

# Metabolic Syndrome Model Definitions Predicting Type 2 Diabetes and Cardiovascular Disease

CÉCILE M. POVEL, PHD<sup>1,2</sup>  
 JOLINE W. BEULENS, PHD<sup>3</sup>  
 YVONNE T. VAN DER SCHOUW, PHD<sup>3</sup>  
 MARTIJN E.T. DOLLÉ, PHD<sup>1</sup>

ANNEMIEKE M.W. SPIJKERMAN, PHD<sup>1</sup>  
 W.M. MONIQUE VERSCHUREN, PHD<sup>1</sup>  
 EDITH J.M. FESKENS, PHD<sup>2</sup>  
 JOLANDA M.A. BOER, PHD<sup>1</sup>

**OBJECTIVE**—Metabolic syndrome (MetS) is a cluster of abdominal obesity, hyperglycemia, hypertension, and dyslipidemia, which increases the risk for type 2 diabetes and cardiovascular diseases (CVDs). Some argue that MetS is not a single disorder because the traditional MetS features do not represent one entity, and they would like to exclude features from MetS. Others would like to add additional features in order to increase predictive ability of MetS. The aim of this study was to identify a MetS model that optimally predicts type 2 diabetes and CVD while still representing a single entity.

**RESEARCH DESIGN AND METHODS**—In a random sample ( $n = 1,928$ ) of the EPIC-NL cohort and a subset of the EPIC-NL MORGEN study ( $n = 1,333$ ), we tested the model fit of several one-factor MetS models using confirmatory factor analysis. We compared predictive ability for type 2 diabetes and CVD of these models within the EPIC-NL case-cohort study of 545 incident type 2 diabetic subjects, 1,312 incident CVD case subjects, and the random sample, using survival analyses and reclassification.

**RESULTS**—The standard model, representing the current MetS definition (EPIC-NL comparative fit index [CFI] = 0.95; MORGEN CFI = 0.98); the standard model excluding blood pressure (EPIC-NL CFI = 0.95; MORGEN CFI = 1.00); and the standard model extended with hsCRP (EPIC-NL CFI = 0.95) had an acceptable model fit. The model extended with hsCRP predicted type 2 diabetes (integral discrimination index [IDI]: 0.34) and CVD (IDI: 0.07) slightly better than did the standard model.

**CONCLUSIONS**—It seems valid to represent the traditional MetS features by a single entity. Extension of this entity with hsCRP slightly improves predictive ability for type 2 diabetes and CVD.

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**M**etabolic syndrome (MetS) is a cluster of multiple correlated metabolic features that is associated with a fivefold increased risk of type 2 diabetes and a twofold increased risk of cardiovascular disease (CVD) (1). According to the joint interim statement of International Diabetes Federation and American Heart Association/National Heart, Lung, and Blood Institute, MetS is defined as the presence of three or

more of the following five features: abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia, and low HDL cholesterol levels (1).

Nevertheless, the debate around the definition of MetS is still ongoing. First, several expert groups including the World Health Organization, National Heart, Lung, and Blood Institute, and International Diabetes Federation are considering the inclusion of additional features in the

definition of MetS (1,2) such as markers of subclinical inflammation (2), markers of liver function (3), uric acid (4), and albumin (2). This could increase the predictive ability of MetS for type 2 diabetes and CVD. Second, when MetS is to be regarded as a single disorder, all features included in the definition of MetS should represent a single entity, i.e., should be captured in a single factor. Currently, it is unclear whether MetS can still be considered a single entity after inclusion of additional features. Some even argue that under the current definition, MetS does not represent a single disorder and favor exclusion of blood pressure from MetS (5).

Whether the current MetS definition or MetS definitions extended with additional features represent a single entity can be tested with factor analysis. Factor analysis is a data reduction technique that can be used to amalgamate data. Two-factor analysis techniques exist: explanatory factor analysis (EFA), which is a data-driven technique, and confirmatory factor analysis (CFA), which is hypothesis driven. In most studies, EFA has been used (6). However, owing to the explorative and subjective nature of EFA, results of EFA studies on MetS are inconsistent (7). In contrast, conclusions of CFA studies have thus far been quite consistent, suggesting that the MetS features included in the current definition represent one entity (4,7–12). However, as CFA MetS models including additional features, such as hsCRP (8), uric acid (4), albumin, and liver enzymes, have rarely been studied, it is unknown whether they represent one entity. Furthermore, to the best of our knowledge, the different one-factor CFA MetS models have never been compared with respect to their ability to predict development of type 2 diabetes and CVD. Once a MetS model that optimally predicts type 2 diabetes and CVD, while still representing one disorder, has been identified, future research could focus on the pathophysiology behind this single MetS entity. A deeper understanding of this pathophysiology may eventually lead to development of treatment strategies targeting the mechanism responsible for the co-occurrence of MetS features.

