Metabolic Syndrome, Independent of Its Components, Is a Risk Factor for Stroke and Death But Not for Coronary Heart Disease Among Hypertensive Patients in the ASCOT-BPLA

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OBJECTIVE — To evaluate whether in hypertensive patients the risk of cardiovascular disease is greater in association with the metabolic syndrome (MetS) or the sum of its individual components.

RESEARCH DESIGN AND METHODS — Cox regression analysis models were developed to assess the influence of age, sex, ethnicity, and the individual components of MetS on risk associated with the MetS (using several definitions) of coronary outcomes, stroke, and all-cause mortality.

RESULTS — MetS was significantly associated with coronary outcomes, stroke, and all-cause mortality after adjusting for age, sex, and ethnicity. However, when the model was further adjusted for the individual components, MetS was associated with significantly increased risk of stroke (hazard ratio 1.34 [95% CI 1.07–1.68]) and all-cause mortality (1.35 [1.16–1.58]) but not coronary outcomes (fatal coronary heart disease plus nonfatal myocardial infarction 1.16 [0.95–1.43] and total coronary events 1.06 [0.91–1.24]).

CONCLUSIONS — MetS, independent of its individual components, is associated with increased risk of stroke and all-cause mortality but not coronary outcomes.

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Studies in the recent past evaluating the usefulness of the metabolic syndrome (MetS) have provided equivocal results (1–4). The database from the blood pressure–lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) (5) provides an excellent opportunity to evaluate whether in hypertensive patients the risk of cardiovascular (CV) disease and death is greater in association with the MetS or the sum of its individual components.

RESEARCH DESIGN AND METHODS

— Details of the study design and methods of the ASCOT-BPLA have been described previously (5).

Definitions

BMI >30 kg/m^2 was used instead of waist circumference in defining MetS because waist circumference was not measured in ASCOT-BPLA. The original National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) definition (6) of MetS (ATP 6.1) was considered as the primary definition in these analyses. In addition, the updated NCEP-ATP III (ATP 5.6) (7), International Diabetes Federation (IDF) (8), and two other definitions, ASCOT 6.1 and ASCOT 5.6 (modified from ATP 6.1 and ATP 5.6, respectively, by excluding the "or presence of diabetes" component from the fifth criterion), were also considered. The latter two were included to reduce some of the increased CV risk conferred by the presence of diabetes at baseline.

Outcomes

Fatal coronary heart disease (CHD) plus nonfatal myocardial infarction (MI), total coronary events, stroke, and all-cause mortality were prespecified outcomes.

Statistical analyses

Three separate Cox regression analysis models were developed for each of the prespecified outcomes using the ATP 6.1 definition of MetS: model 1, unadjusted MetS; model 2, adjusted for age, sex, and ethnicity; and model 3, included model 2 plus all the individual components (used as continuous variables where linear) of the MetS. Risk (hazard ratios) associated with all five definitions of the MetS for each of the four prespecified outcomes was compared. Sensitivity assessments, which excluded all subjects with the presence of diabetes (or missing values) at baseline, were done in Cox regression analysis models using the ATP 6.1 definition.

RESULTS

— Of 19,257 hypertensive patients randomized in ASCOT-BPLA, 8,434 (43.8%) had the MetS based on the ATP 6.1 definition.

MetS and rates of coronary and stroke events and death using the ATP 6.1 definition

