One year follow-up of patients with screen-detected metabolic syndrome in primary care: an observational study

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Background. Early detection and appropriate treatment of metabolic syndrome (MetS) can modify cardiometabolic risk factors and prevent cardiovascular disease. Optimal screening outcomes require follow-up management of MetS.

Objective. To investigate the natural course of events in the first year after positive screening for MetS in primary care with regard to follow-up behavior, medication prescription and lifestyle changes.

Methods. Screening of 1721 apparently healthy primary care patients (20–70 years old) detected 473 new MetS cases. These people were asked to contact their general practice for subsequent advice and treatment. Data about follow-up behavior of the screening participants and prescription of cardiovascular medication were collected from the electronic medical file, and changes in lifestyle were collected by the practice nurse.

Results. Of the 424 participants with screen-detected MetS for whom data about follow-up were available, 306 (72.2%) spontaneously contacted the practice. Antihypertensive, lipid-lowering and blood glucose-lowering medications were prescribed in 21.5%, 21.2% and 1.9% of the participants, respectively. Half of the participants for whom data about self-reported lifestyle changes were available reported to have increased their physical activity; 16.9% of the smokers quit smoking. Average weight loss was 2.1 kg.

Conclusions. Screening for MetS followed by the advice to contact the general practice for lifestyle counseling and treatment had a substantial spontaneous follow-up. Although the changes in physical activity, weight loss and smoking abstinence are promising, further research will have to demonstrate whether they are sustainable.

Keywords. Metabolic syndrome, screening, abdominal obesity, primary care, prevention.

Introduction

With the increasing prevalence of overweight and obesity, the number of people with hypertension, dyslipidemia and an impaired glucose is rising, leading to an increase of cardiovascular disease and type 2 diabetes. Early detection and treatment could diminish cardiovascular risk factors and prevent cardiovascular disease.1–4 A combined screening for risk factors such as diabetes, hypertension and dyslipidemia is most cost-effective.5 The metabolic syndrome (MetS) refers to a clustering of such risk factors.6 MetS is associated with an increased risk of developing both type 2 diabetes and cardiovascular disease and an up to 4-fold increased risk of mortality from cardiovascular disease.7–10 Ideally, detection of MetS should be followed by relevant counseling and treatment. Patients should be encouraged to adapt a healthier lifestyle, since positive lifestyle modifications are the cornerstones of the treatment of MetS.11 The IJsselstein Study of Central Obesity to detect metabolic syndrome (IJSCO) is a longitudinal study that evaluates the feasibility and yield of screening for MetS among apparently healthy individuals as well
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as the short- and long-term results of the screening. This paper focuses on the short-term results. Our aim was to investigate follow-up behavior, medication prescription and lifestyle changes in the first year after positive screening for MetS in primary care. Our design was pragmatic, in accordance with daily practice rather than a tightly regulated trial protocol: upon contacting the general practice for their screening results, the people with screen-detected MetS were subsequently invited to visit the general practice for usual care according to existing guidelines. This design enables us to follow the natural course of events after the screening.

Methods

Setting and participants

The screening study took place in IJsselstein, The Netherlands, in five cooperating general practices. Almost 12 000 patients between 20- and 70-years and not previously diagnosed with diabetes, hypertension, dyslipidemia or cardiovascular disease were eligible. The first screening step was self-measurement of waist circumference with a home-mailed tape measure, followed by a physical examination (height, weight, waist circumference and blood pressure) and laboratory investigation (fasting glucose and lipid profile) when self-measured waist circumference was ≥88 cm in women or ≥102 cm in men. Further details have been described elsewhere;12,13 1721 individuals with an increased self-measured waist circumference underwent follow-up examinations and 473 were subsequently diagnosed with MetS, defined according to The National Cholesterol Education Program’s Adult Treatment Panel III (NCEP ATP III) criteria (Table 1).6 People who participated in the examinations were asked to contact their general practice for their test results. All participants with newly diagnosed MetS were subsequently invited to visit the practice nurse for a consultation.