From the <sup>1</sup>National Institute for Public Health and the Environment, Bilthoven, the Netherlands; the <sup>2</sup>Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands; and the <sup>3</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands.

Corresponding author: Cécile M. Povel, cecile.povel@wur.nl.

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The first aim of this paper was to test whether the traditional MetS features represent a single entity and if so, whether this was still the case after inclusion of novel MetS features. The second aim was to identify a MetS model that best predicts type 2 diabetes and CVD while still representing a single entity.

## RESEARCH DESIGN AND METHODS

### EPIC-NL: study design

The European Investigation into Cancer and Nutrition (EPIC)-NL cohort consists of the two Dutch contributions to the EPIC project: the Prospect cohort and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohorts. Both cohorts were initiated in 1993 and combined into the EPIC-NL study. The study design of this combined cohort has previously been described in detail (13). In brief, Prospect is a prospective cohort study among 17,357 women aged 49–70 years who participated in the breast cancer screening between 1993 and 1997. The MORGEN cohort consists of 22,654 men and women aged 20–59 years recruited from three Dutch towns (Amsterdam, Doetinchem, and Maastricht). From 1993 to 1997, each year a new random sample of ~5,000 individuals was examined for the MORGEN cohort. Both studies complied with the Declaration of Helsinki. The Prospect-EPIC study was approved by the institutional review board of the University Medical Center Utrecht, and the MORGEN project was approved by the medical ethics committee of TNO, the Netherlands (13).

### Study population

Analyses were performed in two subsets composed of EPIC-NL participants, in whom all MetS features were measured: the EPIC-NL case-cohort study (13) and a subset of EPIC-NL MORGEN participants (14).

The EPIC-NL case-cohort study consists of a subcohort, i.e., 6.5% baseline random sample of the total EPIC-NL study ( $n = 2,604$ ), all incident diabetes cases ( $n = 924$ ), and all incident CVD cases ( $n = 2,030$ ). By virtue of the random selection of a subcohort and use of the appropriated statistics for this type of research design, the results are expected to be generalizable to the entire cohort (15). In the EPIC-NL case-cohort study, blood status was nonfasting and glucose status was assessed with HbA<sub>1c</sub>. In addition to

information on traditional MetS features, information on nontraditional MetS features, such as high-sensitivity C-reactive protein (hsCRP), was available.

The EPIC-NL MORGEN subset was used as a replication sample for the analysis on model fit. This subset consists of 1,379 nondiabetic participants, who indicated that their last meal was on the day before blood sampling. In contrast to the EPIC-NL case-cohort study, plasma glucose was measured instead of HbA<sub>1c</sub>, while information on nontraditional MetS features was not available.

Participants with missing blood samples (157 participants in the random sample, 174 incident CVD case subjects, and 66 incident type 2 diabetes case subjects), participants who were taking glucose-lowering or blood pressure-lowering medication (282 participants in the random sample, 409 incident CVD case subjects, and 279 incident type 2 diabetes case subjects and 46 participants of the MORGEN subset) or participants with missing values for one of the MetS or MetS-related features (237 participants in the random sample, 34 incident diabetes case subjects, and 135 incident CVD case subjects) were excluded (Supplementary Fig. 1). Subjects with missing blood samples were on average 2.4 years older and had a 1.1 kg/m<sup>2</sup> higher BMI than those without missing blood samples. Age and BMI were similar between subjects with and without missing values for one of the MetS or MetS-related features. Finally, the EPIC-NL case-cohort study consisted of 545 incident diabetes case subjects, 1,312 incident CVD case subjects, and 1,928 participants in the random sample. Of the random-sample participants, 53 were incident type 2 diabetes case subjects and 88 were incident CVD case subjects. An overlap between the case set and the random sample is a design feature of a case-cohort study. For the risk prediction analyses, prevalent type 2 diabetes and CVD case subjects were excluded from the random sample. The EPIC-NL MORGEN subset consisted of 1,333 participants, including 133 participants who were also included in the EPIC-NL case-cohort study.

### Ascertainment of diabetes in EPIC-NL

The ascertainment and verification of diabetes cases has previously been described in detail (16). In short, diabetes was ascertained via self-report, a urinary glucose strip test, and linkage to registers of hospital discharge diagnoses.

Self-reported diabetes status was assessed in the baseline questionnaire and in two follow-up questionnaires, which were sent out at regular intervals of 3–5 years. For Prospect participants only, a urinary glucose strip was sent out with the first follow-up questionnaire. Follow-up by linkage to registers of hospital discharge diagnoses was completed on 1 January 2006. Potential cases were verified against participants' general practitioner or pharmacist information. Only verified type 2 diabetes cases were included.