In model 1, MetS was associated with a significantly increased risk of coronary

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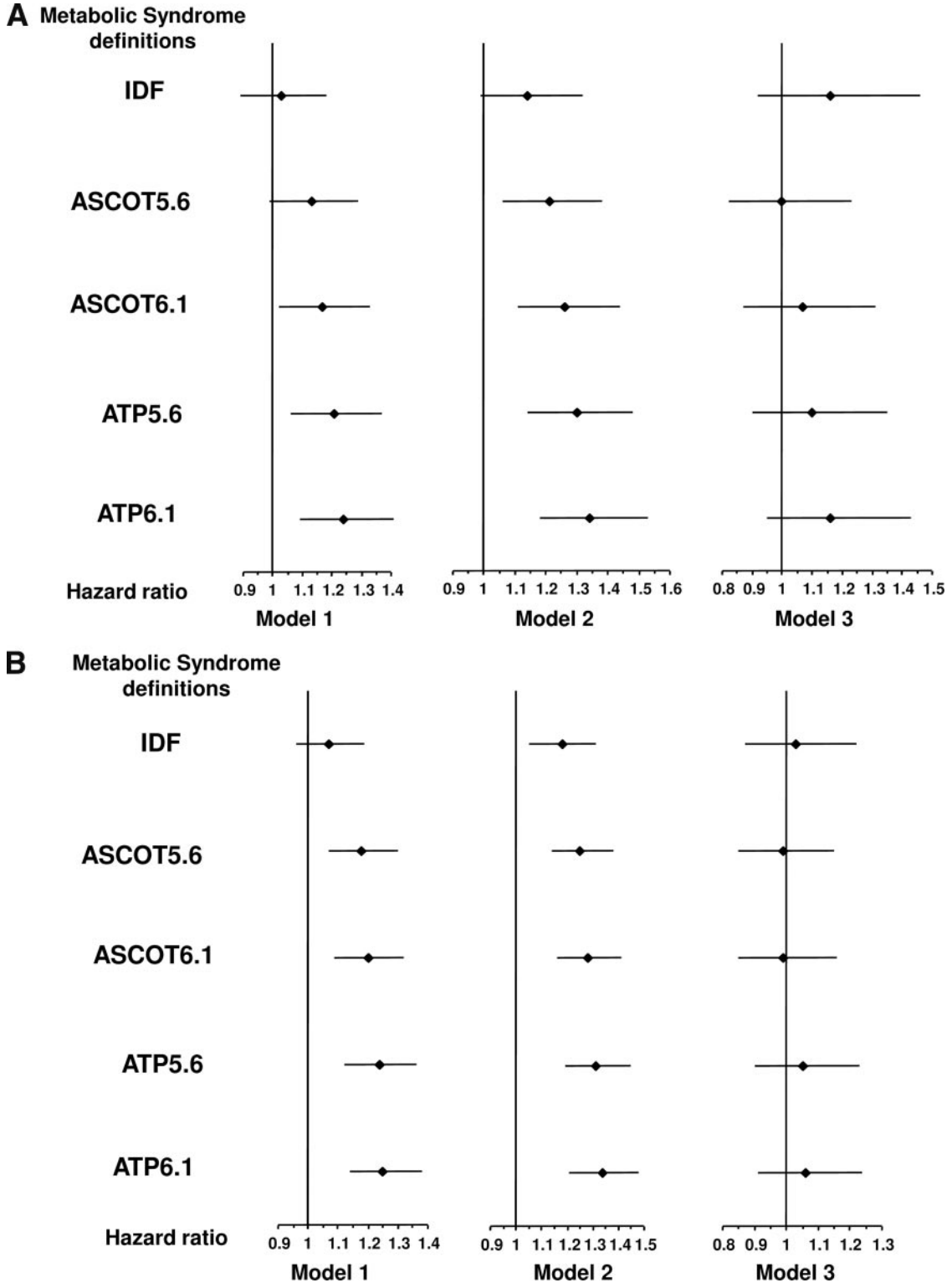
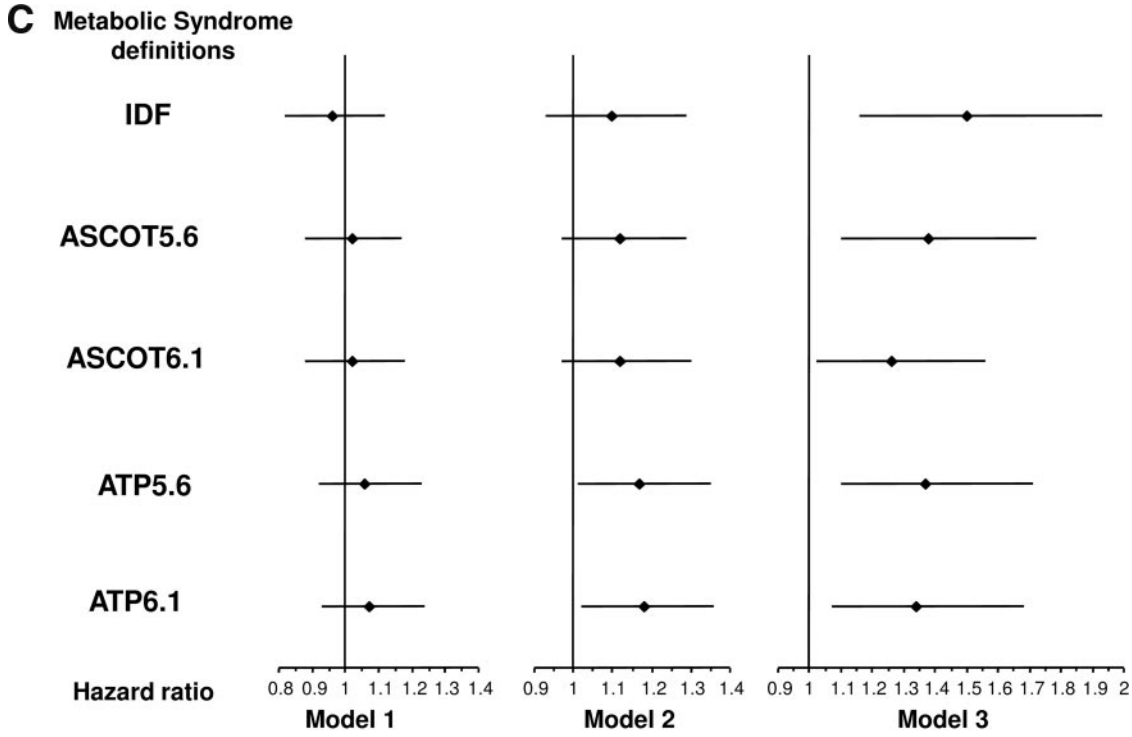


