Identifying Metabolic Syndrome without Blood Tests in Young Adults
The Terneuzen Birth Cohort

Marlou L.A. De Kroon ¹
Carry M. Renders ²
Esther C.C. Kuipers ¹
Jacobus P. Van Wouwe ³
Guus A. de Jonge ²
Stef Van Buuren ²,³
Remy A. Hirasing ¹


¹ Department of Public and Occupational Health, The EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, The Netherlands, ² Netherlands Organisation for Applied Scientific Research, TNO Quality of Life, Prevention and Health Care, Leiden, The Netherlands, ³ Department of Methodology and Statistics, Faculty of Social Sciences, University of Utrecht, Utrecht, The Netherlands
ABSTRACT

Background
Within the context of the obesity epidemic identifying young adults at risk for type 2 diabetes and cardiovascular disease is important. A practical approach is based on the identification of metabolic syndrome (MetS). Our objective was to develop a simple and efficient stepwise strategy to identify MetS in young adults.

Methods
Subjects were part of a birth cohort (n=2,599) in Terneuzen, the Netherlands, born in 1977-1986. In 2004-2005: 642 of these young adults participated in a physical examination and blood tests. Tree regression was used to determine the optimal decision strategy to identify MetS.

Results
Overall prevalence of MetS, defined according to the NCEP ATPIII, was 7.5%. The tree regression yielded an optimal stepwise strategy that eliminated the need for blood tests for the diagnosis of MetS in 50-90% of the cases, depending on the accepted level of error. A large group (52% of the total) with BMI <35 had a normal waist circumference (WC) and normal blood pressure (BP). None of them had MetS. Subjects with BMI $\geq$35 all had MetS. If BMI <30, 38% had an increased WC or increased BP with a risk of MetS of only 6%. So for them the omission of blood tests could also be considered.

Conclusion
In most young adults MetS can be identified or excluded without blood tests by a simple and stepwise strategy, based on the measurement of BMI, WC and BP. This makes it possible to develop simple prevention strategies for young adults at risk for type 2 diabetes and cardiovascular disease.
INTRODUCTION

The dramatic increase in the prevalence of obesity\textsuperscript{1-4} results in an increase in adverse levels of insulin and lipids, high blood pressure and type 2 diabetes, also in young adults.\textsuperscript{5} Consequently, vascular damage will also occur in younger age-groups.\textsuperscript{6,7} It is even anticipated that in the future more people will die from the complications of overnutrition than from starvation.\textsuperscript{5-7} For the development of prevention strategies early detection of persons who are at high risk for these complications of overweight and obesity is a prerequisite. MetS, is a cluster of risk factors for type 2 diabetes and cardiovascular disease.\textsuperscript{8-12} It is not sure that MetS as a cluster is better than its components in the prediction of cardiovascular disease. Besides, every component of MetS, in itself, merits specific attention and should be dealt with. However, it is also clear that the combined occurrence of these risk factors is associated with a high risk of the development of diabetes and cardiovascular disease, and - moreover - happens more often than could be expected on the basis of chance.\textsuperscript{13,14} This makes identification of MetS a practical approach and a useful tool to identify people who are at high risk. According to most definitions, MetS is based on concentrations of triglycerides, cholesterol, HDL-cholesterol and glucose. The blood tests that are necessary for the identification of MetS are an invasive and costly procedure. The objective of this study was to develop an efficient and simple stepwise strategy to identify MetS in young adults, based on data from the population-based Terneuzen Prevention Study. (Table 1).

METHODS

Design and study population

The Terneuzen Birth Cohort consists of all 2,599 children who were born between 1977 and 1986 in the city of Terneuzen. In 2004-2005, a total of 2,022 persons from the original cohort could be traced, and were invited to participate in a follow-up study. The follow-up study included measurements of weight, height, blood pressure (BP), and waist circumference (WC). Data on baseline characteristics were obtained from questionnaires. Information about cigarette smoking was also gathered because smoking is an important short and long term risk factor, that might cause dislipidemie, high triglycerides and low HDL cholesterol. The participants were also asked to
undergo a vena puncture, following a fast of at least 12 hours. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam, and written informed consent was obtained from all participants. Of the 2,022 subjects who were invited, 920 (45%) responded, 158 of whom did not participate for logistic reasons. Of the remaining 762 participants, 642 had a vena puncture, and the analyses presented here apply to these cases. No differences from the original cohort were found with regard to mean age, the age of the mother at birth, birth weight or parity. However, there was a significant gender difference: the percentage men in the original cohort was higher than in our study population.