Outcome measures

The main outcome measures were follow-up behavior of the screened participants (contacting the general practice, visits to the practice nurse or general practitioner, the need for a reminder), prescription of cardiovascular medication and changes in lifestyle with regard to smoking status, physical activity, consultation with a dietician and weight loss in the first year after screening.

Data collection

A detailed description of the baseline measurements has been published previously.13 At baseline participants completed a questionnaire to determine ethnicity, education level and lifestyle factors (smoking and physical activity). Physical activity was assessed using the SQUASH questionnaire, which has proven to be fairly reliable and reasonably valid.15 It measures habitual activities with respect to occupation, leisure time, household tasks, transportation means and other daily activities.

Data about follow-up behavior and prescription of antihypertensive, lipid- or blood glucose-lowering medications were collected from the electronic medical record. Data regarding change in smoking status, consultation with a dietician and change in physical activity level were collected on a case report form by the practice nurse. The latter data are only available for the screening participants who actually visited the practice nurse.

Data analysis

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviations (SD) and non-normally distributed variables as median with interquartile range (IQR).

Differences between patients who did and did not spontaneously contact the general practice for their screening results were tested using Chi-square tests for categorical variables, independent t-tests for normally distributed continuous variables and Mann-Whitney tests for non-normally distributed continuous variables.

General practitioners and practice nurse had access to the guideline ‘Cardiovascular Risk Management’ of the Dutch College of General Practitioners (Fig. 1).14 The use of this guideline was at the discretion of the general practitioners and practice nurse. Notably, we did not instruct the general practitioner or the practice nurse to follow any protocol; we simply informed them which patients were detected with MetS at screening.

The practice staff made a phone call or sent a postal reminder to the participants who were diagnosed with MetS but did not contact their general practice, as well as to those who contacted the practice but did not visit the practice nurse, to invite them for a consultation with the practice nurse.

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Table 1: The metabolic syndrome according to the definition of the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP ATP III)

<table>
<thead>
<tr>
<th>Metabolic syndrome component</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>≥102 cm in men</td>
</tr>
<tr>
<td></td>
<td>≥88 cm in women</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>≥1.7 mmol/l</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Systolic ≥130 mmHg or Diastolic ≥85 mmHg</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;1.0 mmol/l in men</td>
</tr>
<tr>
<td></td>
<td>&lt;1.3 mmol/l in women</td>
</tr>
<tr>
<td>Fasting serum glucose</td>
<td>≥6.1 mmol/l</td>
</tr>
</tbody>
</table>

The metabolic syndrome is present, when one has at least three of the abovementioned five components.

HDL cholesterol, high-density lipoprotein cholesterol.
Analyses were performed using SPSS for Windows version 17.0.

Of the 306 participants who spontaneously contacted the general practice, 228 did not need a reminder (group 1), but 130 participants did (group 2). Thirty-five participants visited the practice after a reminder, but no risk profile was recorded (group 3), and 31 participants visited as a result of the screening. They also had a mean systolic blood pressure of 140 mmHg.

For 49 participants with screen-detected MetS, data about spontaneously contacting the practice were not available, since the general practitioner took the initiative to contact them because of an impaired fasting glucose.

Participants who spontaneously contacted the general practice were significantly older (48.4 versus 45.3 years, \( P < 0.01 \)), more often of Western European origin (96.1 versus 91.3\%, \( P = 0.05 \)) and had a lower body mass index (BMI) (30.0 versus 31.2 kg/m\(^2\), \( P = 0.01 \)) and waist circumference (99.1 versus 102.6 cm in women, \( P = 0.02 \); 109.5 versus 111.4 cm in men, \( P = 0.13 \)) than participants who needed a reminder for contacting the general practice.

Of the 306 participants who spontaneously contacted the general practice, 79 received a reminder because they did not visit the practice nurse, on average 4.0 months after the screening.

