables and, to an important extent, of body fatness. Moderate alcohol consumption protects against cardiovascular disease through mechanisms such as increases in insulin sensitivity, reduction of blood pressure, and increases in high-density lipoprotein cholesterol levels. Mechanisms that could, therefore, explain the beneficial associations with the metabolic syndrome.

Being a smoker seemed not to be associated with the metabolic syndrome, which might be explained by the relatively young age of the study population, the low prevalence of smoking during the adolescent period, and the fact that, in the present population, smoking was inversely associated not only with cardiopulmonary fitness but also with body fatness and blood pressure.

Lifestyle variables (such as physical activity and dietary intake) are difficult to measure, because they are subject to recall and misclassification bias, unlike cardiopulmonary fitness and body fatness, which can be more objectively measured. Another aspect is the well-known underreporting phenomenon of dietary intake among overweight and obese subjects. As such, the differences reported in the present study with regard to these variables may have been underestimated. In addition, these phenomena may also explain the somewhat less consistent associations found between the lifestyle variables and the metabolic syndrome compared with biological variables (fatness and fitness).

In conclusion, we investigated the time course of potential determinants of the metabolic syndrome from adolescence to adulthood. Our findings support the existence of multiple mechanisms in the pathogenesis of the metabolic syndrome, and these mechanisms may have their roots early in life. Our data support the usefulness of public health interventions targeting young people and relating to modifiable risk factors, such as weight control and promotion of physical activity, specifically, of vigorous intensity. These strategies may prevent the development of the metabolic syndrome and, therefore, its complications, such as cardiovascular disease and type 2 diabetes mellitus. Promotion of moderate drinking could also be beneficial, but implementation of such a strategy may be difficult, especially in young people, because the adverse effects of such a strategy may easily outweigh its beneficial effects.

Accepted for Publication: June 15, 2004.
Correspondence: Coen D. A. Stehouwer, MD, PhD, Department of Internal Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands (cda.stehouwer@vumc.nl)
Funding/Support: Dr Ferreira was supported by a joint research grant from the Foundation for Science and Technology (State Secretary of Science and Technology of Portugal) and the European Social Fund (Third European Community Framework Program).

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