Table 1. Adult Treatment Panel III definition of metabolic syndrome: at least three out of five criteria.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cut-off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Central obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td></td>
<td>Men &gt;102 cm</td>
</tr>
<tr>
<td></td>
<td>Women &gt;88 cm</td>
</tr>
<tr>
<td>2. Elevated triglycerides</td>
<td>Triglycerides ≥1.7 mmol/l</td>
</tr>
<tr>
<td>3. Reduced HDL-cholesterol</td>
<td>HDL-cholesterol</td>
</tr>
<tr>
<td></td>
<td>Men &lt;1.0 mmol/l</td>
</tr>
<tr>
<td></td>
<td>Women &lt;1.3 mmol/l</td>
</tr>
<tr>
<td>4. Raised blood pressure</td>
<td>Systolic ≥130 mmHg</td>
</tr>
<tr>
<td>5. Elevated fasting plasma glucose</td>
<td>Fasting plasma glucose ≥5.6 mmol/l</td>
</tr>
</tbody>
</table>

Physical examination and blood tests
The physical examinations were performed by two assistants who received standardized training at the Municipal Health Service in Terneuzen (GGD Zeeland). Weight was measured, with the subject in underwear, to the nearest 0.1 kg on an electronic self-zeroing scale. Standing height was measured to the nearest 0.1 cm with the aid of a stadiometer. WC was measured mid-way between the lower side of the lowest rib and the upper side of the pelvis, on bare skin, after a normal expiration, and
with muscles relaxed. BP was measured twice (with a 5 minute rest interval) on the left upper arm with the Omron 5-1, which is a fully automatic blood pressure monitor. The mean values were used as outcomes. Fasting venous blood samples were drawn in the clinical chemistry laboratory of the Community Hospital in Terneuzen. After centrifugation (10 minutes 1500xG), plasma was analyzed with a routine clinical chemical analyser, Synchron LX20PRO (Beckman Coulter Inc, USA). The parameters that were measured were glucose, cholesterol, HDL cholesterol, and triglycerides. External quality control was performed.\textsuperscript{15-17}

\textit{Statistical analysis}

The characteristics of the participants were summarized by means, standard deviations and percentages, sub-divided into three Body Mass Index (BMI=weight/height^2) categories. Age and gender-specific international BMI criteria for overweight and obesity were applied for the 17 years-olds, and adult cut-off points for all older participants.\textsuperscript{18} Differences in baseline characteristics and the prevalence of (components of) MetS between weight groups were assessed with \textit{t}-tests, ANOVA and \textit{\chi}^2 tests. Linear regression analysis was performed to study the relationships between variables, and the correlation between smoking and the components of MetS were tested with \textit{\chi}^2 tests, ANOVA and logistic regression analyses. Analyses were performed with SPSS statistical software, version 14.0 for Windows (SPSS Inc. Chicago ILL).

Tree regression analyses were performed with the S-PLUS 7 tree( ) function. Given a set of predictors, this method searches for the cut-off point on any of the predictor that will optimally discriminate MetS from non-MetS. Subsequently, the sample is split into two parts, and the process is repeated for each part. The process is repeated again until no further useful splits can be made. The result is a binary tree.\textsuperscript{19-20} BMI, WC, BP and the biochemical measurements were used as predictors. The binary tree was pruned and adapted in such a way that easily measured variables (BMI, WC, BP) were located at the top of the tree.
RESULTS

The mean age of the 642 participants was 23.1 years (23.2 for men and 23.0 for women), 68.5% were of normal weight, 21.2% were overweight (not obese), and 5.6% were obese. No differences in baseline characteristics were found between these three groups. The percentages of MetS components were substantially higher in overweight and obese subjects (Table 2). Significant linear associations were found between BMI and all MetS components ($p<0.001$). The overall prevalence of MetS in this group of young adults was 7.5%. In those with normal weight, overweight (not obese) and obesity, the percentage was respectively 1.7%, 16.2% and 50.0%. The percentage of smokers was respectively 29.7, 30.5, and 44.8% (Table 2).