### Ascertainment of CVD in EPIC-NL

Data on CVD morbidity were obtained through linkage with the national medical registry. Vital status was obtained through linkage with the municipal population registries. Subsequently, primary and secondary causes of death were obtained through linkage with Statistics Netherlands. Follow-up was completed on 1 January 2006. Coronary heart disease (CHD) was coded with ICD-9 codes (410–414) or with ICD-10 codes (I20–I25), and cerebrovascular accident (CVA) was coded with ICD-9 codes (430–434 and 436) or with ICD-10 codes (I60–I66). CVD was defined as the presence of CHD, CVA, or both (17).

### Baseline measurements in EPIC-NL

The study protocol of the EPIC-NL MORGEN study and the study protocol of the EPIC-NL Prospect study were essentially similar. At baseline, a physical examination was performed and nonfasting blood samples were drawn. Furthermore, a general questionnaire and a Food Frequency Questionnaire (FFQ) were filled out by each participant (13).

The protocol for the anthropometric measurements and the blood sampling protocol were identical for the EPIC-NL Prospect and the EPIC-NL MORGEN studies. Waist circumference and height were measured to the nearest 0.5 cm. Body weight was measured with light indoor clothing without shoes on to the nearest 100 g. During the physical examination, systolic and diastolic blood pressure measurements were performed twice in the supine position on the right arm using a Boso Oscillomat (Bosch & Son, Jungingen, Germany) (Prospect) or twice on the left arm using a random zero sphygmomanometer (MORGEN). The mean of the two measurements was taken. Blood levels of established biochemical parameters were measured in EDTA or citrate plasma. HbA<sub>1c</sub> was measured in

erythrocytes using an immunoturbidimetric latex test. HDL was measured with a homogeneous assay with enzymatic end point. Triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$  glutamyltransferase (GGT), uric acid, and glucose were measured using enzymatic methods, whereas hsCRP was measured with a turbidimetric method. Albumin was measured using a colorimetric method (Jaffe method). These assays were all performed on an autoanalyzer (LX20; Beckman Coulter, Mijdrecht, the Netherlands) (13,14).

Data on smoking habits, educational level, self-reported medication use, physical activity, and alcohol intake were obtained by general questionnaires and an FFQ. Physical activity was categorized by calculating the Cambridge physical activity score (18).

**Statistics**

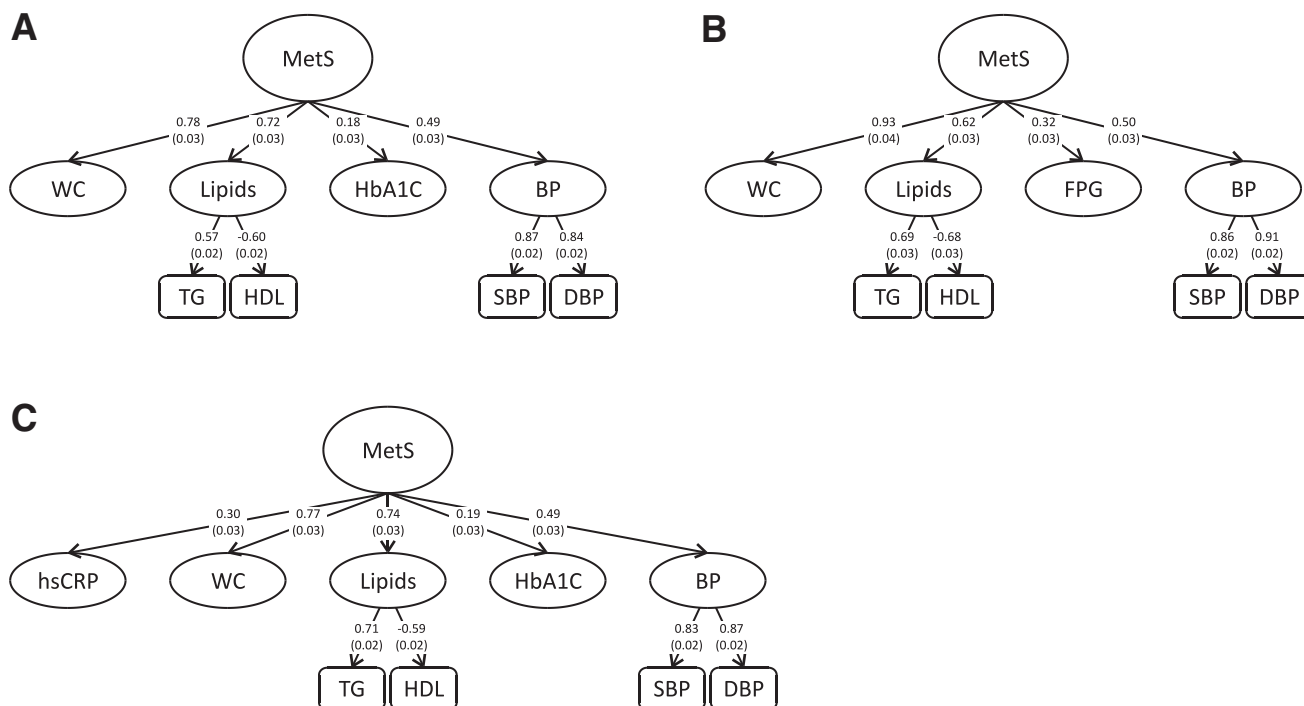
Triglycerides, hsCRP, ALT, AST, and GGT were log transformed to improve normality. Using CFA, we designed several second-order one-factor MetS models based on the MetS model of Shen et al. (9) consisting of three levels: a single MetS factor; several first-order factors (e.g., lipids), which defined the single MetS factor; and some second-order factors (e.g.,