Figure 1—*Different definitions of the MetS and risk of coronary, stroke, and death outcomes.* A*: Risk of fatal CHD (includes death from MI, acute coronary syndrome, or sudden death attributable to ischemic heart disease) and nonfatal MI associated with MetS.* B*: Risk of total coronary events (includes fatal and nonfatal CHD, unstable angina, fatal and nonfatal heart failure) associated with MetS.* C*: Risk of stroke associated with MetS.* D*: Risk of all-cause mortality associated with MetS. Model 1: Univariate MetS. Model 2: Model 1 plus age, sex, and ethnicity. Model 3: Model 2 plus fasting plasma glucose, triglycerides, HDL cholesterol, systolic blood pressure, and BMI.*

events (fatal CHD plus nonfatal MI, hazard ratio [HR] 1.24 [95% CI 1.09–1.41], and total coronary events 1.25 [1.14–1.35]), but was not associated with total stroke (1.07 [0.93–1.24]), or all-cause mortality (1.07 [0.97–1.19]). In model 2, the relationship of the MetS with coronary outcomes became more significant and stronger, and it signifi-



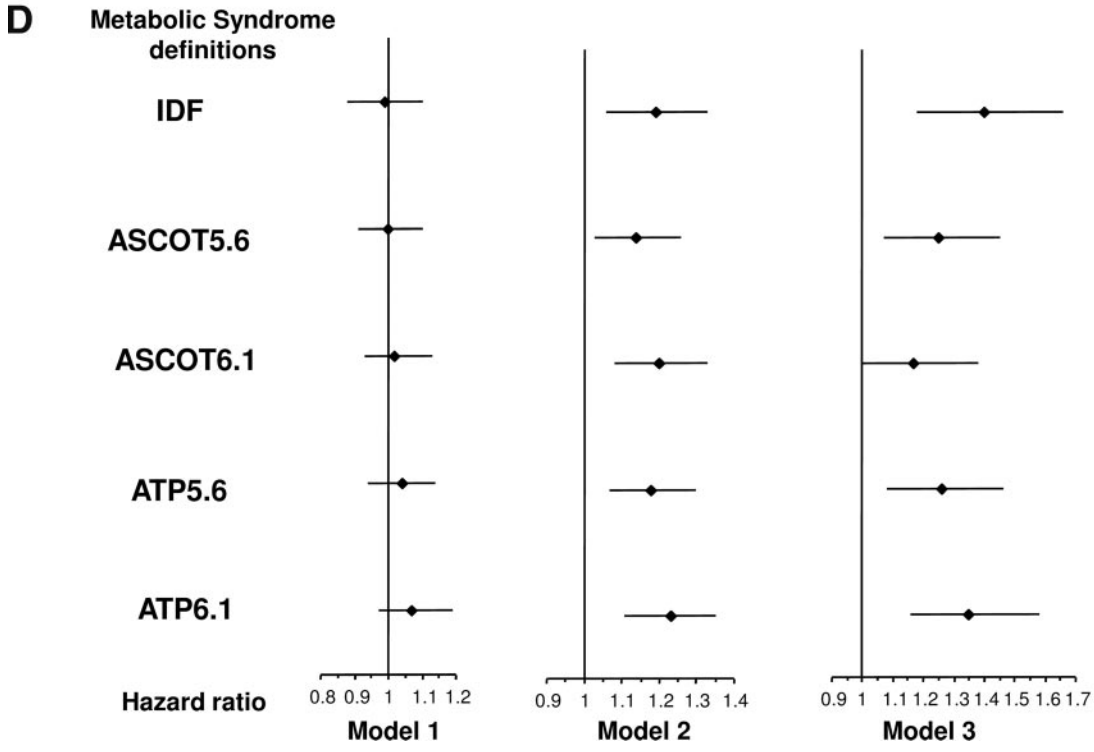


Figure 1—*Continued.*

cantly predicted total stroke (1.18 [1.02–1.36]) and all-cause mortality (1.23 [1.11–1.35]). However, when model 2 was further adjusted for the individual components of the MetS (model 3), the association between MetS and total stroke (1.34 [1.07–1.68]) and all-cause mortality (1.35 [1.16–1.58]) became stronger and remained significant, while the association with coronary outcomes attenuated and became insignificant (fatal CHD plus nonfatal MI 1.16 [0.95–1.43] and total coronary events 1.06 [0.91–1.24]) (see the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc09-2208/DC1). These relationships remained unchanged on sen-

sitivity analyses after excluding patients with diabetes at baseline.

Different definitions of MetS and coronary and stroke events, and death

The results, for each of the definitions used, showed a consistent trend of the MetS to significantly predict fatal CHD plus nonfatal MI and total coronary events in models 1 and 2 but not in model 3 (Fig. 1*A* and *B*). By contrast, the association between the MetS, regardless of the definition used, with stroke and all-cause mortality was not apparent in model 1 but became increasingly apparent in models 2 and 3 such that in model 3 the results consistently showed the MetS to be an independent predictor of total stroke and all-cause mortality after adjusting for its individual components (Fig. 1*C* and *D*).

CONCLUSIONS — These analyses of 19,257 hypertensive patients suggest that the MetS, independently of its components, is associated with increased risk of stroke and death but not of coronary outcomes.

