Objective—To examine whether a quantitatively derived metabolic syndrome definition predicts incident cardiovascular disease (CVD) events better than do existing definitions.

Research Design and Methods—Data were pooled from the Atherosclerosis Risk in Communities, Cardiovascular Health, and Framingham Offspring studies (n = 20,981). Incident coronary heart disease and stroke events were ascertained over 9 years.

Results—The sensitivity for incident CVD events was higher and the specificity lower for the empirically derived versus the Adult Treatment Panel (ATP) III, International Diabetes Federation (IDF), or Harmonized metabolic syndrome definitions (sensitivity/specificity 0.65/0.53 vs. 0.53/0.63, 0.51/0.66, and 0.64/0.56, respectively), resulting in no overall improvement in discrimination. Multivariable-adjusted hazard ratios for incident CVD events were similar across definitions and were 1.7 (95% CI 1.6–1.9) for ATP III, 1.8 (1.6–2.0) for IDF, 1.9 (1.7–2.0) for Harmonized, and 1.7 (1.6–1.9) for the empirically derived definition.

Conclusions—Empirical derivation of the metabolic syndrome definition did not improve CVD discrimination or risk prediction.
RESULTS—Across the three studies (n = 20,581), 1,783 incident CVD events occurred over 9 years of follow-up. In the overall sample, the optimal systolic and diastolic blood pressure and triglyceride cut points were lower than those in existing definitions, whereas the glucose cut point was identical (Table 1). Within demographic subgroups, the optimal cut point varied by component and subgroup.

The presence of ≥3 components at levels above the optimal cut point (below the optimal cutpoint for HDL cholesterol), identified in Table 1, provided the highest sum of sensitivity and specificity, and two empirically derived metabolic syndrome definitions were created: 1) three or more components using cut points derived in the full sample (uniform cut point definition) and 2) three or more components using demographic subgroup-specific cut points.

More people were categorized as having metabolic syndrome using the empirically derived definitions (48.3% for uniform cut points and 51.0% for subgroup-specific cut points) compared with the ATP III (38.4%), IDF (35.6%), or Harmonized (46.0%) definitions. The empirically derived definitions, using uniform and subgroup-specific cut points, had higher sensitivity but lower specificity (0.65/0.53 and 0.67/0.50, respectively) versus the ATP III (0.53/0.63), IDF (0.51/0.66), or Harmonized (0.64/0.56) definitions. The empirically derived definition with uniform cut points provided little improvement over the ATP III (RIDI 5% [95% CI 0.53/0.63], IDF (2% [0.53/0.63]), or Harmonized (0.64/0.56) definitions. The empirically derived definition with uniform cut points provided little improvement over the ATP III (RIDI 5% [95% CI 0.53/0.63], IDF (2% [0.53/0.63]), or Harmonized (0.64/0.56) definitions. Results were markedly similar when subgroup-specific cut points were used.

All metabolic syndrome definitions were associated with an increased HR for incident CVD in multivariable-adjusted analyses (1.7 [95% CI 1.6–1.9], 1.8 [1.6–2.0], and 1.9 [1.7–2.0] for ATP III, IDF, and Harmonized, respectively, and 1.7 [1.6–1.9] and 1.8 [1.6–1.9] for the empirically derived uniform and subgroup-specific cut point definitions, respectively). Results were similar among individuals without hypertension or diabetes or when the HRs were adjusted for antihypertensive and lipid-lowering medication use. A fivefold cross-validation study resulted in identical cut points and similar performance characteristics.

CONCLUSIONS—The data-derived definitions of the metabolic syndrome resulting from maximization of the sum of sensitivity and specificity for CVD events resulted in little improvement in discrimination compared with existing definitions. Also, the HRs for CVD associated

Table 1—Empirically derived cut points and associated discrimination performance statistics for metabolic syndrome components by demographic subgroups