triglycerides and HDL cholesterol), which defined the first-order factors. We designed the following one-factor MetS models: model 1, a standard MetS model, based on the current definition of MetS (1), including the traditional MetS features, i.e., waist circumference, triglycerides, HDL cholesterol, systolic blood pressure, diastolic blood pressure, and as marker of glucose status, either HbA<sub>1c</sub> or glucose (Fig. 1A and B); model 2, a standard MetS model excluding the blood pressure factor; and model 3, a standard MetS model extended with an hsCRP factor (Fig. 1C), an albumin factor, a uric acid factor, or a liver enzymes factor. The liver enzymes factor was a first-order factor defined by the second-order factors ALT, AST, and GGT. In all models, the factor variance of the MetS factor, the factor loading of triglycerides, and the factor loading of systolic blood pressure were fixed to 1. For model 3, the MetS model excluding blood pressure, not enough df were available to calculate model fit. Therefore, the error variance of the factor with the highest factor loading (waist circumference) was fixed to 1 for the model fit calculations of this model.

Model fit of MetS models composed of traditional MetS features was calculated

in the random sample of EPIC-NL and in the EPIC-NL MORGEN subset. Model fit of MetS models including nontraditional features was calculated only in the random sample of EPIC-NL. We compared the model fit of all alternative MetS models with the model fit of the standard one-factor MetS model (model 1). Factor loadings and SEs were obtained using the maximum likelihood method. The  $\chi^2$  test, the comparative fit index (CFI), the standardized root means square residual (SRMR), and the root mean square error of approximation (RMSEA) were used to assess model fit. Models with RMSEA >0.10, CFI <0.95, or SRMR >0.08 were rejected (19). The  $\chi^2$  difference test was used to compare model fit across different models.

For MetS models with an acceptable model fit, we compared the predictive ability of the factor scores for incidence of type 2 diabetes, CVD, CHD, and CVA in the EPIC-NL case-cohort study. We calculated the factor scores using the factor score coefficients of the different MetS features extracted by the regression method from the random sample. All factor score coefficients were standardized to the means and SEs of the MetS features in the random sample. For all



**Figure 1**—A: The standard second-order one-factor MetS model in the random sample of EPIC-NL. B: The standard second-order one-factor MetS model in the subset of the MORGEN study. C: The standard second-order one-factor MetS model extended with hsCRP in the random sample of EPIC-NL. Data are presented as factor loading (SE). All factor loadings are significant ( $P < 0.05$ ). The first-order factors are waist circumference (WC), lipids, HbA<sub>1c</sub>, FPG, and blood pressure. The second-order factors are triglyceride (TG), HDL, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

factor scores, we calculated Cox proportional hazard ratios (HRs), C statistics, and integral discrimination indices (IDIs) for incidence of type 2 diabetes, CVD, CHD, and CVA.

HRs were adjusted for the overrepresentation of cases in the case-cohort study with a pseudolikelihood method (20), whereas IDIs and C statistics were adjusted for this overrepresentation by inverse probability weighing. HRs were calculated per SD of the factor score and adjusted for age, sex, cohort, smoking (current, former, and never), educational level, Cambridge physical activity index, and alcohol intake. The change in C statistics and the IDIs were used to compare predictive ability of the standard MetS model, model 1, with the alternative models. The C statistic is equivalent to the probability that the predicted risk is higher for a case than for a noncase subject (21). The IDI can be viewed as the difference in the proportion of variance explained by two models (22). Model calibration was tested by the Hosmer-Lemeshow  $\chi^2$  test.

CFA analyses were performed in MPLUS, sixth edition (Muthén & Muthén,

Los Angeles, CA). HRs, C statistics, and IDIs were calculated in SAS version 9.2 (SAS Institute, Cary, NC).