In the year after the screening, the cardiovascular risk profile was recorded for 358 of the 424 participants (84.4\%) with screen-detected MetS. Of those, 228 did not need a reminder (group 1), but 130 participants did (group 2). Thirty-five participants visited the practice once, but no risk profile was recorded (group 3), and 31 screening participants never visited the practice, despite reminders (group 4) (Fig. 2). Participants who never visited the general practice were significantly younger (42.3 versus 47.9 years, \( P < 0.01 \)) and more often male (67.7 versus 49.4\%, \( P < 0.05 \)) than the participants who visited as a result of the screening. They also had a higher BMI (32.2 versus 30.2 kg/m\(^2\), \( P < 0.01 \)) and waist circumference (113.8 versus 109.7 cm in men, \( P = 0.01 \); 102.8 versus 99.9 cm in women, \( P = 0.35 \)). Patient characteristics of the different groups are shown in Table 2.

Results

Follow-up behavior

For 49 participants with screen-detected MetS, data about follow-up were not available for various reasons (Fig. 2). Follow-up data were collected for 424 participants. Of these, 306 (72.2\%) participants spontaneously contacted the general practice for their screening results; 115 (27.1\%) received a reminder to do so, on average after 3.2 months. For three participants (0.7\%), data about spontaneously contacting the practice were not available, since the general practitioner took the initiative to contact them because of an impaired fasting glucose.

Participants who spontaneously contacted the general practice were significantly older (48.4 versus 45.3 years, \( P < 0.01 \)), more often of Western European origin (96.1 versus 91.3\%, \( P = 0.05 \)) and had a lower body mass index (BMI) (30.0 versus 31.2 kg/m\(^2\), \( P = 0.01 \)) and waist circumference (99.1 versus 102.6 cm in women, \( P = 0.02 \); 109.5 versus 111.4 cm in men, \( P = 0.13 \)) than participants who needed a reminder for contacting the general practice.

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screening was 157.3 mmHg (range 130–225 mmHg, SD 17.2 mmHg). Angiotensin-converting-enzyme (ACE) inhibitors (46.2%) and diuretics (45.1%) were the antihypertensive drugs most often prescribed, followed by beta blockers (22.0%), angiotensin II receptor antagonists (20.9%) and calcium channel blockers (6.6%). Twenty-one participants (23.1%) used antihypertensive drugs from two of these groups, eight (8.8%) used antihypertensive drugs from three different groups. In 90 participants (21.2%) lipid-lowering medication was started (96.7% a statin, 3.3% a statin combined with ezetimibe). The mean low-density lipoprotein (LDL) cholesterol for these patients was 4.3 mmol/l (range 3.0–6.0 mmol/l, SD 0.8 mmol/l).

Eight participants (1.9%) started blood glucose-lowering medication. Their mean fasting blood glucose at screening was 9.6 mmol/l (range 6.2–16.0 mmol/l). Six were diagnosed with type 2 diabetes at screening and started blood glucose-lowering medication within several weeks, the other two started medication several months after screening. Blood glucose-lowering medication was only prescribed for diagnosed type 2 diabetes, not for prevention. Seven participants used metformin monotherapy, one combined metformin with a sulfonylurea.

For 274 participants (64.6%), none of the above-mentioned drugs was prescribed.

Changes in lifestyle
In 315 participants (74.3%), data about self-reported lifestyle changes were collected within 12 months of positive screening.

Smoking. At baseline, 71 (22.5%) were current smokers. Twelve participants (16.9%) had stopped smoking at the end of the follow-up period. Four of the 244 (1.6%) non-smokers at screening started to smoke (again).

Physical activity. At baseline, 176 participants (55.9%) adhered to the Dutch Standard Healthy Movement, and 138 did not (43.8%). Within the first year after screening, 40.9% of those who did adhere and 59.4% of those who did not adhere reported that they had increased their level of physical activity; 80.1% of the first group and 59.4% of the latter group now considered themselves adherent to the Dutch Standard Healthy Movement.