|                     | White men (aged <65 years) | White women (aged <65 years) | Black men (aged <65 years) | Black women (aged <65 years) | White men (aged ≥65 years) | White women (aged ≥65 years) | Black men (aged ≥65 years) | Black women (aged ≥65 years) |
|---------------------|---------------------------|-----------------------------|---------------------------|----------------------------|---------------------------|-----------------------------|---------------------------|----------------------------|
| **N**               | 20,581                    | 5,720                       | 6,577                     | 1,332                      | 2,198                     | 1,667                       | 2,443                     | 238                       |
| **Systolic blood pressure (mmHg)** |                       |                             |                           |                             |                           |                             |                           |                           |
| N                   | 14,543                    | 4,556                       | 5,022                     | 889                        | 1,197                     | 1,064                       | 1,526                     | 133                       |
| Optimal cut point   | 125                       | 120                         | 120                       | 125                        | 130                       | 130                         | 135                       | 140                       |
| Sensitivity         | 0.62                      | 0.59                        | 0.56                      | 0.72                       | 0.62                      | 0.69                        | 0.56                      | 0.48                       |
| Specificity         | 0.64                      | 0.57                        | 0.64                      | 0.56                       | 0.71                      | 0.51                        | 0.62                      | 0.67                       |
| **Diastolic blood pressure (mmHg)** |                       |                             |                           |                             |                           |                             |                           |                           |
| N                   | 14,543                    | 4,556                       | 5,022                     | 889                        | 1,197                     | 1,064                       | 1,526                     | 133                       |
| Optimal cut point   | 75                        | 75                          | 70                        | 80                         | 75                        | 75                          | 75                        | 75                        |
| Sensitivity         | 0.47                      | 0.54                        | 0.60                      | 0.62                       | 0.55                      | 0.43                        | 0.46                      | 0.37                       |
| Specificity         | 0.62                      | 0.56                        | 0.52                      | 0.55                       | 0.51                      | 0.65                        | 0.57                      | 0.50                       |
| **Glucose (mmol/L)** |                           |                             |                           |                             |                           |                             |                           |                           |
| N                   | 18,479                    | 5,254                       | 6,129                     | 1,151                      | 1,840                     | 1,410                       | 2,193                     | 186                       |
| Optimal cut point   | 5.6                       | 5.6                         | 5.3                       | 5.6                        | 5.6                       | 5.3                         | 5.6                       | 5.3                       |
| Sensitivity         | 0.45                      | 0.51                        | 0.56                      | 0.44                       | 0.46                      | 0.52                        | 0.62                      | 0.46                       |
| Specificity         | 0.63                      | 0.57                        | 0.53                      | 0.56                       | 0.60                      | 0.53                        | 0.43                      | 0.38                       |
| **Triglycerides (mmol/L)** |                       |                             |                           |                             |                           |                             |                           |                           |
| N                   | 19,939                    | 5,541                       | 6,373                     | 1,320                      | 2,161                     | 1,606                       | 2,330                     | 229                       |
| Optimal cut point   | 1.4                       | 1.4                         | 1.4                       | 1.4                        | 1.4                       | 1.4                         | 1.4                       | 1.4                       |
| Sensitivity         | 0.50                      | 0.59                        | 0.59                      | 0.38                       | 0.39                      | 0.51                        | 0.50                      | 0.28                       |
| Specificity         | 0.61                      | 0.54                        | 0.65                      | 0.68                       | 0.72                      | 0.56                        | 0.53                      | 0.69                       |
| **HDL cholesterol (mmol/L)** |                       |                             |                           |                             |                           |                             |                           |                           |
| Optimal cut point   | 1.3                       | 1.0                         | 1.4                       | 1.2                        | 1.4                       | 1.2                         | 1.4                       | 1.3                       |
| Sensitivity         | 0.58                      | 0.57                        | 0.73                      | 0.48                       | 0.64                      | 0.51                        | 0.47                      | 0.40                       |
| Specificity         | 0.51                      | 0.56                        | 0.51                      | 0.58                       | 0.52                      | 0.55                        | 0.58                      | 0.50                       |
| **Waist circumference (mm)** |                       |                             |                           |                             |                           |                             |                           |                           |
| Optimal cut point   | 96                        | 98                          | 96                        | 96                         | 98                        | 98                          | 92                        | 96                        |
| Sensitivity         | 0.55                      | 0.59                        | 0.53                      | 0.56                       | 0.62                      | 0.49                        | 0.46                      | 0.49                       |
| Specificity         | 0.55                      | 0.51                        | 0.68                      | 0.53                       | 0.51                      | 0.55                        | 0.59                      | 0.42                       |

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Empirical metabolic syndrome definition

with each metabolic syndrome definition were similar.

The empirical derivation resulted in cut points similar to those based on expert opinion used in existing metabolic syndrome definitions. The exception was the empirically derived triglyceride cut point (1.4 mmol/L), which was substantially lower than that used in existing definitions (1.7 mmol/L). The lower triglyceride cut point resulted in a higher prevalence of the metabolic syndrome but no overall improvement in discrimination or meaningful difference in the HR for CVD.

For the ATP III, IDF, and Harmonized definitions, sex-specific cut points are applied for HDL cholesterol and waist circumference criteria. In the current study, subgroup-specific cut points resulted in higher sensitivity in some groups at the expense of lower specificity. In other subgroups, specificity was higher but sensitivity lower. Given this, the lack of improvement in discrimination when using subgroup-specific cut points, and the similarity of HRs between the empirically derived uniform cut point definition and existing definitions, which use sex-specific cut points, these data suggest that uniform cut points in all subgroups may be sufficient for discrimination and assessing associations. This results in a simplified clinical application.

Although measurement protocols were not identical across the three studies, findings were similar within each study (data not shown). The strength of this study comes from the use of a large sample with over 1,700 incident CVD events.

Although the ATP III, IDF, and Harmonized definition cut points were not empirically derived, the improvements in CVD risk prediction seen with empirically derived cut points were small, suggesting that the existing metabolic syndrome definitions will be sufficient for use in clinical practice and research studies should the metabolic syndrome debate conclude in a recommendation for its continued use.

Acknowledgments—This study was supported by a grant from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (R21 HL089625 [to R.P.W.]). The CHS, ARIC, and Framingham Offspring Study are conducted and supported by the NHLBI in collaboration with the CHS, ARIC, and Framingham Offspring Study investigators, respectively.

No potential conflicts of interest relevant to this article were reported.

R.P.W. was involved in the design of the study and wrote the manuscript. A.P.M. designed data analysis programs, wrote the statistical methods section, and edited the manuscript. M.K. was involved in the design of the study and edited the manuscript. P.M. was involved in the design of the study, assisted with data analysis, and edited the manuscript. D.W. performed the statistical analysis. H.W.C. was involved in the design of the study and edited the manuscript. A.D.O. edited the manuscript. K.R. was involved in the design of the study and edited the manuscript. V.F. was involved in the design of the study and edited the manuscript.

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