**RESULTS**—Baseline characteristics of the study population are provided in Table 1. Participants in the EPIC-NL case-cohort study were on average 51.8 years old, and 28.5% was male. MetS prevalence was higher in incident diabetes case subjects (70.5%) and incident CVD case subjects (38.6%) than in the random sample (21.2%). In the MORGEN subset, participants were on average 39.1 years old, and 50.5% was male. MetS prevalence was somewhat lower (14.9%) than in the random sample of EPIC-NL (21.2%).

The standard one-factor MetS model (model 1) (Fig. 1A and B), which is based on the current definition of MetS, had an acceptable model fit with a CFI of 0.95 (Table 2). Other one-factor MetS models with a good model fit were the MetS model excluding blood pressure (model 2) and the MetS model extended with hsCRP (model 3) (Fig. 1C). The CFIs of one-factor MetS models extended with

uric acid, liver enzymes, or albumin were <0.95, indicating that their model fit was unacceptable. These extended MetS models also did not fit well after the exclusion of the blood pressure factor (data not shown). Compared with the standard MetS model (model 1), the standard MetS model excluding blood pressure (model 2) fitted better, whereas the model extended with hsCRP (model 3) fitted worse.

HRs for type 2 diabetes (HR 2.71 [95% CI 2.30–3.18]) and CVD (1.25 [1.13–1.39]) were lowest in the MetS model excluding blood pressure (model 2), whereas they were highest in the MetS model extended with hsCRP (type 2 diabetes HR 3.94 [3.28–4.74]; CVD 1.28 [1.16–1.42]) (Table 3). HRs were essentially similar after additional adjustment for fiber and energy intake (data not shown). Of all MetS models, the model extended with hsCRP (model 3) predicted type 2 diabetes, CHD, CVA, and CVD the best (type 2 diabetes C index 0.8013; CVD C index 0.6352). For all models, the Hosmer-Lemeshow test was not significant, indicating a good calibration.

**Table 1—Baseline characteristics of the EPIC-NL study**

|                                       | EPIC-NL case cohort           |                               |                               | Subset of EPIC-MORGEN |
|---------------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------|
|                                       | Random sample                 | Type 2 diabetes               | CVD                           |                       |
| n                                     | 1,928                         | 545                           | 1,312                         | 1,333                 |
| Sex, % men (n)                        | 25.9 (500)                    | 27.2 (148)                    | 33.5 (440)                    | 50.5 (673)            |
| Age (years)                           | 48.9 (11.7)                   | 55.7 (7.3)                    | 55.0 (8.9)                    | 39.1 (10.6)           |
| Waist circumference (cm)              | 85.5 (11.4)                   | 96.7 (11.5)                   | 89.6 (12.0)                   | 86.5 (12.6)           |
| BMI (kg/m <sup>2</sup> )              | 25.8 (3.9)                    | 29.5 (4.5)                    | 26.6 (4.0)                    | 25.2 (4.0)            |
| HbA <sub>1c</sub> (%)                 | 5.40 (0.61)                   | 6.33 (1.30)                   | 5.64 (0.83)                   | —                     |
| Plasma glucose (mmol/L)               | —                             | —                             | —                             | 5.31 (0.97)           |
| HDL cholesterol (mmol/L)              | 1.28 (0.34)                   | 1.05 (0.26)                   | 1.18 (0.32)                   | 1.32 (0.36)           |
| Triglyceride (mmol/L)                 | 1.31 (0.92–1.94) <sup>a</sup> | 2.01 (1.40–2.74) <sup>a</sup> | 1.54 (1.12–2.27) <sup>a</sup> | 0.94 (0.69–1.40)      |
| Systolic blood pressure (mmHg)        | 124.8 (17.7)                  | 137.3 (22.0)                  | 134.8 (21.1)                  | 118.7 (15.6)          |
| Diastolic blood pressure (mmHg)       | 77.3 (10.2)                   | 82.9 (10.9)                   | 81.4 (11.3)                   | 77.5 (10.3)           |
| MetS prevalence, % (n) <sup>a,b</sup> | 21.2 (409)                    | 70.5 (384)                    | 38.6 (506)                    | 14.9 (199)            |
| hsCRP (mg/L)                          | 1.22 (0.57–2.67)              | 2.50 (1.15–4.75)              | 1.74 (0.81–3.53)              | —                     |
| ALT (IU/L)                            | 14.5 (11.9–18.4)              | 16.8 (13.2–22.7)              | 14.6 (11.9–18.8)              | —                     |
| AST (IU/L)                            | 20.0 (17.4–23.5)              | 20.9 (17.5–25.5)              | 20.1 (17.5–24.1)              | —                     |
| GGT (IU/L)                            | 20.7 (16.5–28.1)              | 28.5 (22.6–40.2)              | 24.4 (19.2–33.1)              | —                     |
| Albumin (g/L)                         | 38.9 (4.9)                    | 37.7 (4.8)                    | 38.2 (4.9)                    | —                     |
| Uric acid (mmol/L)                    | 258.5 (67.7)                  | 284.9 (70.4)                  | 269.0 (70.9)                  | —                     |
| Cambridge physical activity index     | 2.8 (1.0)                     | 2.7 (1.1)                     | 2.7 (1.1)                     | 2.6 (1.1)             |
| Current smokers, % (n)                | 32.2 (620)                    | 29.3 (158)                    | 42.7 (556)                    | 51.9 (686)            |
| Alcohol abstainers, % (n)             | 9.5 (176)                     | 11.2 (59)                     | 6.5 (83)                      | 13.9 (184)            |
| Alcohol (g/day) <sup>c</sup>          | 12.3 (15.5)                   | 9.5 (13.8)                    | 12.6 (16.5)                   | 17.9 (23.0)           |
| Highly educated, % (n) <sup>d</sup>   | 21.6 (412)                    | 9.5 (51)                      | 14.5 (189)                    | 18.6 (248)            |