When comparing the baseline characteristics of the total study population with those of subjects with MetS, it appeared that MetS more often occurred between 23 and 28 years of age than between 18 and 22 years of age (OR 1.27, 95%CI 1.09-1.45). The prevalence of MetS appeared to be higher in smokers than in non-smokers (9.2 vs 5.6%), but this difference was not statistically significant. Logistic regression showed a significant relation between smoking and triglycerides and HDL cholesterol, independent of BMI and gender. The frequencies of all components of MetS were higher in subjects with MetS than in subjects with no MetS, especially reduced HDL-cholesterol (70.8%) central obesity (77.1%) and elevated BP (87.5%) (Table 3).

Several binary regression trees were calculated. Figure 1 presents the final model, in which several branches have been combined into one branch to reduce complexity. The tree analysis showed that the most efficient categorization of BMI was very close to the usual discretization of BMI in obesity versus no obesity, but differed from the usual categories of BMI in normal weight, overweight and obesity (Table 2). If BMI $<30$, refining the BMI-categories was of no additional value in estimating the risk of MetS. However if the BMI $\geq 30$ estimates improved by dividing this category in two categories.
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Table 2. Subject characteristics, and (components of) metabolic syndrome related to BMI groups (n=642)

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Normal weight BMI &lt; 25</th>
<th>Overweight BMI ≥ 25 ≤ 30</th>
<th>Obesity BMI ≥ 30</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (%)</td>
<td>470 (68.5)</td>
<td>136 (21.2)</td>
<td>36 (5.6)</td>
<td>642 (100)</td>
</tr>
<tr>
<td>Subject Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) mean (SD)†</td>
<td>22.8 (2.9)</td>
<td>23.7 (2.7)</td>
<td>24.4 (2.9)</td>
<td>23.1 (2.9)</td>
</tr>
<tr>
<td>Gender, men in % (n)†</td>
<td>42.6 (200)</td>
<td>40.4 (55)</td>
<td>30.6 (11)</td>
<td>41.4 (266)</td>
</tr>
<tr>
<td>BMI: mean (SD) ‡</td>
<td>21.6 (2.0)</td>
<td>26.9 (1.3)</td>
<td>33.2 (3.0)</td>
<td>23.4 (3.7)</td>
</tr>
<tr>
<td>Smoking cigarettes, in % †</td>
<td>29.7</td>
<td>30.5%</td>
<td>44.8%</td>
<td>30.6%</td>
</tr>
<tr>
<td>Level of education % (n)†</td>
<td>441</td>
<td>129</td>
<td>34</td>
<td>604†</td>
</tr>
<tr>
<td>low, in % (n)†</td>
<td>18.1 (80)</td>
<td>24.8 (32)</td>
<td>23.5 (8)</td>
<td>19.9 (120)</td>
</tr>
<tr>
<td>medium, in % (n)†</td>
<td>60.1 (265)</td>
<td>54.3 (70)</td>
<td>58.8 (20)</td>
<td>58.8 (355)</td>
</tr>
<tr>
<td>high, in % (n)†</td>
<td>21.8 (96)</td>
<td>20.9 (27)</td>
<td>17.6 (6)</td>
<td>21.4 (129)</td>
</tr>
<tr>
<td>(Components of) MetS in %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central obesity‡</td>
<td>1.1</td>
<td>30.9</td>
<td>86.1</td>
<td>12.1</td>
</tr>
<tr>
<td>High blood pressure§</td>
<td>39.4</td>
<td>48.5</td>
<td>63.9</td>
<td>42.7</td>
</tr>
<tr>
<td>Low HDL-cholesterol§</td>
<td>24.9</td>
<td>36.0</td>
<td>58.3</td>
<td>29.1</td>
</tr>
<tr>
<td>High triglycerides§</td>
<td>5.1</td>
<td>14.0</td>
<td>19.4</td>
<td>7.8</td>
</tr>
<tr>
<td>High fasting plasma glucose§</td>
<td>9.8</td>
<td>14.7</td>
<td>25.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Metabolic syndrome‡</td>
<td>1.7</td>
<td>16.2</td>
<td>50.0</td>
<td>7.5</td>
</tr>
</tbody>
</table>

*Persons with underweight (BMI < 18.50; n=30) are included in the normal weight category: no statistical differences concerning subject characteristics and MetS (components) were found between underweight and normal weight persons, † no statistical significance, ‡ p<0.001, § p=0.005, §§ p=0.011, * missing data for n=38, ** missing data for n=57.