Dietician. In total, 42 (13.3%) participants reported that they had consulted a dietician. There were no significant differences in age, gender distribution, BMI or mean levels of MetS components between the participants who did and did not consult a dietician (data not shown).

Weight loss. A weight measurement was obtained for 285 individuals from the electronic medical file. After an interval of 7.6 months the average weight loss was 2.1 kg (range –28.0 to 14.0 kg, SD 5.1).

Discussion

Comparison with existing literature
Our aim was to investigate the natural course of events in the first year after positive screening for MetS in primary care with regard to follow-up
behavior, medication prescription and lifestyle changes. The participants had to take the first step to get their screening results, which makes our design unique. In publications concerning pharmacy-based screening studies the results were immediately given to the screened participants, usually accompanied by lifestyle recommendations and if necessary the advice to consult a doctor.17–20 One study provided data on uptake of follow-up care, which was 83%.20 In this study, the participants were actively referred to a doctor and already informed about their condition and the need for medical treatment, which is likely to have influenced their decision to visit a doctor. In none of the studies, participants had to take the initiative. To the best of our knowledge, no studies describing spontaneous follow-up behavior after cardiometabolic screening in general practice have been published.

About half of the patients reported to have increased their level of physical activity, which is less than the almost 70% adherence to physical activity recommendations described by Yang et al., among patients with prediabetes.21 The measurements by Yang et al. with an activity monitor were probably more objective than our measurements. However, the difference between the populations with regard to their baseline physical activity level (56% of our study population versus 6% of Yang’s population engaged in moderate or vigorous physical activity) was rather big.

Seventeen percent of the smokers quit smoking. This is comparable to the rate reported in a meta-analysis (16.3% after 2–3 intervention sessions).22 The majority of our screening participants visited the practice nurse at least twice. It is likely that in both consultations smoking behavior received attention. We hypothesize that suddenly being confronted with an increased cardiovascular risk might have been an extra motivation to quit smoking.

### Consequences for the general practices

The number of participants spontaneously contacting the practice for their test results is considerably high. Of course, they had already shown their interest by participating in the physical examination after their own waist circumference measurement. The high spontaneous contact rate saves the practice staff the effort of actively contacting all participants and sending reminders. Because the practices already had a recall system it