Data are presented as means (SD) or median (25th–75th percentile) unless otherwise indicated. Subjects with blood pressure-lowering or glucose-lowering medication are excluded. <sup>a</sup>Nonfasting values. <sup>b</sup>MetS is defined as having three or more of the following features: hyperglycemia, HbA<sub>1c</sub> ≥5.7% (33) or fasting plasma glucose ≥5.6 mmol/L; abdominal obesity, men ≥102 cm, women ≥88 cm; low HDL cholesterol, men <1.0 mmol/L, women <1.3 mmol/L; nonfasting hypertriglyceridemia ≥2.5 mmol/L (34) or fasting hypertriglyceridemia, ≥1.7 mmol/L; and hypertension, ≥130/85 mmHg. <sup>c</sup>Among alcohol users. <sup>d</sup>People who completed higher vocational education or university.

Table 2—Model fit indices of several MetS models in the random sample of the EPIC-NL study and in a subset with participants of the MORGEN study

|                                     | Random sample EPIC-NL (n = 1,928) |    |        |       |       |      | Subset of MORGEN (n = 1,333) |    |        |       |       |      |
|-------------------------------------|-----------------------------------|----|--------|-------|-------|------|------------------------------|----|--------|-------|-------|------|
|                                     | $\chi^2$                          | df | P      | RMSEA | SRMR  | CFI  | $\chi^2$                     | df | P      | RMSEA | SRMR  | CFI  |
| Standard one-factor model (model 1) | 150.2                             | 7  | <0.001 | 0.10  | 0.045 | 0.95 | 56.0                         | 7  | <0.001 | 0.07  | 0.039 | 0.98 |
| Model 1 + blood pressure (model 2)  | 43.1                              | 2  | <0.001 | 0.10  | 0.040 | 0.95 | 2.2                          | 2  | 0.34   | 0.01  | 0.01  | 1.00 |
| Model 1 + hsCRP (model 3)           | 163.3                             | 12 | <0.001 | 0.08  | 0.040 | 0.95 |                              |    |        |       |       |      |
| Model 1 + uric acid (model 4)       | 289.4                             | 12 | <0.001 | 0.11  | 0.059 | 0.92 |                              |    |        |       |       |      |
| Model 1 + liver enzymes (model 5)   | 440.5                             | 24 | <0.001 | 0.10  | 0.056 | 0.92 |                              |    |        |       |       |      |
| Model 1 + albumin (model 6)         | 665.2                             | 12 | <0.001 | 0.09  | 0.168 | 0.80 |                              |    |        |       |       |      |
| Difference (model 2 – model 1)      | –107.1 <sup>a</sup>               | 5  | <0.001 |       |       |      | –53.8 <sup>a</sup>           | 5  | <0.001 |       |       |      |
| Difference (model 3 – model 1)      | 13.1                              | 5  | 0.03   |       |       |      |                              |    |        |       |       |      |
| Difference (model 4 – model 1)      | 139.2                             | 5  | <0.001 |       |       |      |                              |    |        |       |       |      |
| Difference (model 5 – model 1)      | 290.3                             | 17 | <0.001 |       |       |      |                              |    |        |       |       |      |
| Difference (model 6 – model 1)      | 515.0                             | 5  | <0.001 |       |       |      |                              |    |        |       |       |      |

<sup>a</sup>Absolute values are used to calculate significance of  $\chi^2$ .