Figure 1 shows the following:
- In participants with BMI ≥35, the risk of MetS is 100%.
- In participants with BMI ≥30 and BMI <35, the overall risk is 35.7%. The risk greatly depends on WC and BP. When both are elevated the risk is 64.3%,
when only one is elevated the risk is 8.3%, but when neither are elevated the risk is zero.

- With a BMI <30, the overall risk is 5.0%. If both WC and BP were elevated the risk is 66.7%, if only one of these is elevated it is 5.6%, but if neither are elevated the risk is zero.

Note that: 1) 48 out of 642 participants were definitely classified as having MetS, 2) 334 out of 642 participants were definitely classified as not having MetS, and 3) 250 out of 642 participants could be classified as not having MetS with an error rate of 5.6%. If we are prepared to accept this error, then 583 out of 642 (90%) can be classified with a tiny error without the need for a blood sample.

Table 3. Subject characteristics and components of metabolic syndrome in subjects with MetS compared to subjects with no MetS (in %).

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>MetS (n=48)</th>
<th>No MetS (n=594)</th>
<th>All participants* (n=642)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) mean (SD)†</td>
<td>24.0 (2.8)</td>
<td>23.0 (2.9)</td>
<td>23.1 (2.9)</td>
</tr>
<tr>
<td>Gender (men %)†</td>
<td>35.4</td>
<td>41.9</td>
<td>41.4</td>
</tr>
<tr>
<td>BMI category (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight (in %)</td>
<td>16.7</td>
<td>77.8</td>
<td>73.2</td>
</tr>
<tr>
<td>Overweight (in %)</td>
<td>45.8</td>
<td>19.2</td>
<td>21.2</td>
</tr>
<tr>
<td>Obesity (in %)</td>
<td>37.5</td>
<td>3.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Smoking, (%)†</td>
<td>39.6</td>
<td>26.9</td>
<td>27.9</td>
</tr>
<tr>
<td>Level of education (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>34.1</td>
<td>18.8</td>
<td>19.9</td>
</tr>
<tr>
<td>Medium</td>
<td>47.7</td>
<td>59.6</td>
<td>58.3</td>
</tr>
<tr>
<td>High</td>
<td>18.2</td>
<td>21.6</td>
<td>21.4</td>
</tr>
<tr>
<td>Components of MetS(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central obesity‡</td>
<td>77.1</td>
<td>6.9</td>
<td>12.1</td>
</tr>
<tr>
<td>High triglycerides‡</td>
<td>45.8</td>
<td>4.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Low HDL-cholesterol‡</td>
<td>70.8</td>
<td>25.8</td>
<td>29.1</td>
</tr>
<tr>
<td>High blood pressure‡</td>
<td>87.5</td>
<td>39.1</td>
<td>42.7</td>
</tr>
<tr>
<td>High fasting plasma glucose‡</td>
<td>43.8</td>
<td>9.1</td>
<td>11.7</td>
</tr>
</tbody>
</table>

† p <0.05, ‡ p <0.001, † not statistically significant
Figure 1. Tree model for the risk on MetS in percent (n = number of subjects) and decision to perform lab tests.
**DISCUSSION**

The results of this observational study shows that with this simple stepwise strategy most young adults with MetS can be identified or excluded by use of BMI, waist circumference and blood pressure without any need for blood tests.

Tree regression analysis showed that MetS is present in all young adults with a BMI $\geq 35$. For these young adults no additional blood tests or measurements are needed to identify those who are at high risk of developing type 2 diabetes and/or cardiovascular disease. If BMI $<35$, BP and WC should be measured. If both are normal, there is no risk of MetS, and blood tests are of no additional value in assessing MetS. If BMI $<35$, and both WC and BP are elevated, the risk of MetS is high, and additional blood tests should be performed. If only WC or only BP is elevated, the risk of MetS is comparable to the risk in the general population of young adults. In such cases the decision to perform additional diagnostic blood tests might depend on other factors, such as the absolute WC or BP, and smoking habits.