### Table 2  Different categories of patients with screen-detected metabolic syndrome, based on follow-up behavior

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group</th>
<th>Group 1a</th>
<th>Group 2b</th>
<th>Group 3c</th>
<th>Group 4d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 424</td>
<td>n = 228</td>
<td>n = 130</td>
<td>n = 35</td>
<td>n = 31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.5 ± 10.2</td>
<td>48.0 ± 10.1</td>
<td>47.8 ± 10.3</td>
<td>47.8 ± 11.4</td>
<td>42.3 ± 8.2^f</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>50.7</td>
<td>47.8</td>
<td>50.8</td>
<td>54.3</td>
<td>67.7</td>
</tr>
<tr>
<td>Ethnicity (% Western European)</td>
<td>94.6</td>
<td>96.1</td>
<td>93.1</td>
<td>94.3</td>
<td>90.3</td>
</tr>
<tr>
<td>Higher education level (%)</td>
<td>31.4</td>
<td>27.8</td>
<td>33.6</td>
<td>42.9</td>
<td>38.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.4 ± 3.9</td>
<td>30.0 ± 3.7</td>
<td>30.5 ± 3.7</td>
<td>30.1 ± 4.4</td>
<td>32.2 ± 5.1^b</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>110.1 ± 7.3</td>
<td>109.6 ± 6.1</td>
<td>110.0 ± 8.3</td>
<td>108.9 ± 7.7</td>
<td>113.8 ± 8.5^b</td>
</tr>
<tr>
<td>Women</td>
<td>100.0 ± 9.5</td>
<td>99.2 ± 9.8</td>
<td>100.4 ± 8.7</td>
<td>103.0 ± 9.5</td>
<td>102.8 ± 10.5</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>144.3 ± 15.4</td>
<td>145.1 ± 14.8</td>
<td>142.9 ± 15.6</td>
<td>147.7 ± 18.0</td>
<td>139.7 ± 15.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>88.8 ± 8.0</td>
<td>89.1 ± 7.6</td>
<td>88.2 ± 8.5</td>
<td>90.0 ± 8.2</td>
<td>87.6 ± 8.3</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.09 ± 0.26</td>
<td>1.10 ± 0.28</td>
<td>1.10 ± 0.25</td>
<td>1.11 ± 0.22</td>
<td>1.02 ± 0.25</td>
</tr>
<tr>
<td>Women</td>
<td>1.32 ± 0.32</td>
<td>1.31 ± 0.33</td>
<td>1.35 ± 0.30</td>
<td>1.34 ± 0.33</td>
<td>1.18 ± 0.21</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.9 (1.6-2.4)</td>
<td>1.9 (1.6-2.4)</td>
<td>1.9 (1.5-2.3)</td>
<td>2.0 (1.7-2.4)</td>
<td>1.8 (1.7-2.6)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.2 ± 1.0</td>
<td>5.2 ± 1.2</td>
<td>5.2 ± 0.6</td>
<td>5.3 ± 1.0</td>
<td>5.1 ± 0.6</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.4 ± 0.9</td>
<td>3.4 ± 0.9</td>
<td>3.4 ± 0.9</td>
<td>3.5 ± 0.9</td>
<td>3.1 ± 0.8</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>24.8</td>
<td>25.0</td>
<td>23.1</td>
<td>31.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Adherence to Dutch Standard Healthy Movement (%)^e</td>
<td>55.5</td>
<td>55.5</td>
<td>58.5</td>
<td>52.9</td>
<td>45.2</td>
</tr>
</tbody>
</table>

Data are reported as means ± standard deviation or percentage. Not normally distributed variables are reported as median (25th to 75th percentile).

^aGroup 1: Spontaneously contacted the general practice for the screening results, paid at least one visit and had their cardiovascular risk profile recorded, without needing a reminder.

^bGroup 2: As group 1, but with the need of a reminder.

^cGroup 3: Paid a visit but needed a reminder to do so, no recording of cardiovascular risk profile.

^dGroup 4: No visit, despite a reminder.

^eDutch Standard Healthy Movement: A minimum of 30 minutes of moderately intensive exercise at least five days a week.

^fP < 0.05 for group 4 versus all other groups.

^gP < 0.05 for group 4 versus group 1.

^hP < 0.05 for group 4 versus group 1 and 2.

BMI, body mass index; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol.
was relatively easy to include the newly detected MetS patients into this system, thereby limiting the extra administrative workload. A benefit of the screening for the general practices was that it provided them with an overview of previously unknown high-risk patients. For 84% of the participants in whom MetS was detected, the practice had a complete cardiovascular risk profile one year after the screening. In these high-risk patients, this risk profile provides the opportunity for recommending appropriate lifestyle modifications. After lifestyle, residual risk for cardiovascular disease needs to be treated with appropriate drugs.23

A requirement for successfully initiating a screening is the availability of an effective treatment for patients identified through early detection. The guidelines for Cardiovascular Risk Management and Type 2 diabetes mellitus of the Dutch College of General Practitioners give clear guidance on how to treat the patients.14,24

Another requirement is the infrastructure to handle the extra clinical workload resulting from screening; successful implementation may increase the demand on practice nurse services. The general practices involved in our study anticipated the expected increase in patients qualifying for cardiovascular risk management. They employed one additional practice nurse; she had office hours in all the participating practices.

Consequences for the screening participants

This screening may have had several benefits for the participants. They became aware of their increased cardiovascular risk and possibly unhealthy lifestyle, and counseling and guidance were offered to improve their health. Both medical treatment and a healthier lifestyle might have led to cardiovascular risk reduction.