**CONCLUSIONS**—We have examined the factor structure of MetS using CFA in two population-based study samples. The good model fit of the standard one-factor MetS model, representing the current definition, indicated that it is valid to compose one entity out of the traditional MetS features. When the standard MetS model was extended with hsCRP, predictive ability for type 2 diabetes and CVD increased slightly, while model fit was still acceptable. In line with the results of previous CFA

Table 3—Predictive ability of several MetS models for type 2 diabetes and CVD

|                           | Standard MetS model (reference), included features: TG, HDL, HbA <sub>1c</sub> , WC, SBP, and DBP | Standard MetS model minus blood pressure, included features: TG, HDL, HbA <sub>1c</sub> , and WC | Standard MetS model extended with hsCRP, included features: TG, HDL, HbA <sub>1c</sub> , WC, SBP, DBP, and hsCRP |
|---------------------------|---|--|--|
| <b>Diabetes (n = 545)</b> |   |  |  |
| HR (95% CI) <sup>a</sup>  | 3.58 (3.05–4.20)  | 2.70 (2.37–3.11)   | 3.77 (3.21–4.42)   |
| HR (95% CI) <sup>b</sup>  | 3.70 (3.09–4.42)  | 2.71 (2.30–3.18)   | 3.94 (3.28–4.74)   |
| C index                   | 0.7949  | 0.7539   | 0.8013   |
| C index change (P)        | —   | –0.0411 (<0.0001)  | 0.0064 (0.0001)  |
| IDI (95% CI)              | —   | –1.58 (–1.89 to –1.28)   | 0.34 (0.25–0.44)   |
| P value Hosmer-Lemeshow   | 0.36  | 0.21   | 0.87   |
| <b>CVD (n = 1,312)</b>    |   |  |  |
| HR (95% CI) <sup>a</sup>  | 1.31 (1.20–1.43)  | 1.28 (1.17–1.39)   | 1.33 (1.22–1.46)   |
| HR (95% CI) <sup>b</sup>  | 1.26 (1.14–1.40)  | 1.25 (1.13–1.39)   | 1.28 (1.16–1.42)   |
| C index                   | 0.6315  | 0.6153   | 0.6352   |
| C index change (P)        | —   | –0.0162 (<0.0001)  | 0.0037 (0.01)  |
| IDI (95% CI)              | —   | –0.22 (–0.28 to –0.20)   | 0.07 (0.04–0.09)   |
| P Hosmer-Lemeshow         | 0.76  | 0.94   | 0.95   |
| <b>CHD (n = 956)</b>      |   |  |  |
| HR (95% CI) <sup>a</sup>  | 1.40 (1.27–1.55)  | 1.37 (1.24–1.52)   | 1.42 (1.29–1.57)   |
| HR (95% CI) <sup>b</sup>  | 1.35 (1.20–1.51)  | 1.30 (1.16–1.47)   | 1.36 (1.21–1.53)   |
| C index                   | 0.6496  | 0.6336   | 0.6519   |
| C index change (P)        | —   | –0.0161 (<0.0001)  | 0.0022 (0.16)  |
| IDI (95% CI)              | —   | –0.19 (–0.23 to –0.15)   | 0.04 (0.02–0.06)   |
| P Hosmer-Lemeshow         | 0.88  | 0.95   | 0.96   |
| <b>CVA (n = 375)</b>      |   |  |  |
| HR (95% CI) <sup>a</sup>  | 1.11 (0.98–1.25)  | 1.07 (0.95–1.21)   | 1.13 (1.00–1.29)   |
| HR (95% CI) <sup>b</sup>  | 1.08 (0.93–1.25)  | 1.04 (0.90–1.19)   | 1.10 (0.95–1.28)   |
| C index                   | 0.5760  | 0.5603   | 0.5828   |
| C index change (P)        | —   | –0.0157 (<0.0001)  | 0.0068 (0.004)   |
| IDI (95% CI)              | —   | –0.04 (–0.05 to –0.02)   | 0.02 (0.01–0.03)   |
| P Hosmer-Lemeshow         | 0.68  | 0.83   | 0.90   |

HRs are presented per SD; IDIs are presented as % improvement. DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference. <sup>a</sup>Adjusted for age, sex, and cohort. <sup>b</sup>Adjusted for age, sex, cohort, smoking (current, former, or none), education level, Cambridge physical activity index, and alcohol intake.

studies (7–9), we found that it is valid to compose one entity, i.e., one factor out of the five traditional MetS features.

The model fit of a one-factor MetS model, composed of the traditional MetS features, was even better after exclusion of the blood pressure factor. This is consistent with other studies indicating that blood pressure is distinct from the other traditional MetS features, both from a physiological (23) and a statistical point of view. For example, blood pressure generally has the lowest factor loading in CFA MetS models (7–11). Furthermore, blood pressure is identified as a separate factor in most EFA studies (6). Although omitting the blood pressure factor improved model fit, it also considerably decreased the predictive ability for type 2 diabetes, CVA, and CHD. Since this predictive ability is of clinical relevance, removal of blood pressure from the MetS definition is questionable.