The overall prevalence of MetS in our study sample was 7.5%, which is comparable with the prevalence (5.2-10.3%) of MetS among young adults in Finland. However, it was lower than that found in two other Dutch studies among young adults, in which the age of the subjects was higher than in our study. This is consistent with the finding that the prevalence of the MetS depends on age. The frequencies of (components of) MetS were significantly higher in overweight or obese subjects. The components of MetS that were most frequently found were a high WC, high BP and a low HDL-cholesterol. However, the stepwise method does not require the assessment of HDL-cholesterol in the majority of cases. The frequencies of obesity and a high WC in our study correspond with the frequencies reported in young adults in the Netherlands. However, the percentage of young adults with an elevated BP in our study was higher than in other studies. This could be the consequence of increased childhood obesity carrying over into adulthood. The prevalences of low HDL-cholesterol and raised triglycerides are similar to those reported in other studies.

Of the 2,022 subjects who were invited to participate, 642 provided all data. Our sample might therefore be selective. However, we found no statistically significant
differences in any of the known variables of the original cohort, with the exception of gender. We do not expect that this gender difference will influence the findings, because we found no gender differences in the main analysis.

The cut-off points for the different components of MetS according to the NCEP ATP III 2005 definition, are based on samples that are older than our study population. Since the levels of cardiovascular risk factors are associated with age, these cut-off points might under-estimate the number of young adults who are at risk of developing type 2 diabetes and cardiovascular disease.

MetS increases the risk of cardiovascular morbidity and mortality 1.3 to 3 times and triples the risk of diabetes. The prognosis of type 2 diabetes with onset at an earlier age is even worse, causing a decline in quality of life and a shorter life-expectancy. Since MetS was found in over 7% of our sample, there is an urgent need to identify young adults with MetS and to develop prevention and treatment programs for this specific age-group. This is especially important because these youngsters seldom consult medical professionals.

Note that the tree model was based on just one single data set, and is restricted to people under 30 years of age. Because of the risk of data-fitting, we recommend that our results should be validated in other samples. As the prevalence of MetS increases with age, optimal trees for samples of other ages may be potentially quite different. However, the same methodology can be applied to suitable data from other age groups.

Despite the limitations in the study design, our results show great potential for the development of prevention strategies for young adults who are at high risk for type 2 diabetes and cardiovascular disease in the primary health care setting. Also in less frequent combinations, such as a BMI between 30 and 35 and a normal WC and BP (5.6% of the persons with this BMI), the omission of blood tests may have an important impact at population level. A blood test is not a very high risk test, and has a relatively limited burden at individual level. But, from a public health point of view, the burden is of much more concern. With regard to the rapid increase in the prevalence of overweight and obesity, the medical burden, the costs and time investments are enormous. Additional information on WC and BP, especially in those
with a BMI <30 will result in the need for fewer blood tests. The public health focus is
on the management of excess weight, and not primarily on blood tests for lipid
profiling. Lifestyle modification may be sufficient to prevent disease progression.
Serological tests for lipid profiling are often not needed to assess or exclude MetS.
However, for high risk groups the decision to request blood tests will also depend on
therapeutic considerations, certainly if lifestyle modification does not succeed or does
not produce the required result (Figure 1).

By following simple, stepwise methods in the diagnosis of MetS tremendous savings
could be made in terms of laboratory and consultancy costs. Depending on the accepted
level of error, between 50% and 90% of blood tests are superfluous for the diagnosis of
MetS. Because there is a need for identifying young adults who are at risk for type 2
diabetes and cardiovascular disease, cost-effective prevention and effective treatment
programs must be developed. Because of the prevalence and the risk of smoking, this is
a very important lifestyle factor that should be dealt with in young people, especially in
those with even more risk factors related to overweight. Youngsters who smoke and
are diagnosed with MetS, should be offered an even more rigorous prevention program
that focuses on several lifestyle factors, directed at both smoking and weight reduction.
Our results can contribute to the development of more efficient, cheaper, and less
invasive ways to assess the presence of MetS in young adults.

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manuscript and principal investigator had full access to all the data in the study, and
takes responsibility for the integrity of the data and the accuracy of the data-analysis.
REFERENCES