We found no significant differences in baseline characteristics between the participants who did (group 2) and did not (group 1) need a reminder before entering a follow-up regimen. It might just have escaped their attention to contact the general practice for the results or make an appointment. However the people who did not visit the practice at all, despite a reminder, were younger, more often male, and had a higher BMI and waist circumference. We do not know whether these patients experienced benefits due to the screening. Men are less likely to use health services and seek help from health professionals than women.25 An important explanation for this reluctance, especially among younger white men, is the belief that health seeking behavior is not masculine.25–27 This might be a reason why a small subset of males in our study seems reluctant to seek health advice. Participating in the screening might not so much be regarded as health seeking; contacting the general practice however is health seeking behavior.

In a cardiovascular screening program in supermarkets, participants had their cardiovascular risk factors determined, immediately followed by a 10-minute debriefing counseling session. Participants who saw a physician after the screening were more likely to be older individuals, women and individuals with a lower education level.28 In our population the participants more involved in follow-up care (groups 1 and 2) also had a lower education level than the participants less involved (groups 3 and 4), although this difference was not significant. This is a remarkable finding, since other studies showed that lower educated people are a difficult group to keep involved in health-promoting activities.29–31 The follow-up setting—inside the general practice—and the deliverance of care by familiar health care providers is likely to enhance their participation; trust seems to be crucial in health care settings.32

Strengths and limitations of the study

The main strength of the current study was its observational design, allowing for an investigation of the real-life impact of cardiometabolic screening. This design has some limitations as well. Our main data source was the electronic medical record. We expect data with regard to the number of consultations to be reliable, since this was also linked with declaration of the costs to the health care insurance. There might be missing data with regard to the content of the consultations. The recordings of the practice nurse however were very structured. The cardiovascular risk profile was a separate option in the electronic medical file, which makes it less likely to oversee items. So, in general, we expect to have a good overview of the one-year follow-up. We assumed that if a cardiovascular risk profile was recorded in the electronic medical file, the patient also was educated about his health status and received lifestyle advice.

The practice nurse was asked to collect data about changes in lifestyle, which could have made her more alert to addressing lifestyle issues. This may have led to an overestimation of the delivery of care.

Data about changes in level of physical activity were self-reported and might be too optimistic.

Public health consequences

As demonstrated previously, a population-based screening for MetS with self-measurement of waist circumference as a first step is a feasible and reliable method to identify people with MetS. The negative predictive value of 96% indicates that with the used screening method and cut-off point for waist circumference the majority of people with MetS are identified.12,13 The present paper shows that screening for MetS in general practice followed by the advice to contact the general practice for the screening results and care as usual has a substantial spontaneous follow-up and promising short-term results with regard to lifestyle modifications and weight loss. Long-term outcomes will be awaited.
for. Screening costs were €366.97 per detected MetS case ($n = 473$). Cost-effectiveness analyses have shown that costs per quality adjusted life year could improve if screening for diabetes, hypertension and dyslipidemia is combined. Treatment of cardiovascular risk factors to prevent cardiovascular disease was also proven to be cost-effective. Considering these facts, we think that our policy might be cost-effective.

There are no general practices in The Netherlands routinely screening for MetS among apparently healthy people. In 2011 a guideline was published to improve the early detection and management of patients with an increased risk for cardiovascular disease and type 2 diabetes. Individuals between 45 and 70 years of age without known cardiometabolic diseases and who do not use anti-hypertensive or lipid-lowering treatment are eligible for this Prevention Consultation. Pilots showed that with a ‘passive’ recruitment (with only posters and brochures), screening uptake was limited. Our more active approach with a personal invitation from the general practitioner was more effective. To detect people with MetS, our approach with self-measurement of waist circumference as a first step is probably more effective: evidence now indicates that MetS all begins with central obesity.

**Conclusions**

Stepwise screening for MetS in general practice followed by the advice to contact the general practice for the screening results and care as usual had a substantial spontaneous follow-up with benefits for both screening participants and general practices. The short-term results with regard to lifestyle and weight loss are promising, but further research will have to demonstrate whether they are sustainable.

**Acknowledgements**

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**Declaration**

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