The lack of any synergy among the individual components of the MetS on the risk of coronary outcomes seen in our analyses is in keeping with findings of some (3,4) but not all previous reports (1,2). To compare our findings with the studies that adjusted for classical confounders, we further adjusted our model 3 for confounders such as smoking, alcohol intake, number of CV risk factors, and randomized antihypertensive regimen, but this did not change the association of the MetS with either fatal CHD plus nonfatal MI (HR 1.10 [95% CI 0.90–1.35]) or total coronary events (1.01 [0.96–1.17]).

The finding of an increased risk of incident stroke associated with the MetS, independent of its constituent components and regardless of the definition used, extends the findings of previous reports (9,10). Given the potential implications of these findings, we further adjusted model 3 to include confounders such as previous history of stroke or transient ischemic attack, number of CV risk factors, alcohol intake, smoking, history of previous antihypertensive therapy, and randomized treatment allocation and found no change in association of the MetS and incident stroke (HR 1.31[95% CI 1.04–1.64]).

None of the previous studies (11,12) have reported on the risk of death associated with the MetS adjusted for all its constituent components. Because in our analyses, the MetS independently of its components was not associated with a significantly increased risk of CV mortality (HR 1.19 [95% CI 0.93–1.53]), this suggests that if the increased risk of all-cause mortality associated with the MetS is true, the increase must be due to non-CV causes. Two-thirds of the 953 non-CV deaths in the ASCOT population were due to cancer, which has previously been found to be associated with the MetS in observational studies (13).

The use of BMI instead of waist circumference in our definition of the MetS is a possible limitation of this study. However, BMI has been used as part of previous widely accepted studies of MetS (11,14) and has been shown to have a comparable predictive capability (15). The major strength of this study is its power to examine several CV outcomes and all-cause mortality while using different definitions of the MetS in the same population.

In summary, our findings suggest that, after adjusting for its individual components, the MetS is associated with increased risk of strokes and all-cause mortality but not coronary outcomes in the hypertensive population.

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A.K.G. researched and analyzed data and wrote the manuscript. N.R.P. contributed to the discussion and reviewed the manuscript. P.S.S. and B.D. reviewed the manuscript.

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