Of the one-factor MetS models extended with nontraditional MetS features, only the MetS model extended with hsCRP had an acceptable model fit. In 645 non-Hispanic whites or African Americans, an essentially similar MetS model also had a good model fit (8). In our data, the MetS model extended with hsCRP predicted type 2 diabetes, CVA, and CHD slightly better than the standard MetS model. In contrast to type 2 diabetes and CVA, the improvement in C index was not significant for CHD. This suggests that in our data, the improvement in C index for CVDs is mainly driven by the improvement for CVA. In two large prospective cohort studies, hsCRP added substantial prognostic information to MetS (24,25). Though our findings are in line with these previous studies, the addition of hsCRP to MetS was clinically relevant in the earlier reports but not in our study. The reason for this discrepancy might be explained by a difference in study population; e.g., in our study compared with the previous studies, hsCRP levels were lower. Part of the added predictive power of hsCRP may be explained by the association of hsCRP with insulin resistance and fibrinolysis. Both increase the risk of type 2 diabetes and CVD but are not included in the current definition of MetS (26).

In our study, the model fit of other one-factor MetS models extended with additional features, i.e., albumin, liver enzymes, or uric acid, was not acceptable. To the best of our knowledge, models extended with albumin or liver enzymes have not previously been studied. Our results are, however, in line with several EFA studies (24–27). Contrary to our

results, among 410 Spanish participants a one-factor MetS model extended with uric acid had a very good model fit (CFI 0.99) (4). The relatively low factor loading of MetS features strongly associated with uric acid, such as glucose (28), may explain the bad model fit of the model extended with uric acid in our data.

The strength of our study was the hypothesis-driven CFA approach, which we used to compare the model fit of a standard MetS model with several modified MetS models. Results of CFA studies are generally much more reproducible than results of EFA studies. Furthermore, we tested the model fit of the MetS models in two relatively large study samples, and results were very similar. We have adjusted the HRs for several lifestyle factors. As the HRs were similar before and after adjustment, the confounding effect of these lifestyle factors was probably small. The use of nonfasting triglycerides and HbA<sub>1c</sub> instead of the conventional MetS features, i.e., fasting triglycerides and glucose, in the EPIC-NL case-cohort study may have affected model fit. As postprandial triglyceride levels are more strongly correlated with the other MetS features than fasting triglyceride levels (29), the use of postprandial triglycerides levels may have improved model fit and increased the factor loadings of the lipid factor in the EPIC-NL case-cohort. In contrast, for most MetS features the correlations with HbA<sub>1c</sub> and fasting plasma glucose were similar in 160 EPIC-NL participants with both measurements available. Only the correlation of waist circumference and HbA<sub>1c</sub> was weaker than the correlation of waist circumference and fasting plasma glucose. This weak correlation resulted in a relative low factor loading for the glucose factor (based on HbA<sub>1c</sub>) and perhaps in somewhat lower model fit. However, although nonfasting triglycerides and HbA<sub>1c</sub> were used in the EPIC-NL case-cohort study, conclusions regarding model fit in the EPIC-NL case-cohort study were similar to the MORGEN subset in which fasting plasma glucose and triglycerides were used. Compared with fasting plasma glucose, HbA<sub>1c</sub> predicts type 2 diabetes and possibly also CVD better (30,31). Therefore, inclusion of HbA<sub>1c</sub> instead of fasting glucose in the EPIC-NL MetS models has most likely increased predictive ability. However, as this applies to all MetS models, the comparisons between the different MetS models would probably have

yielded similar conclusions if fasting plasma glucose had been included. Moreover, as fasting plasma glucose levels were not available, we may have missed some undiagnosed type 2 diabetes cases. Underestimation of diabetic cases may have weakened the associations with diabetes we found in EPIC-NL. The participants (~7%) we excluded from the EPIC-NL case-cohort owing to missing blood samples had on average a 1.1 kg/m<sup>2</sup> higher BMI. As the correlations between waist circumference and other MetS features were slightly higher in the group with missing blood samples, exclusion of these participants may have resulted in somewhat lower factor loadings for the waist circumference factor. Additionally, the two datasets we used were not completely independent, as 133 subjects were present both in the EPIC-NL case-cohort study and in the MORGEN subset. However, when we excluded these 133 participants from the MORGEN subset, results were essentially similar. Finally, in order to be able to estimate model fit of the MetS model excluding blood pressure, we fixed the error variance of waist circumference in this model to one. This fixation has probably worsened the model fit. Therefore, we may have underestimated the improvement in model fit obtained by deleting the blood pressure factor.

In conclusion, it is valid to compose out of the traditional MetS features one entity and consequently to view MetS as a single disorder. A model additionally including hsCRP still represented a single entity and predicted type 2 diabetes, CVA, and CHD somewhat better than a MetS model with only the traditional features. CFA MetS models, like ours, including the traditional MetS features and possibly hsCRP may be used as the basis to develop a new continuous MetS definition with differential weights for the different MetS features, using an approach described by Hillier et al. (32).

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